Inflammatory Response to Trauma – Does Early Cytokine Modulation Improve Patient Outcome?

NCT03671746

08/22/2023

University of Kentucky | Office of Research Integrity
IRB, RDRC

FL Continuation Review

Approval Ends:	IRB Number:
8/21/2024	43611

TO: Arun Aneja, MD, PhD
Orthopaedic Surgery
PI phone #: 859-218-3063

PI email: arun.aneja@uky.edu

FROM: Chairperson/Vice Chairperson
Medical Institutional Review Board (IRB)

SUBJECT: Approval for Continuation

DATE: 8/22/2023

On 8/22/2023, the Medical Institutional Review Board approved your protocol entitled:

Inflammatory Response to Trauma – Does Early Cytokine Modulation Improve Patient Outcome?

Approval is effective from 8/22/2023 until 8/21/2024 and extends to any consent/assent form, cover letter, and/or phone script. If applicable, the IRB approved consent/assent document(s) to be used when enrolling subjects can be found in the "All Attachments" menu item of your E-IRB application. [Note, subjects can only be enrolled using consent/assent forms which have a valid "IRB Approval" stamp unless special waiver has been obtained from the IRB.] Prior to the end of this period, you will be sent a Continuation Review (CR)/Annual Administrative Review (AAR) request which must be completed and submitted to the Office of Research Integrity so that the protocol can be reviewed and approved for the next period.

In implementing the research activities, you are responsible for complying with IRB decisions, conditions and requirements. The research procedures should be implemented as approved in the IRB protocol. It is the principal investigator's responsibility to ensure any changes planned for the research are submitted for review and approval by the IRB prior to implementation. Protocol changes made without prior IRB approval to eliminate apparent hazards to the subject(s) should be reported in writing immediately to the IRB. Furthermore, discontinuing a study or completion of a study is considered a change in the protocol's status and therefore the IRB should be promptly notified in writing.

For information describing investigator responsibilities after obtaining IRB approval, download and read the document "PI Guidance to Responsibilities, Qualifications, Records and Documentation of Human Subjects Research" available in the online Office of Research Integrity's IRB Survival Handbook. Additional information regarding IRB review, federal regulations, and institutional policies may be found through ORI's web site. If you have questions, need additional information, or would like a paper copy of the above mentioned document, contact the Office of Research Integrity at 859-257-9428.

seeblue.
405 Kinkead Hall | Lexington, KY 40506-0057 | P: 859-257-9428 | F: 859-257-8995 | www.research.uky.edu/ori/
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IRB Approval
8/22/2023
IRB # 43611
IRB1

PROTOCOL TYPE (VERSION 4)

Which IRB

◉ Medical ○ NonMedical

Protocol Process Type

○ Exemption
◉ Expedited (Must be risk level 1)
○ Full

IMPORTANT NOTE: You will not be able to change your selections for "Which IRB" and "Protocol Process Type" after saving this section. If you select the wrong IRB or Protocol Process Type, you may need to create a new application.

See below for guidance on these options, or refer to ORI's "Getting Started" page. Please contact the Office of Research Integrity (ORI) at 859-257-9428 with any questions prior to saving your selections.

Which IRB

The **Medical IRB** reviews research from the Colleges of:

- Dentistry
- Health Sciences
- Medicine
- Nursing
- Pharmacy and Health Sciences
- and Public Health.

The **Nonmedical IRB** reviews research from the Colleges of:

- Agriculture
- Arts and Sciences
- Business and Economics
- Communication and Information
- Design; Education
- Fine Arts
- Law
- and Social Work

Note: Studies that involve administration of drugs, testing safety or effectiveness of medical devices, or invasive medical procedures must be reviewed by the **Medical IRB** regardless of the college from which the application originates.

Which Protocol Process Type

Under federal regulations, the IRB can process an application to conduct research involving human subjects in one of three ways:

- by exemption certification
- by expedited review.
- by full review;

The investigator makes the preliminary determination of the type of review for which a study is eligible. Please refer to ORI's "Getting Started" page for more information about which activities are eligible for each type of review.

The revised Common Rule expanded exemption certification category 4 for certain secondary research with identifiable information or biospecimens. The regulations no longer require the information or biospecimens to be existing. For more information see the Exemption Categories Tool.

CONTINUATION REVIEW/FINAL REVIEW

0 unresolved comment(s)

In accordance with federal regulations and/or local policies, the IRB conducts periodic review of all currently approved projects. If you need your IRB approval to continue and you do not complete and submit the required materials in a timely manner, IRB approval will expire at the end of your current approval period.

If you have any questions, please contact the Office of Research Integrity at 859-257-9428 or email IRBsubmission@uky.edu.

To initiate your continuation review (CR)/annual administrative review (AAR), or properly close your study, complete this section and update/correct all other sections of your IRB application as applicable.
*****IMPORTANT*** Before leaving this page to update other sections of your application, be sure to SAVE this section first.**

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1. Status of the Research

Check the statement(s) that best describe(s) the current status of your research:

- ☐ No subjects have enrolled to date.
- ☐ Recruitment and/or enrollment of new subjects or review of records/specimens continue.
- ☐ Study is closed to enrollment, but subjects still receive research-related interventions (e.g., treatment, blood draws).
- ☐ Study enrollment is permanently closed; subjects have completed all research-related interventions; and the study remains active only for long-term follow-up of subjects (see Tool Tip above for info on long-term follow-up of subjects).*
- ☐ Research has progressed to the point that it involves 1) Data analysis, including analysis of identifiable private information or identifiable biospecimens; and/or 2) Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.*
- ☑ The remaining research activities are limited only to data analysis. There is access to records or specimens either directly or through codes or links to the data.*
- ☐ The remaining research activities are limited only to data analysis. There is no subject/record/specimen identifying codes or links to the data; the researcher or research team cannot readily ascertain the subject's identity.*
- ☐ All study activities are complete. IRB approval can be inactivated.

*Possibility that review will move from Full to Expedited.

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2. If subjects have been enrolled within the last year, and the IRB approved a consent/assent form for your study:

Please attach a complete, signed copy for the last two subjects enrolled with **each** consent/assent form/HIPAA form since the last annual review.
(Example: If 3 different approved consent forms were used since the last annual review, please provide the two most recent signed copies of each version for a total of six.)

Attachments

Attach Type	File Name
Entire Signed Consent Form	20230731180556007-combined.pdf
Entire Signed Consent Form	20230731180652481.pdf

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3. Informed Consent

If the study is **open to subject enrollment, please go to the Informed Consent section of the E-IRB Application and verify attachment(s) include:**

- One clean copy in PDF (without the IRB Approval stamp) of the currently approved consent/assent document(s), or,
- If requesting changes to the consent/assent document(s), submit one copy with the changes highlighted (and designate Document Type as "Highlighted"), and one clean copy in PDF (without the changes highlighted).

If the study is **open to subject enrollment and the IRB has waived the requirement to document informed consent, please go to the Informed Consent section of the E-IRB Application and verify attachment(s) include:**

- One clean copy in PDF of the currently approved document used for the informed consent process (e.g., cover letter, phone script), or,
- If requesting changes to the consent/assent document(s), submit one copy with the changes highlighted (and designate Document Type as "Highlighted"), and one clean copy in PDF (without the changes highlighted).

If the study is **closed to subject enrollment, please go to the Informed Consent section of the E-IRB Application and remove Informed Consent Documents designated to get an IRB approval stamp to avoid having them appear valid for enrollment.**

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4. Unanticipated Problems Involving Risk to Subjects or Others/Adverse Events Summary & Assessment

Did any **problems/adverse events** occur during the last 12 months?

○ Yes ◉ No

In the space below, provide a written summary of both unanticipated problems* and available information regarding adverse events since the last review (e.g., initial review or annual/continuing review). The amount of detail provided in such a summary will vary depending on the type of research being conducted; in many cases, such a summary could be a brief statement that there have been no unanticipated problems and that adverse events have occurred at the expected frequency and level of severity as documented in the research protocol, the informed consent document, and investigator's brochure (if applicable). **The summary must include the PI's assessment whether the problems/adverse events warrant changes to the protocol, consent process, or risk/benefit ratio.**

Note: It is the IRB's expectation that all unanticipated problems involving risk to subjects or others or related deaths requiring prompt reporting are submitted in the appropriate time frame (See Policy [PDF]). Your response to this Annual/Continuing Review is considered assurance that all prompt reportable problems/adverse events have been submitted for IRB review.

*For multisite studies, the written summary should describe external events determined to be unanticipated problems involving risk to subjects or others.

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5. Subject Info To-Date

Our records for the previously approved IRB application indicate the **IRB approved estimate** of subjects to be enrolled (or records/specimens reviewed) is:

200

Enter the number of enrolled subjects (or records/specimens reviewed) that **have not been previously reported** to the IRB

1

Our records for the previously approved IRB application indicate the previous total # of subjects enrolled (or records/specimens reviewed) since activation of the study is:

107

The new total number of subjects enrolled (or records/specimens reviewed) since activation of the study:

108

Please review the Project Info section for the IRB approved estimate of subjects to be enrolled (or records/specimens reviewed). If this new total exceeds your approved estimate of subjects to be enrolled (or records/specimens reviewed), please update the number in the field for Number of Human Subjects in the Project Info section.

6. Data and Safety Monitoring Board (DSMB)/Plan (DSMP)

If your study is monitored by a DSMB or under a DSMP, attach all documentation (i.e. summary report; meeting minutes) representing Data and Safety Monitoring activities that have not been previously reported to the IRB.

Attachments

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7. Since the most recent IRB Initial/Continuation Review Approval:

Have there been any **participant complaints** regarding the research?

○ Yes ◉ No

If yes, in the field below, provide a summary describing the complaints.

Have any **subjects withdrawn** from the research voluntarily or by you as the PI for reasons related to safety, welfare, or problems related to the conduct of the research? If a participant does not meet the screening criteria for a study even if they signed a screening consent it is NOT considered a withdrawal.

○ Yes ◉ No

If yes, in the field below, provide a detailed explanation to the withdrawal(s) including if participants were lost to contact.

Has any **new and relevant literature** been published since the last IRB review, especially literature relating to risks associated with the research?

○ Yes ◉ No

If yes, attach a copy of the literature as well as a brief summary of the literature including, if pertinent, the impact of the findings on the protection of human subjects.

Attachments

Have there been any **interim findings?**

◉ Yes ○ No

If yes, attach a copy of **Interim Findings**.

Attachments

Attach Type	File Name
Interim Findings	OTA IM Abstract VAS and MME 2.10.23.docx

Have **subjects experienced any benefits?**

◉ Yes ○ No

If yes, in the field below, provide a description of benefits subjects have experienced.

Results:
In total, 70 participants were enrolled, with 35 randomized to the ketorolac group and 35 to the placebo group. Study groups were balanced with respect to age, BMI, and NISS. Over the 5-day treatment period, average opioid intake (p = 0.0039) and VAS pain scores (p = 0.0481) were significantly reduced in the ketorolac group compared to the placebo group. The ketorolac group experienced a 43.2% reduction in mean MME compared to the placebo group.

Conclusion:
Scheduled, short-term use of low-dose ketorolac was associated with significantly reduced opioid use and pain in orthopedic polytrauma patients with no apparent short-term adverse effects. The results support the use of low-dose short-term schedule ketorolac for pain control among orthopaedic polytrauma patients.

Have there been any **inspections/audits/quality improvement reviews** of your research protocol resulting in the need for corrective action in order to protect the safety and welfare of subjects?

○ Yes ◉ No

If yes, please attach documentation evidencing the outcome(s) and any corrective action(s) taken as a result.

Attachments

Was an FDA 483 issued as a result of any inspections/audits?

○ Yes ◉ No

If yes, submit documentation using attachment button above.

8. Risk Level:

Our records for the previously approved IRB application show your research is:

Risk Level: **2**

Has something during the course of your research changed the level of risk?

○ Yes ◉ No

If yes, go to the Risk Level section, mark the appropriate risk level, and in the field below, describe why the risk level has changed:

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9. Funding/Support:

Our records for the **previously approved** IRB application indicate your research is being submitted to, supported by, or conducted in cooperation with the following external or internal agency(ies) or funding program(s):

- ☐ Grant application pending
- ☐ (HHS) Dept. of Health & Human Services
  - ☐ (NIH) National Institutes of Health
  - ☐ (CDC) Centers for Disease Control & Prevention
  - ☐ (HRSA) Health Resources and Services Administration
  - ☐ (SAMHSA) Substance Abuse and Mental Health Services Administration
- ☐ (DoJ) Department of Justice or Bureau of Prisons
- ☐ (DoE) Department of Energy
- ☐ (EPA) Environmental Protection Agency
- ☐ Federal Agencies Other Than Those Listed Here
- ☐ Industry (Other than Pharmaceutical Companies)
- ☑ Internal Grant Program w/ proposal
- ☐ Internal Grant Program w/o proposal
- ☐ National Science Foundation
- ☐ Other Institutions of Higher Education
- ☐ Pharmaceutical Company
- ☑ Private Foundation/Association
- ☐ U.S. Department of Education
- ☐ State

Other:

Please **update the Funding/Support section of your IRB application** if needed, including the following attachments if they contain changes not previously reported to the IRB:

- A current copy of your **protocol if you are conducting industry/pharmaceutical research;**
- A current **Investigator Brochure** (submit a copy with all changes underlined).
- A **new or revised grant application** for this project.

Did your project receive extramural funding?

○ Yes ◉ No

If yes, please review and correct if necessary, the OSPA Account # information under the **Funding/Support section** of your IRB application.

If the project is externally funded, has the sponsor offered any of the research team enrollment incentives or other personal benefit bonuses? (e.g., cash/check, travel reimbursements, gift checks, etc.)

○ Yes ◉ No ○ N/A

Note: It is University of Kentucky policy that personal benefit bonuses are not allowed. If these conditions change during the course of the study, please notify the IRB.

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10. Project Information

Our records for the previously approved IRB application indicate your estimated project end date is:

08/31/2023

If you have a new estimated project end date, please go to the Project Info section and change the date in the field for Anticipated Ending Date of Research Project.

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11. Study Personnel

Our records for the previously approved IRB application indicate the following individuals are study personnel on this project (if applicable):

Last Name	First Name
Bernard	Andrew
Feola	David
Foster	Jeffrey
Griffin	Jarod
Herndon	Brooke
Matuszewski	Paul
Moghadamian	Eric
Noehren	Brian
Oyler	Douglas
Primm	Daniel
Wright	Raymond
Zuelzer	David

Please review the individuals listed above and update your records as needed in the Study Personnel section of the E-IRB application, being sure that each individual listed has completed or is up-to-date on the mandatory human research protection training [see the policy on Mandatory Human Subject Protection Training FAQs (required every three years)].

12. Progress of the Research

To meet federal requirements the IRB is relying on your RESEARCH DESCRIPTION as a protocol summary and their expectation is that it is up-to-date. If the currently approved protocol (or research description) in your E-IRB application is outdated, please make applicable changes, and describe in the field below any substantive changes and explain why they are essential. If none, insert "N/A" in the text field below. If you are closing your study, you may use the space below to summarize the final status of the research.

N/A

Note: No changes in the research procedures should have occurred without previous IRB review. Approval from the IRB must be obtained before implementing any changes.

Provide a brief **summary** of any **modifications that affect subject safety and/or welfare** approved by the IRB since the last initial or continuation review (If none, insert "N/A" in the text field below.):

N/A

Attach one copy of the most recent progress report sent to the FDA, if available. All PI-sponsored IND/IDE studies are required to submit a copy of the FDA progress report.

Attachments

13. Confidentiality/Security

Review your Research Description section and update the Confidentiality portion, if necessary, to describe measures for security of electronic and physical research records (e.g., informed consent document(s), HIPAA Authorization forms, sensitive or private data).

14. Subject Demographics

Our records for the previously approved IRB application indicate the following categories of subjects and controls are included in your research:

- ☐ Children (individuals under age 18)
- ☐ Wards of the State (Children)
- ☐ Emancipated Minors
- ☐ Students
- ☐ College of Medicine Students
- ☐ UK Medical Center Residents or House Officers
- ☐ Impaired Consent Capacity Adults
- ☐ Pregnant Women/Neonates/Fetal Material
- ☐ Prisoners
- ☐ Non-English Speaking
- ☐ International Citizens
- ☐ Normal Volunteers
- ☐ Military Personnel and/or DoD Civilian Employees
- ☑ Patients
- ☐ Appalachian Population

Please review the Subject Demographics section of your IRB application for accuracy, and note the following:

If during the course of your research 1) any prisoners have been enrolled, OR 2) subjects have been enrolled that became involuntarily confined/detained in a penal institution that have not been previously reported to the IRB, go to Subject Demographic section in your E-IRB application and mark “prisoners” in the categories of subjects to be included in the study, if it is not already marked.

Note: If either 1 or 2 above apply, and you have received funding from the Department of Health and Human Services (HHS), a Certification Letter should have been submitted to the Office for Human Research Protections (OHRP); prisoners and individuals who have become involuntarily confined/detained in a penal institution cannot continue participation in the research until OHRP issues approval. If the Certification has not been submitted, contact the Office of Research Integrity.

Based on the **total # of subjects** who have enrolled, complete the subject demographic section below:

	Participant Demographics			
	Cisgender Man	**Cisgender Woman**	**TGNB/TGE**	**Unknown/Not Reported**
American Indian/Alaskan Native				
Asian				
Black or African American	3	1		
Latinx				
Native Hawaiian or Other Pacific Islander				
White	40	26		
American Arab/Middle Eastern/North African				
Indigenous People				

Around the World				
More than One Race				
Unknown or Not Reported				

If unknown, please explain why:

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15. Research Sites

Our records for the previously approved IRB application indicate that you are conducting research at the following sites:

UK Sites

- ☐ UK Classroom(s)/Lab(s)
- ☐ UK Clinics in Lexington
- ☐ UK Clinics outside of Lexington
- ☐ UK Healthcare Good Samaritan Hospital
- ☑ UK Hospital

Schools/Education Institutions Schools/Education Institutions

- ☐ Fayette Co. School Systems *
- ☐ Other State/Regional School Systems
- ☐ Institutions of Higher Education (other than UK)

Other Medical Facilities

- ☐ Bluegrass Regional Mental Health Retardation Board
- ☐ Cardinal Hill Hospital
- ☐ Eastern State Hospital
- ☐ Nursing Homes
- ☐ Shriner's Children's Hospital
- ☐ Other Hospitals and Med. Centers

- ☐ Correctional Facilities
- ☐ Home Health Agencies
- ☐ International Sites

Other:

If the above listed sites are not accurate, go to the Research Sites section of the E-IRB application to update the facilities at which research procedures have been or will be conducted.

If you are adding a new off-site facility, you may also need to update your E-IRB application Research Description, Research Sites, Informed Consent, and other affected sections as well as any documents which will list the off-site facility. Documents needing updating may include, but not limited to:

- Consent forms (attachment under Informed Consent section)
- Brochures (attachment under Additional Info section)
- Advertisements (attachment under Research Description section) ;
- Letter of support (attachment under Research Sites section)).

Please revise applicable sections and attachments as necessary.

16. Disclosure of Significant Financial Interest

Disclosure of Significant Financial Interest:

Our records for the previously approved IRB application indicate that you, your investigators, and/or key personnel (KP) have a significant financial interest (SFI) related to your/their responsibilities at the University of Kentucky (that requires disclosure per the UK administrative regulation 7:2):

○ Yes ◉ No

If you need to update your records, please go to the PI Contact Information section and/or Details for individuals listed in the Study Personnel section to change your response to the applicable question(s).

17. Supplementals

To ensure the IRB has the most accurate information for your protocol you are expected to re-visit the E-IRB application sections and make corrections or updates as needed. At a minimum you are being asked to review the following sections for accuracy:

STUDY DRUG INFORMATION—Please review for accuracy.
STUDY DEVICE INFORMATION—Please review for accuracy.
RESEARCH ATTRIBUTES—Please review for accuracy.
OTHER REVIEW COMMITTEES -- Please review for accuracy.

PROJECT INFORMATION

0 unresolved comment(s)

Title of Project: (Use the exact title listed in the grant/contract application, if applicable).
If your research investigates any aspect of COVID-19, please include "COVID19" at the beginning of your Project Title and Short Title

Inflammatory Response to Trauma – Does Early Cytokine Modulation Improve Patient Outcome?

Short Title Description
Please use a few key words to easily identify your study - this text will be displayed in the Dashboard listing for your study.

Inflammatory Markers

Anticipated Ending Date of Research Project: 10/31/2023

Maximum number of human subjects (or records/specimens to be reviewed) 200

After approval, will the study be open to enrollment of new subjects or new data/specimen collection? ○ Yes ◉ No

PI CONTACT INFORMATION

0 unresolved comment(s)

Principal Investigator (PI) role for E-IRB access
The PI is the individual holding primary responsibility on the research project with the following permissions on the E-IRB application:

1. Read;
2. write/edit;
3. receive communications; and
4. submit to the IRB (IR, CR, MR, Other Review*).

If research is being submitted to or supported by an extramural funding agency such as NIH, a private foundation or a pharmaceutical/manufacturing company, the PI listed on the grant application or the drug protocol must be listed as PI here.

Please fill in any blank fields with the appropriate contact information (gray shaded fields are not editable). Required fields left blank will be highlighted in pink after you click "Save".

To change home and work addresses, go to myUK and update using the Employee Self Service (ESS) portal. If name has changed, the individual with the name change will need to submit a 'Name Change Form' to the Human Resources Benefits Office for entering into SAP. The new name will need to be associated with the individual's Link Blue ID in SAP before the change is reflected in E-IRB. Contact the HR Benefits Office for additional information.

The Principal Investigator's (PI) contact information is filled in automatically based on who logged in to create the application.

If you are not the Principal Investigator, do NOT add yourself as study personnel.
To change the PI contact information on an application in Researcher edit status:

- click "Change Principal Investigator";
- search for the PI's name using the search feature;
- click "Select" by the name of the Principal Investigator, then "Save Contact Information".

  You will automatically be added as study personnel with editing permissions to continue editing the application.

Change Principal Investigator:

First Name:	Arun	Room# & Bldg:	740 S. Limestone, Suite K401
Last Name:	Aneja	Speed Sort#:	40536
Middle Name			
Department:	Orthopaedic Surgery - 7H859	Dept Code:	7H859
PI's Employee/Student ID#:	12223247	Rank:	
PI's Telephone #:	859-218-3063	Degree:	MD, PhD
PI's e-mail address:	arun.aneja@uky.edu	PI's FAX Number:	
PI is R.N.	○ Yes ◉ No	HSP Trained:	Yes
		HSP Trained Date:	6/9/2023
		RCR Trained:	Yes

Do you, the PI, have a significant financial interest related to your responsibilities at the University of Kentucky (that requires disclosure per the UK administrative regulation 7:2)?

○ Yes ◉ No

RISK LEVEL

0 unresolved comment(s)

Indicate which of the categories listed below accurately describes this protocol

- (●) (Risk Level 1) Not greater than minimal risk
- ( ) (Risk Level 2) Greater than minimal risk, but presenting the prospect of direct benefit to individual subjects
- ( ) (Risk Level 3) Greater than minimal risk, no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.
- ( ) (Risk Level 4) Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of subjects.

*"Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves from those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests.

*****For Expedited and Exempt Applications, the research activities must be Risk Level 1 (no more than minimal risk to human subjects).*****

Refer to UK's guidance document on assessing the research risk for additional information.

SUBJECT DEMOGRAPHICS **0 unresolved comment(s)**

Age level of human subjects: (i.e., 6 mths.; 2yrs., etc..) 18 to 75

Study Population:

Describe the characteristics of the subject population, including age range, gender, ethnic background and health status. Identify the criteria for inclusion and exclusion.

Provide the following information:

- A description of the subject selection criteria and rationale for selection in terms of the scientific objectives and proposed study design;
- A compelling rationale for proposed exclusion of any sex/gender or racial/ethnic group;
- Justification for the inclusion of vulnerable groups such as children, prisoners, adults with impaired consent capacity, or others who may be vulnerable to coercion or undue influence.

Please consider these resources:
NIH Diversity Policy
FDA Diversity Guidance

The study population will consist of 200 patients (100 control, 100 treated with Ketorolac) that are admitted to the inpatient surgical service at our level I trauma center for management of trauma care. Trauma patients that are between the ages of 18-75 and with NISS > 9 (moderate injury) will be enrolled [24, 25]. All patients will be treated according to the standard Advance Trauma Life Support (ATLS) protocol. Those admitted to the ICU will be treated according to standard ICU protocols.
Patient demographics are expected to be consistent with the general trauma patient population in central Kentucky. We will prospectively identify skeletal mature patients for inclusion in our research protocol. The detailed inclusion and exclusion criteria are listed in Table 1.

Attachments

Indicate the targeted/planned enrollment of the following members of minority groups and their subpopulations. Possible demographic sources: Census Regional Analyst Edition, Kentucky Race/Ethnic Table, Kentucky Population Data.
(Please note: The IRB will expect this information to be reported at Continuation Review time for Pre-2019 FDA-regulated Expedited review and Full review applications):

Participant Demographics

	Cisgender Man	Cisgender Woman	TGNB/TGE	Unknown/Not Reported
American Indian/Alaskan Native:				
Asian:	3	3		
Black/African American:	3	3		
Latinx:				
Native Hawaiian/Pacific Islander:				
White:	94	94		
American Arab/Middle Eastern/North African:				
Indigenous People Around the World:				
More than One Race:				
Unknown or Not Reported:				

If unknown, please explain why:

Indicate the categories of subjects and controls to be included in the study. You may be required to complete additional forms depending on the subject categories which apply to your research. If the study does not involve direct intervention or direct interaction with subjects, (e.g., record-review research, outcomes registries), do not check populations which the research does not specifically target. For example: a large record review of a diverse population may incidentally include a prisoner or an international citizen, but you should not check those categories if the focus of the study has nothing to do with that status.

Check All That Apply (at least one item must be selected)

- ☐ Children (individuals under age 18)
- ☐ Wards of the State (Children)
- ☐ Emancipated Minors
- ☐ Students
- ☐ College of Medicine Students
- ☐ UK Medical Center Residents or House Officers
- ☐ Impaired Consent Capacity Adults
- ☐ Pregnant Women/Neonates/Fetal Material
- ☐ Prisoners
- ☐ Non-English Speaking (translated long or short form)
- ☐ International Citizens
- ☐ Normal Volunteers
- ☐ Military Personnel and/or DoD Civilian Employees
- ☑ Patients
- ☐ Appalachian Population

ADDITIONAL INFORMATION:

Please visit the IRB Survival Handbook for more information on:

- Children/Emancipated Minors
- Students as Subjects
- Prisoners
- Impaired Consent Capacity Adults
- Economically or Educationally Disadvantaged Persons

Other Resources:

- UKMC Residents or House Officers [see requirement of GME]
- Non-English Speaking [see also the E-IRB Research Description section on this same topic]
- International Citizens [DoD SOP may apply]
- Military Personnel and/or DoD Civilian Employees

Assessment of the potential recruitment of subjects with impaired consent capacity (or likelihood):

☐ Check this box if your study does NOT involve direct intervention or direct interaction with subjects (e.g., record-review research, secondary data analysis). If there is no direct intervention/interaction you will not need to answer the impaired consent capacity questions.

Does this study focus on adult subjects with any conditions that present a high *likelihood* of impaired consent capacity or *fluctuations* in consent capacity? (see examples below)

○ Yes ◉ No

If Yes and you are not filing for exemption certification, go to "Form T", complete the form, and attach it using the button below.

Examples of such conditions include:

- Traumatic brain injury or acquired brain injury
- Severe depressive disorders or Bipolar disorders
- Schizophrenia or other mental disorders that involve serious cognitive disturbances
- Stroke
- Developmental disabilities
- Degenerative dementias
- CNS cancers and other cancers with possible CNS involvement
- Late stage Parkinson's Disease
- Late stage persistent substance dependence
- Ischemic heart disease
- HIV/AIDS
- COPD
- Renal insufficiency
- Diabetes
- Autoimmune or inflammatory disorders
- Chronic non-malignant pain disorders
- Drug effects
- Other acute medical crises

Attachments

INFORMED CONSENT/ASSENT PROCESS/WAIVER

0 unresolved comment(s)

For creating your informed consent attachment(s), please download the most up-to-date version listed in "All Templates" under the APPLICATION LINKS menu on the left, and edit to match your research project.

Additional Resources:

- Informed Consent/Assent Website
- Waiver of Consent vs. Waiver of Signatures
- Sample Repository/Registry/Bank Consent Template

Consent/Assent Tips:

- If you have multiple consent documents, be sure to upload each individually (not all in a combined file).
- If another site is serving as the IRB for the project, attach the form as a “Reliance Consent Form” so the document will not receive a UK IRB approval stamp; the reviewing IRB will need to stamp the consent forms.
- Changes to consent documents (e.g., informed consent form, assent form, cover letter, etc...) should be reflected in a 'tracked changes' version and uploaded separately with the Document Type "Highlighted Changes".
- It is very important that only the documents you wish to have approved by the IRB are attached; DELETE OUTDATED FILES -- previously *approved* versions will still be available in Protocol History.
- Attachments that are assigned a Document Type to which an IRB approval stamp applies will be considered the version(s) to be used for enrolling subjects once IRB approval has been issued.
  Document Types that do NOT get an IRB approval stamp are:
  - "Highlighted Changes",
  - "Phone Script", and
  - "Reliance Consent Form",
  - "Sponsor's Sample Consent Form".

How to Get the Section Check Mark

1. You must:

   a) provide a response in the text box below describing how investigators will obtain consent/assent, and
   b) check the box for at least one of the consent items and/or check mark one of the waivers

2. If applicable attach each corresponding document(s) **as a read-only PDF**.
3. If you no longer need a consent document approved (e.g., closed to enrollment), or, the consent document submitted does not need a stamp for enrolling subjects (e.g., umbrella study, or sub-study), only select "Stamped Consent Doc(s) Not Needed".
4. After making your selection(s) be sure to scroll to the bottom of this section and SAVE your work!

Check All That Apply

- ☐ Informed Consent Form (and/or Parental Permission Form and/or translated short form)
- ☐ Assent Form
- ☐ Cover Letter (for survey/questionnaire research)
- ☐ Phone Script
- ☑ Informed Consent/HIPAA Combined Form
- ☐ Debriefing and/or Permission to Use Data Form
- ☐ Reliance Consent Form
- ☐ Sponsor's sample consent form for Dept. of Health and Human Services (DHHS)-approved protocol
- ☐ Stamped Consent Doc(s) Not Needed

Attachments

Informed Consent Process:

Using active voice, describe how investigators will obtain consent/assent. Include:

- the circumstances under which consent will be sought and obtained
- the timing of the consent process (including any waiting period between providing information and obtaining consent)

- who will seek consent
- how you will minimize the possibility of coercion or undue influence
- the method used for documenting consent
- if applicable, who is authorized to provide permission or consent on behalf of the subject
- if applicable, specific instruments or techniques to assess and confirm potential subjects' understanding of the information

Note: all individuals authorized to obtain informed consent should be designated as such in the E-IRB "Study Personnel" section of this application.

Special considerations may include:

- Obtaining consent/assent for special populations such as children, prisoners, or people with impaired decisional capacity
- *Research Involving Emancipated Individuals*
  If you plan to enroll some or all prospective subjects as emancipated, consult with UK legal counsel **prior to submitting this application to the IRB**. Include research legal counsel's recommendations in the "Additional Information" section as a separate document.
- *Research Involving Non-English Speaking Subjects*
  For information on inclusion of non-English speaking subjects, or subjects from a foreign culture, see IRB Application Instructions for Recruiting Non-English Speaking Participants or Participants from a Foreign Culture.
- *Research Repositories*
  If the purpose of this submission is to establish a research repository describe the informed consent process. For guidance regarding consent issues, process approaches, and sample language see the Sample Repository/Registry/Bank Consent Template.

Consent and/or Authorization by a Legally Authorized Representative (LAR)

Eligible patients will be approached for their consent to participate. Informed consent will be obtained prior to the collection of any study related data. To encourage a high level of participation from eligible patients, the attending surgeon may be involved in the consent conversation. The research coordinator and surgeon may initiate the conversation together.

By virtue of the types of injuries studied (resulting from high energy mechanisms such as high speed motor vehicle crashes, high falls, and blast injuries) it is expected that a large proportion (> 30%) to have an associated traumatic brain injury which my render them unable to provide consent for the study. It will be important not to exclude these patients from the study, as it would significantly reduce our ability to produce generalizable knowledge. These patients are at no greater risk of adverse consequences by virtue of their participation in the study, and should be given the same opportunity to participate.

Consistent with Kentucky health care decision statutes for choosing a legally authorized representative for adult subjects unable to consent, one of the following responsible parties, in the following order of priority (if no individual in a prior class is reasonably available, willing, and competent to act), is authorized to make research participation decisions on behalf of the person: (a) the judicially-appointed guardian of the person, if the guardian has been appointed and if the decisions to be made under the consent are within the scope of the guardianship; (b) the attorney-in-fact named in a durable power of attorney, if the durable power of attorney specifically includes authority for the decisions to be made under the consent; (c) the spouse of the person; (d) an adult child of the person, or if the person has more than one (1) child, the majority of the adult children who are reasonably available for consultation; (e) the parents of the subject; (f) the nearest living relative, or if more than one of the same relation, a majority of the nearest living relatives.

Consent by a legally authorized representative should involve all the same considerations that informed consent from a competent subject involves.

Guidance will be provided to assist the LAR in making the consent decision. They will advised to base the decision on the participant's expressed wishes, or, if these are not known, what they believe the participant would have desired under the circumstances of the injury, their beliefs and values. If the LAR does not know what the participant would have wanted, the LAR will advised to base the decision with the participant's best interest in mind. They will be asked to carefully consider how much leeway the participant would likely give the LAR in making the choice about participation in the study.

Recognizing that consent is an ongoing process, the study team will encourage the participants to ask additional questions that may arise during the course of their participation in the study.
Not Applicable

☐ Request for Waiver of Informed Consent Process

If you are requesting IRB approval to waive the requirement for the informed consent process, or to alter some or all of the elements of informed consent, complete, Section 1 and Section 2 below.

Note: The IRB does not approve waiver or alteration of the consent process for greater than minimal risk research, except for planned emergency/acute care research as provided under FDA regulations. Contact ORI for regulations that apply to single emergency use waiver or acute care research waiver (859-257-9428).

SECTION 1.

Check the appropriate item:

☐ I am requesting a waiver of the requirement for the informed consent process.

☐ I am requesting an alteration of the informed consent process.

If you checked the box for this item, describe which elements of consent will be altered and/or omitted, and justify the alteration.

SECTION 2.

Explain how each condition applies to your research.

a) The research involves no more than minimal risk to the subject.

b) The rights and welfare of subjects will not be adversely affected.

c) The research could not practicably be carried out without the requested waiver or alteration.

d) Whenever possible, the subjects or legally authorized representatives will be provided with additional pertinent information after they have participated in the study.

Request for Waiver of Signatures

If you are requesting IRB approval to waive the requirement for signatures on informed consent forms, **your research activities must fit into one of three regulatory options**:

1. The only record linking the participant and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality (e.g., a study that involves participants who use illegal drugs).
2. The research presents no more than minimal risk to the participant and involves no procedures for which written consent is normally required outside of the research context (e.g., a cover letter on a survey, or a phone script).
3. The participant (or legally authorized representative) is a member of a distinct cultural group or community in which signing forms is not the norm, the research presents no more than minimal risk to the subject, and there is an appropriate alternative mechanism for documenting that informed consent was obtained.

Select the option below that best fits your study.

If the IRB approves a waiver of signatures, participants must still be provided oral or written information about the study. To ensure you include required elements in your consent document, use the ***Cover Letter Template*** *as a guide. There is an English and a Spanish version.*

Option 1

Describe how your study meets these criteria:

a) The only record linking the participant and the research would be the consent document:

b) The principal risk would be potential harm resulting from a breach of confidentiality (i.e., a study that involves subjects who use illegal drugs).

Under this option, each participant (or legally authorized representative) must be asked whether (s)he wants to sign a consent document; if the participant agrees to sign a consent document, only an IRB approved version should be used.

Option 2

Describe how your study meets these criteria:

a) The research presents no more than minimal risk to the participant:

b) Involves no procedures for which written consent is normally required outside of the research context (i.e. a cover letter on a survey, or a phone script):

Option 3

Describe how your study meets these criteria:

a) The subject (or legally authorized representative) is a member of a distinct cultural group or community in which signing forms is not the norm.

b) The research presents no more than minimal risk to the subject.

c) There is an appropriate alternative mechanism for documenting that informed consent was obtained.

STUDY PERSONNEL **1 unresolved comment(s)**

Do you have study personnel who will be assisting with the research?
After selecting 'Yes' or 'No' you must click the 'Save Study Personnel Information' button.

◉ Yes ○ No

Manage Study Personnel

Identify other study personnel assisting in research project:

- The individual listed as PI in the 'PI Contact Information' section should NOT be added to this section.
- If the research is required for a University of Kentucky academic program, the faculty advisor is also considered study personnel and should be listed below. ***Residents and students who are PI's are encouraged to designate the faculty advisor or at least one other individual as a contact with an editor role (DP).***
- Role: DP = Editor (individual can view, navigate, and edit the application for any review phase (IR, CR/FR, MR) or 'Other Review", and submit Other Reviews on behalf of the PI.)
- Role: SP = Reader (individual can view and navigate through the currently approved application only.)

To add an individual via the below feature:

- Search for personnel;
- Click "select" by the listing for the person you want to add;
- For each person, specify responsibility in the project, whether authorized to obtain informed consent, AND denote who should receive E-IRB notifications (contact status).

NOTE: Study personnel must complete human subject protection (HSP) and Responsible Conduct of Research (RCR) training before implementing any research procedures. For information about training requirements for study personnel, visit UK's HSP FAQ page, the RCR Getting Started page, or contact ORI at 859-257-9428. If you have documentation of current HSP training other than that acquired through UK CITI, you may submit it to ORI (HSPTrainingSupport@uky.edu) for credit.

Study personnel assisting in research project:

Last Name	First Name	Responsibility In Project	Role	AC	Contact	Degree	StatusFlag	(HSP)	(HSP)Date	(RCR)	Removed?	Last Updated	SFI
Bernard	Andrew	Co-Investigator	DP	Y	N		P	Y	10/03/2021	Y	N	01/30/2018	N
Feola	David	Co-Investigator	DP	Y	N		P	Y	12/29/2021	Y	N	01/30/2018	N
Foster	Jeffrey	Study Coordinator	DP	Y	Y	MD	P	Y	05/18/2022	Y	N	05/19/2022	N
Griffin	Jarod	Study Coordinator	DP	Y	Y	BS	P	Y	04/13/2021	Y	N	03/27/2023	N
Herndon	Brooke	Study Coordinator	DP	Y	Y		P	Y	01/25/2021	Y	N	11/06/2019	N
Matuszewski	Paul	Sub-Investigator	DP	Y	N	MD	P	Y	04/28/2021	Y	N	11/10/2020	N
Moghadamian	Eric	Sub-Investigator	DP	Y	N	MD	P	Y	11/04/2022	Y	N	11/05/2022	N
Noehren	Brian	Co-Investigator	DP	Y	N		P	Y	11/15/2020	Y	N	08/10/2020	N
Oyler	Douglas	Co-Investigator	DP	Y	N		P	Y	02/25/2021	Y	N	01/30/2018	N
Primm	Daniel	Sub-Investigator	DP	Y	N	MD	P	Y	09/08/2020	Y	N	11/10/2020	N
Wright	Raymond	Sub-Investigator	DP	Y	N	MD	P	Y	11/29/2021	Y	N	11/10/2020	N
Zuelzer	David	Sub-Investigator	DP	Y	N	MD	P	Y	11/30/2021	Y	N	11/10/2020	N
Abbenhaus	Eric	Study Coordinator	DP	Y	N	MD	P	N	05/01/2020	Y	Y	01/13/2022	N
Albano	Ashley	Study Coordinator	DP	Y	Y		P	N	07/21/2020	Y	Y	05/24/2022	N
Belza	Daniel	Data Collection	SP	Y	N		S	N	09/30/2018	Y	Y	04/18/2022	N
Boyle	Maxwell	Data Collection	SP	Y	N		S	Y	05/18/2021		Y	01/13/2022	N
Collofello	Brandon	Co-Investigator	SP	Y	N	MD	P	Y	06/29/2022	N	Y	01/13/2022	N
Comadoll	Shea	Co-Investigator	DP	Y	N	MD	P	N	07/09/2017		Y	04/18/2022	N

Last Name	First Name	Responsibility In Project	Role	AC	Contact	Degree	StatusFlag	(HSP)	(HSP)Date	(RCR)	Removed?	Last Updated	SFI
Hautala	Gavin	Study Coordinator	DP	Y	N	MD	P	Y	06/28/2022	Y	Y	01/13/2022	N
Isla	Alexander	Study Coordinator	DP	Y	Y		P	Y	10/09/2020	N	Y	01/13/2022	N
Jacobs	Cale	Co-Investigator	DP	Y	N		P	N	06/18/2020	Y	Y	03/10/2023	N
Kavolus	Matthew	Study Coordinator	DP	Y	N	MD	P	Y	05/12/2021	Y	Y	03/10/2023	N
Kinchelow	Daria	Study Coordinator	DP	Y	Y	BA	P	Y	07/08/2022	Y	Y	06/09/2023	N
Liu	Boshen	Co-Investigator	DP	Y	N	MD	P	N	06/20/2020		Y	08/10/2020	N
Pease	Tyler	Study Coordinator	DP	Y	N	BS	P	Y	04/18/2021	N	Y	03/10/2023	N
Pectol	Richard	Study Coordinator	DP	Y	Y	B.S.	P	Y	12/13/2021	N	Y	03/10/2023	N
Raffetto	Michael	Study Coordinator	DP	Y	Y		P	N	05/18/2020	N	Y	01/13/2022	N
Smith	April	Study Coordinator	DP	Y	Y		P	N	03/02/2020		Y	08/10/2020	N
Sneed	Chandler	Study Coordinator	DP	Y	Y	BS	P	Y	05/21/2021	Y	Y	06/09/2023	N
Stringer	Paul	Study Coordinator	DP	Y	Y		P	Y	05/08/2023	Y	Y	01/13/2022	N
Teasdall	Robert	Study Coordinator	DP	Y	Y		P	Y	12/11/2022	N	Y	01/13/2022	N

RESEARCH DESCRIPTION

0 unresolved comment(s)

You may attach a sponsor's protocol pages in the "Additional Information" section and refer to them where necessary in the Research Description. However, each prompt that applies to your study should contain at least a summary paragraph.

Pro Tips:

- **Save your work often to avoid losing data.**
- **Use one of the attachment buttons in this section or under the Additional Information section to include supplemental information with your application. During the document upload process, you will be able to provide a brief description of the attachment.**

Background

Include a brief review of existing literature in the area of your research. You should identify gaps in knowledge that should be addressed and explain how your research will address those gaps or contribute to existing knowledge in this area. For interventional research, search PubMed and ClinicalTrials.gov for duplicative ongoing and completed trials with same condition and intervention(s).

Accidental trauma is the 4th leading cause of death in the United States, and it is associated with a complex inflammatory response [1]. This response is associated with post-traumatic complications such as; multi-organ dysfunction syndrome (MODS), bacterial pneumonia, acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS), and post traumatic pain (PTP) [2-7]. It is unknown whether early modulation of inflammatory cytokines is associated with improved patient outcomes, reduced narcotic requirements, and improved patient subjective pain after hospital discharge.

Our preliminary data has shown: (1) elevated blood cytokine concentrations during the acute phase of trauma are correlated with the development of fatal post-traumatic complications [8], (2) that early administration of a non-steroidal anti-inflammatory drug (NSAID) resulted in decreased blood serum levels of IL-6, Prostaglandin E2 (PGE2), improved pulmonary edema, and enhanced arterioles ability to vasoconstrict in response to hemorrhage in animal models [9], and (3) that the addition of the internal physiologic parameters (inflammatory cytokines) to New Injury Severity Score (NISS – a marker of the external anatomical insult) significantly improves the ability to predict hospital length of stay of trauma patients when compared to NISS alone [10]. Our group is the first to use an integrative approach that combines the external anatomic injury data with the internal physiologic response for accurate prediction of patient's clinical outcome. Therefore, if we apply this same mindset to treatment, we can improve the trauma patients' care by addressing both parameters as opposed to solely focusing on the external injury as done in the past. Our ability to modify post-traumatic physiologic response via short-term administration of a NSAID may lead to improved patient outcome.

Over the last decade, clinicians remain puzzled over the safety of NSAID administration after fracture in terms of bone union [11-15]. In addition, given the current landscape for opioid epidemic in the United States [16, 17], alternative non-opioid pain management during acute trauma has the potential to reduce opioid consumption and represents a pivotal component of multimodal analgesia strategy.

Objectives

List your research objectives. Please include a summary of intended research objectives in the box below.

Aim 1: Determine if a brief and low dose scheduled administration of an NSAID (Ketorolac) will reduce the inflammatory cascade and improve the clinical outcomes of orthopaedic trauma patients. Ketorolac will be used as the NSAID of choice because it is of low cost to patients, readily available intravenously, has few side effects, and also decrease opioid consumption in acute trauma [18-21].

Aim 2: Determine whether patients who received Ketorolac treatment require less opioid medication throughout their hospital and post-operative course. The outcome variable will be patient's subjective pain scores, morphine milligram equivalent intake along with other pain modulating medication intake. Inpatient and outpatient subjective pain reports will be collected and analyzed for pain relief and medication use.

Study Design

Describe and explain the study design (e.g., observational, secondary analysis, single/double blind, parallel, crossover, deception, etc.).

- *Clinical Research*: Indicate whether subjects will be randomized and whether subjects will receive any placebo.
- *Community-Based Participatory Research*: If you are conducting community-based participatory research (CBPR), describe strategies for involvement of community members in the design and implementation of the study, and dissemination of results from the study.
- *Qualitative research*: Indicate ranges where flexibility is needed, if a fixed interview transcript is not available, describe interview topics including the most sensitive potential questions.
- *Research Repositories*: If the purpose of this submission is to establish a Research Repository (bank, registry) and the material you plan to collect is already available from a commercial supplier, clinical lab, or established IRB approved research repository, provide scientific justification for establishing an additional repository collecting duplicate material. Describe the repository design and operating procedures. For relevant information to include, see the UK Research Biospecimen Bank Guidance or the UK Research Registry Guidance.

This study is a double blinded, randomized, prospective, and multi-specialty collaborative clinical trial to assess the effect of early administration of Ketorolac as a preventative treatment for the post-traumatic complications associated with the hyperinflammatory response in trauma patients. The second objective is to determine whether patients randomized to ketorolac treatment require less opioid analgesics during their hospital and postoperative course than the standard of care (SOC). Please see protocol for full description of study design.

Attachments

Subject Recruitment Methods & Advertising

Describe how the study team will identify and recruit subjects. Please consider the following items and provide additional information as needed so that the IRB can follow each step of the recruitment process.

- How will the study team identify potential participants?
- Who will first contact the potential subjects, and how?
- Will you use advertisements? If so, how will you distribute those?
- How and where will the research team meet with potential participants?
- If applicable, describe proposed outreach programs for recruiting women, minorities, or disparate populations.
- How you will minimize undue influence in recruitment?
- Attach copies of all recruiting and advertising materials (emails, verbal scripts, flyers, posts, messages, etc.).

For additional information on recruiting and advertising:

- IRB Application Instructions - Advertisements
- PI Guide to Identification and Recruitment of Human Subjects for Research

Potential patients will be prospectively identified either at the time of the initial consultation, at the morning fracture conference, based on the orthopaedic injury diagnosis (Inclusion criteria noted above). Patients will be screened by their inclusion and exclusion criteria, and if met will be considered for enrollment in the study.
Not Applicable

Attachments

Research Procedures

Describe how the research will be conducted.

- What experience will study participants have?
- What will study participants be expected to do?
- How long will the study last?
- Outline the schedule and timing of study procedures.
- Provide visit-by-visit listing of all procedures that will take place.
- Identify all procedures that will be carried out with each group of participants.
- Describe deception and debrief procedures if deception is involved.

Differentiate between procedures that involve standard/routine clinical care and those that will be performed specifically for this research project. List medications that are explicitly forbidden or permitted during study participation.

Aim 1: The study population will consist of 200 patients (100 control, 100 treated with Ketorolac) that are admitted to the inpatient surgical service at our level I trauma centers for management of orthopedic trauma care. All trauma patients that are between the ages of 18-75 and with NISS > 9 (moderate injury) [33, 34] will be enrolled and treated according to the standard Advance Trauma Life Support (ATLS) protocol. 100 patients in the control group will receive placebo intravenous saline every 6 hours for their initial 5 days of hospitalization and no NSAID administration. 100 patients randomized to the treatment group will receive 15 mg of Ketorolac every 6 hours for their initial 5 days of hospitalization. A daily blood sample (10 cc) will be collected on Days 1–5 by blinded health care personnel. These blood samples will be analyzed via sandwich ELISA method for concentrations of IL-1, IL-6, IL-10, and PGE2. Serum concentrations will be compared between the treatment and control groups using two-tailed independent t-tests. In addition to the standard trauma labs, patient demographics, injury data (gender, age, BMI, mechanism of injury, NISS, and types of surgical/procedural interventions), injury outcomes (incidence of bacterial pneumonia, ARDS, SIRS, MODS), complications defined in the National Trauma Dataset, and inflammatory data will be compiled, tracked, and maintained in our clinical database (REDCap). Outcome variables (hospital and ICU length of stay and occurrence of pneumonia and/or ARDS and/or SIRS or death), and the predictor variables of interest (inflammatory markers and NISS) will be compared using Poisson regression. The odds of developing post traumatic complications in the different predictor groups will be determined using multiple logistic regressions. The covariates will be adjusted for in the regression models: age, sex, injury severity, severity of head and/or extremity injury, injury mechanism, and injury outcome.

Aim 2: The enrolled patients will be followed daily by our trained clinical research coordinator. Patient's subjective pain scores will be assessed and documented by the trained nursing staff using Visual Analogue Scale (VAS) daily. Morphine milligram equivalent (MME) along with other pain medication intake will be recorded per day for the duration of Ketorolac or placebo therapy. Patient's clinical course will be monitored closely and daily to ensure no NSAIDs will be administered to the control cohort to ensure consistency and protocol adherence of the study. Once patients are discharged from the hospital, outpatient pain scores will be assessed during routine clinic follow up visits using Patient-Reported Outcomes Measurement Information System (PROMIS) surveys. Opioid and pain modulating medication prescription refills will be monitored using the State All Scheduled Prescription Electronic Reporting system. Patient narcotic requirement will be assessed during all of the routine follow up visits by the same research coordinator in order to maintain consistency. Patients' inpatient and outpatient subjective pain score and MME intake will be compared between the control and treatment groups using two-tailed independent t-tests.

Aim 3:
Finally, analysis will be performed to evaluate the treatment effects between two groups using fracture unions as a dependent variable. The rate of fracture unions will be calculated at 3 month, 6 month and 12 month. Fractures will be considered united if they met the criteria for clinical or radiological union. The baseline clinical factors that are independently associated with fracture unions will be assessed from candidate variables and are entered using a forward ($p<0.05$) and backwards ($p<0.10$) stepwise selection procedure. Finally, the multivariate model will be performed to assess the association of clinical factors with fracture unions starting at 3 month between two groups.

Attachments

Data Collection & Research Materials

In this section, please provide the following:

- Describe all sources or methods for obtaining research materials about or from living individuals (such as specimens, records, surveys, interviews, participant observation, etc.), and explain why this information is needed to conduct the study.
- For each source or method described, please list or attach all data to be collected (such as genetic information, interview scripts, survey tools, data collection forms for existing data, etc.).
- If you will conduct a record or chart review, list the beginning and end dates of the records you will view.

Please see above (Research Procedures Section) for detailed outcome variables

Attachments

Resources

Describe the availability of the resources and adequacy of the facilities that you will use to perform the research. Such resources may include:

- Staffing and personnel, in terms of availability, number, expertise, and experience;
- Computer or other technological resources, mobile or otherwise, required or created during the conduct of the research;
- Psychological, social, or medical services, including equipment needed to protect subjects, medical monitoring, ancillary care, or counseling or social support services that may be required because of research participation;
- Resources for communication with subjects, such as language translation/interpretation services.

All chart reviews will occur at the in the Department of Orthopedics Surgery and Sports Medicine. Documented data will be stored in a password-protected excel spreadsheet stored on a University of Kentucky password-encrypted computer that will be locked in Cale Jacobs' office (Kentucky Clinic, Room K426) when not being used for data collection. There will be a password-protected electronic master list that connects the patient's medical records number and/or encounter number with the spreadsheet being used for data collection. This master list will be kept separate from the data collection spreadsheet file, and the master list will be stored on the department's password-protected network drive. Only study personnel identified in the IRB-approved study personnel list will have access to the master list and data collection spreadsheet files. At this time, we expect that the current study personnel will perform all the study statistical analyses. However, should additional statistical assistance be required, the statistician will be added to the study's personnel list prior to performing any study-related analyses.

Potential Risks & Benefits

Risks

- Describe any potential risks – including physical, psychological, social, legal, ability to re-identify subjects, or other risks. Assess the seriousness and likelihood of each risk.
- Which risks may affect a subject's willingness to participate in the study?
- Describe likely adverse effects of drugs, biologics, devices or procedures participants may encounter while in the study.
- *Qualitative research* - describe ethical issues that could arise while conducting research in the field and strategies you may use to handle those situations.
- Describe any steps to mitigate these risks.

Benefits

- Describe potential direct benefits to study participants – including diagnostic or therapeutic, physical, psychological or emotional, learning benefits. This cannot include incentives or payments.
- State if there are no direct benefits.
- Describe potential benefits to society and/or general knowledge to be gained.

Describe why potential benefits are reasonable in relation to potential risks. If applicable, justify why risks to vulnerable subjects are reasonable to potential benefits.

Long-term non-steroidal anti-inflammatory drug (NSAID) intake has been correlated with impaired or delayed fracture healing in animal and clinical studies with a dose dependent response. However, the evidence in animal studies is conflicting, and there are few retrospective clinical studies and even fewer large scale prospective randomized trials. A recent meta-analysis demonstrated that higher quality studies found no evidence of negative effect of NSAIDs on bone-healing [21]. To our knowledge, the present study will be the largest prospective randomized clinical trial to evaluate the effect of short term and low dose administration of NSAID on trauma patient outcomes, opioid consumption, and fracture union rates.
There is no guarantee that the patient will receive any personal benefit from taking part in this study; however, the collection of this information will in the future, help clinicians better understand patients with similar injuries.

Available Alternative Opportunities/Treatments

Describe alternative treatments or opportunities that might be available to those who choose not to participate in the study, and which offer the subject equal or greater advantages. If applicable, this should include a discussion of the current standard of care treatment(s).

There is no alternative treatment options. Should participants refused to participate in the present study, they will receive the standard medical treatments per standard University of Kentucky Health Care protocols.

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Records, Privacy, and Confidentiality

Specify where the data and/or specimens will be stored and how the researcher will ensure the privacy and confidentiality of both. Specify who will have access to the data/specimens and why they need access.

Describe how data will be managed after the study is complete:

- If data/specimens will be maintained, specify whether identifiers will be removed from the maintained information/material.
- If identifiers will not be removed, provide justification for retaining them and describe how you will protect confidentiality.

- If the data/specimens will be destroyed, verify that this will not violate retention policies and will adhere to applicable facility requirements.

If this study will use de-identified data from another source, describe what measures will be taken to ensure that subject identifiers are not given to the investigator.

If applicable, describe procedures for sharing data/specimens with collaborators not affiliated with UK.

For additional considerations:
Return of Research Results or Incidental Research Findings
HIPAA policies
FERPA policies
Procedures for Transfer agreements
Information regarding multi-site studies
NIH Genomic Data Sharing (GDS) Policy
Digital Data

The sources of research material for this study will include previous documentation of the patient's initial injury and recovery course, clinical documentation, and surgical documentation. Every attempt will be made to ensure patient confidentiality. All data will be stored on a secured computer and backed up on a secured network, which can only be accessed by a member of the research team. The computer and data will be stored inside a locked office when not being used for data collection.
The researchers involved with this study will keep private all research records that identify the subjects to the extent of the law. The information obtained from the research may be combined and presented in written materials, but these materials will not contain any identifying material specific to the patient. There will be a password-protected electronic master list that connects the patient's medical records number and/or encounter number with the spreadsheet being used for data collection. This master list will be kept separate from the data collection spreadsheet file, and the master list will be stored on the department's password-protected network drive. Only study personnel identified in the IRB-approved study personnel list will have access to the master list and data collection spreadsheet files. Immediately upon completion of data collection (estimated to be December, 2017), patient identifiers including name, date of birth, and medical record number will be deleted from the spreadsheet and patients will be instead identified using a study-specific ID number which is not the patient's social security number or medical records number. The password-protected file will be stored on the department's password-protected network drive. Data and records will be kept for at least six years post study closure.
A breach of confidentiality is a risk. Access to all patient information will be password protected and only available to listed research personnel. All information will be kept in the University of Kentucky Department of Orthopedics and Sports Medicine password-protected network drive and will only be available to listed research personnel. While every attempt will be made to prevent a breach of confidentiality, should a breach occur, immediate measures will be taken to prevent further breach and any damage resulting from it. The breach will be immediately reported to the IRB and, in a cooperative effort with the IRB and University, will contact the involved study subject(s) to inform them of the breach and actions taken to resolve it.

UK IRB policies state that IRB-related research records must be retained for a minimum of 6 years after study closure. Do you confirm that you will retain all IRB-related records for a minimum of 6 years after study closure?
◉ Yes ○ No

Payment

Describe the incentives (monetary or other) being offered to subjects for their participation. If monetary compensation is offered, indicate the amount and describe the terms and schedule of payment. Please review this guidance for more information on payments to subjects, including restrictions and expectations.

Not Applicable

Costs to Subjects

Include a list of services and/or tests that will not be paid for by the sponsor and/or the study (e.g., MRI, HIV). Keep in mind that a subject will not know what is "standard" – and thus not covered by the sponsor/study – unless you tell them.

Not Applicable. All of the costs of blood draws and Ketorolac administration will be covered by the principal investigator.

Data and Safety Monitoring

The IRB requires review and approval of data and safety monitoring plans for greater than minimal risk research or NIH-funded/FDA-regulated clinical investigations.

- If you are conducting greater than minimal risk research, or your clinical investigation is NIH-funded, describe your Data and Safety Monitoring Plan (DSMP). Click here for additional guidance on developing a Data and Safety Monitoring Plan.
- If this is a non-sponsored investigator-initiated protocol considered greater than minimal risk research, and if you are planning on using a Data and Safety Monitoring Board (DSMB) as part of your DSMP, click here for additional guidance for information to include with your IRB application.

The study will monitor and report adverse events to ensure patient safety. Definitions and procedures for reporting adverse events are designed to satisfy 45 CFR Part 46, Subpart A; the “Common Rule”, shared by 17 Departments and Agencies as well as 21 CFR 312, the FDA regulation for adverse events. The Common Rule requires written procedures and policies for ensuring reporting of “unanticipated problems” involving risks to participants to IRBs, appropriate institutional officials, and the Department or Agency Head.

Monitoring of the progress of clinical investigations and the safety of participants: The proposed medication for this investigation is a commonly utilized substance for pain control. Patients will be monitored for adverse effects of these medications continuously while they are an inpatient. Please refer to Study Drug information and Informed Consent Appendix B for further details. The research team will work closely with the medical management team daily to note if any of these difficulties should arise. Other minor side effects will be recorded and monitored through chart review (nausea, abdominal pain, minor bruising and bleeding) at the conclusion of the inpatient admission. If necessary, blinding will be broken if any potential side effects are noted and the information regarding treatment would be helpful to the treating team. The clinical medical monitor of the investigation will be obtained with the help of CCTS and that person will be added to the study personnel. The PI will be blinded to the subject treatment arm, and thus limit bias in reporting.

Compliance:
The research team will meet monthly to discuss and review any of the above recorded events and report adverse events to the IRB accordingly. A yearly report will be filed with the IRB with regards to overall data safety. Study suspension/termination: In the event that there is a noted increase in the serious side effects of taking the study drug, the study will be suspended for review.

Data Accuracy:
The research team will meet monthly to go over the collected data and perform spot reviews to determine the accuracy of the data collection from the medical record and study procedures.

Back to Top

Future Use and Sharing of Material (e.g., Data/Specimens/Information)

If the material collected for this study will be used by members of the research team or shared with other researchers for future studies, please address the following:

- list the biological specimens and/or information that will be kept
- briefly describe the types, categories and/or purposes of the future research
- describe any risks of the additional use
- describe privacy/confidentiality protections that will be put into place
- describe the period of time specimens/information may be used
- describe procedures for sharing specimens/information with secondary researchers
- describe the process for, and limitations to, withdrawal of specimens/data

Identifiable information such as the participant's name, medical record number, or date of birth may be removed from the information or samples collected in this study. After removal, the information or samples may be used for future research or shared with other researchers without the participant's additional informed consent.
In addition to the main study, the participant is being asked to allow us to keep and use their information and/or specimens for future research that involves surgical complications and patient outcome research in the trauma patient population. The specimens in this study consist of blood plasma that is being collected to measure inflammatory markers and cytokine levels during the first 5 inpatient days.

Are you recruiting or expect to enroll **Non-English Speaking Subjects or Subjects from a Foreign Culture**? (does not include short form use for incidentally encountered non-English subjects)

○ Yes ◉ No

Non-English Speaking Subjects or Subjects from a Foreign Culture

Recruitment and Consent:

Describe how information about the study will be communicated to potential subjects appropriate for their culture, and if necessary, how new information about the research may be relayed to subjects during the study.
When recruiting Non-English-speaking subjects, provide a consent document in the subject’s primary language. After saving this section, attach both the English and translated consent documents in the “Informed Consent" section.

Cultural and Language Consultants:

The PI is required to identify someone who is willing to serve as the cultural consultant to the IRB.

- This person should be familiar with the culture of the subject population and/or be able to verify that translated documents are the equivalent of the English version of documents submitted.
- The consultant should not be involved with the study or have any interest in its IRB approval.
- Please include the name, address, telephone number, and email of the person who agrees to be the cultural consultant for your study.

- ORI staff will facilitate the review process with your consultant. Please do not ask them to review your protocol separately.

For more details, see the IRB Application Instructions on Research Involving Non-English Speaking Subjects or Subjects from a Foreign Culture.

Local Requirements:

If you will conduct research at an international location, identify and describe:

- relevant local regulations
- data privacy regulations
- applicable laws
- ethics review requirements for human subject protection

Please provide links or sources where possible. If the project has been or will be reviewed by a local ethics review board, attach a copy in the “Additional Information/Materials” section. You may also consult the current edition of the International Compilation of Human Research Standards

Does your study involve **HIV/AIDS research and/or screening for other reportable diseases (e.g., Hepatitis C, etc…)**?
○ Yes ◉ No

HIV/AIDS Research

If you have questions about what constitutes a reportable disease and/or condition in the state of Kentucky, see ORI's summary sheet: "Reporting Requirements for Diseases and Conditions in Kentucky" [PDF].

HIV/AIDS Research: There are additional IRB requirements for designing and implementing the research and for obtaining informed consent. Describe additional safeguards to minimize risk to subjects in the space provided below.

For additional information, visit the online IRB Survival Handbook to download a copy of the "Medical IRB's requirements for Protection of Human Subjects in Research Involving HIV Testing" [D65.0000] [PDF], and visit the Office for Human Research Protections web site for statements on AIDS research, or contact the Office of Research Integrity at 859-257-9428.

PI-Sponsored FDA-Regulated Research

Is this an investigator-initiated study that:

1) involves testing a Nonsignificant Risk (NSR) Device, or
2) is being conducted under an investigator-held Investigational New Drug (IND) or Investigational Device Exemption (IDE)?
○ Yes ◉ No

PI-Sponsored FDA-Regulated Research

If the answer above is yes, then the investigator assumes the regulatory responsibilities of both the investigator and sponsor. The Office of Research Integrity provides a summary list of sponsor IND regulatory requirements for drug trials [PDF], IDE regulatory requirements for SR device trials [PDF], and abbreviated regulatory requirements for NSR device trials [PDF]. For detailed descriptions see FDA Responsibilities for Device Study Sponsors or FDA Responsibilities for IND Drug Study Sponsor-Investigators.

- Describe the experience/knowledge/training (if any) of the investigator serving as a sponsor (e.g., previously held an IND/IDE); and
- Indicate if any sponsor obligations have been transferred to a commercial sponsor, contract research organization (CRO), contract monitor, or other entity (provide details or attach FDA 1571).

IRB policy requires mandatory training for all investigators who are also FDA-regulated sponsors (see Sponsor-Investigator FAQs). A sponsor-investigator must complete the applicable Office of Research Integrity web based training, (drug or device) before final IRB approval is granted.

Has the sponsor-investigator completed the mandatory PI-sponsor training prior to this submission?
○ Yes ○ No

If the sponsor-investigator has completed equivalent sponsor-investigator training, submit documentation of the content for the IRB's consideration.

Attachments

HIPAA

0 unresolved comment(s)

Is HIPAA applicable? ◉ Yes ○ No

(Visit ORI's Health Insurance Portability and Accountability Act (HIPAA) web page to determine if your research falls under the HIPAA Privacy Regulation.)

If yes, check below all that apply and attach the applicable document(s):

☐ HIPAA De-identification Certification Form

☑ HIPAA Waiver of Authorization

Attachments

Attach Type	File Name
Waiver	HIPAA-8-2.pdf

STUDY DRUG INFORMATION

0 unresolved comment(s)

The term drug may include:

- FDA approved drugs,
- unapproved use of approved drugs,
- investigational drugs or biologics,
- other compounds or products intended to affect structure or function of the body, and/or
- complementary and alternative medicine products such as dietary supplements, substances generally recognized as safe (GRAS) when used to diagnose, cure mitigate, treat or prevent disease, or clinical studies of e-cigarettes examining a potential therapeutic purpose.

Does this protocol involve a drug including an FDA approved drug; unapproved use of an FDA approved drug; and/or an investigational drug?

◉ Yes ○ No

If yes, complete the questions below. Additional study drug guidance.

LIST EACH DRUG INVOLVED IN STUDY IN THE SPACE BELOW

Drug Name:

Ketorolac (Toradol)

Note: Inpatient studies are required by Hospital Policy to utilize Investigational Drug Service (IDS) pharmacies (Oncology or Non-Oncology). Use of IDS is highly recommended, but optional for outpatient studies. Outpatient studies not using IDS services are subject to periodic inspection by the IDS for compliance with drug accountability good clinical practices.

Indicate where study drug(s) will be housed and managed:

☑ Investigational Drug Service (IDS) UK Hospital

Other Location:

Is the study being conducted under a valid Investigational New Drug (IND) application?

○ Yes ◉ No

If Yes, list IND #(s) and complete the following:

IND Submitted/Held by:

Sponsor: ☐ Held By:

Investigator: ☐ Held By:

Other: ☐ Held By:

☐ Checkmark if the study is being conducted under FDA's Expanded Access Program (e.g., Treatment IND) or if this is an Individual Patient Expanded Access IND (FDA Form 3926).

FDA's Expanded Access Program Information for Individual Patient Expanded Access INDs, and attach the following:

- FDA Form 3926;
- FDA expanded access approval or correspondence;
- Confirmation of agreement from manufacturer or entity authorized to provide access to the product.

For guidance and reporting requirements at the conclusion of treatment see the Expanded Access SOP.

Complete and attach the required Study Drug Form picking "Study Drug Form" for the document type. Any applicable drug documentation (e.g., Investigator Brochure; approved labeling; publication; FDA correspondence, etc.) should be attached using "Other Drug Documentation" for the document type.

Attachments

Attach Type	File Name
Study Drug Form	Toradol.pdf
Study Drug Form	Form O - Inflammatory Markers.pdf
Study Drug Form	Ketorolac.pdf

STUDY DEVICE INFORMATION

0 unresolved comment(s)

A DEVICE may be a:

- component, part, accessory;
- assay, reagent, or in-vitro diagnostic device;
- software, digital health, or mobile medical app;
- other instrument if intended to affect the structure or function of the body, diagnose, cure, mitigate, treat or prevent disease; or
- a homemade device developed by an investigator or other non-commercial entity and not approved for marketing by FDA.

For additional information, helpful resources, and definitions, see ORI's Use of Any Device Being Tested in Research web page.

Does this protocol involve testing (collecting safety or efficacy data) of a medical device including an FDA approved device, unapproved use of an approved device, humanitarian use device, and/or an investigational device?

○ Yes ◉ No

[Note: If a marketed device(s) is only being used to elicit or measure a physiologic response or clinical outcome, AND, NO data will be collected on or about the device itself, you may answer “no” above, save and exit this section, (Examples: a chemo drug study uses an MRI to measure tumor growth but does NOT assess how effective the MRI is at making the measurement; an exercise study uses a heart monitor to measure athletic performance but no safety or efficacy information will be collected about the device itself, nor will the data collected be used for comparative purposes against any other similar device).]

If you answered yes above, please complete the following questions.

LIST EACH DEVICE BEING TESTED IN STUDY IN THE SPACE BELOW

Device Name:

Is the study being conducted under a valid Investigational Device Exemption (IDE), Humanitarian Device Exemption (HDE) or Compassionate Use?

○ Yes ○ No

If Yes, complete the following:
IDE or HDE #(s)

IDE/HDE Submitted/Held by:

Sponsor: ☐ Held By:

Investigator: ☐ Held By:

Other: ☐ Held By:

☐ Check if this is a Treatment IDE or Compassionate Use under the Food and Drug Administration (FDA) Expanded Access program.

For Individual or Small Group Expanded Access, see FDA's Early Expanded Access Program Information, and attach the following:

- FDA expanded access approval or sponsor’s authorization;
- An independent assessment from an uninvolved physician, if available;
- Confirmation of agreement from manufacturer or entity authorized to provide access to the product.

For guidance and reporting requirements at the conclusion of treatment see the Medical Device SOP.

Does the intended use of any research device being tested (not clinically observed) in this study meet the regulatory definition of Significant Risk (SR) device?

- Yes. Device(s) being tested in this study presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
- No. All devices being tested in this study do not present a potential for serious risk to the health, safety, or welfare of subjects/participants.

Complete and attach the required Study Device Form, picking the "Study Device Form" for the document type. Any applicable device documentation (e.g., Manufacturer information; patient information packet; approved labeling; FDA correspondence, etc.) should be attached using "Other Device Documentation" for the document type.

Attachments

RESEARCH SITES

0 unresolved comment(s)

To complete this section, ensure the responses are accurate then click "SAVE".

A) Check all the applicable sites listed below at which the research will be conducted. If none apply, you do not need to check any boxes.

UK Sites

- ☐ UK Classroom(s)/Lab(s)
- ☐ UK Clinics in Lexington
- ☐ UK Clinics outside of Lexington
- ☐ UK Healthcare Good Samaritan Hospital
- ☑ UK Hospital

Schools/Education Institutions

- ☐ Fayette Co. School Systems *
- ☐ Other State/Regional School Systems
- ☐ Institutions of Higher Education (other than UK)

***Fayette Co. School systems, as well as other non-UK sites, have additional requirements that must be addressed. See ORI's IRB Application Instructions - Off-site Research web page for details.**

Other Medical Facilities

- ☐ Bluegrass Regional Mental Health Retardation Board
- ☐ Cardinal Hill Hospital
- ☐ Eastern State Hospital
- ☐ Norton Healthcare
- ☐ Nursing Homes
- ☐ Shriner's Children's Hospital
- ☐ Veterans Affairs Medical Center
- ☐ Other Hospitals and Med. Centers

- ☐ Correctional Facilities
- ☐ Home Health Agencies
- ☐ International Sites

Research activities conducted at performance sites that are not owned or operated by the University of Kentucky, at sites that are geographically separate from UK, or at sites that do not fall under the UK IRB's authority, are subject to special procedures for coordination of research review. Additional information is required (see IRB Application Instructions - Off-Site Research web page), including:

- A letter of support and local context is required from non-UK sites. See *Letters of Support and Local Context* on the IRB Application Instructions - Off-Site Research web page for more information.
- Supportive documentation, including letters of support, can be attached below.
- NOTE: If the non-UK sites or non-UK personnel are engaged in the research, there are additional federal and university requirements which need to be completed for their participation. For instance, the other site(s) may need to complete their own IRB review, or a cooperative review arrangement may need to be established with non-UK

sites.
- Questions about the participation of non-UK sites/personnel should be discussed with the ORI staff at (859) 257-9428.

List all other non-UK owned/operated locations where the research will be conducted:

Describe the role of any non-UK site(s) or non-UK personnel who will be participating in your research.

Attachments

B) Is this a multi-site study for which **you are the lead investigator or UK is the lead site**? ○ Yes ◉ No

If YES, describe the plan for the management of reporting unanticipated problems, noncompliance, and submission of protocol modifications and interim results from the non-UK sites:

C) If your research involves collaboration with any sites and/or personnel outside the University of Kentucky, then it is considered multisite research and IRB reliance issues will need to be addressed. This may include national multi-center trials as well local studies involving sites/personnel external to UK. If you would like to request that the University of Kentucky IRB (UK IRB) serve as the lead IRB for your study, or if you would like the UK IRB to defer review to another IRB, please contact the IRBReliance@uky.edu.

RESEARCH ATTRIBUTES

0 unresolved comment(s)

Indicate the items below that apply to your research. Depending on the items applicable to your research, you may be required to complete additional forms or meet additional requirements. Contact the ORI (859-257-9428) if you have questions about additional requirements.

☐ Not applicable

Check All That Apply

	For additional requirements and information:
☐ Academic Degree/Required Research	• Cancer Research (MCC PRMC) • Certificate of Confidentiality (look up "Confidentiality/Privacy...") • CCTS (Center for Clinical and Translational Science)
☐ Alcohol/Drug/Substance Abuse Research	• Clinical Research (look up "What is the definition of....)
☐ Biological Specimen Bank Creation (for sharing)	• Clinical Trial
☐ Cancer Research	• Collection of Biological Specimens for Banking (look up "Specimen/Tissue Collection...")
☐ CCTS-Center for Clinical & Translational Science	• Collection of Biological Specimens (look up "Specimen/Tissue Collection...")
☐ Certificate of Confidentiality	• Community-Based Participatory Research (look up "Community-Engaged...")
☑ Clinical Research	• Data & Safety Monitoring Board (DSMB) *For Medical IRB: Service Request Form for CCTS DSMB
☐ Clinical Trial - Phase 1	• Data & Safety Monitoring Plan
☐ Clinical Trial	• Deception* *For deception research, also go to the E-IRB Application Informed Consent section, checkmark and complete "Request for Waiver of Informed Consent Process"
☐ Collection of Biological Specimens for internal banking and use (not sharing)	• Emergency Use (Single Patient) [attach Emergency Use Checklist] (PDF)
☐ Community-Based Participatory Research	• Genetic Research (look up "Specimen/Tissue Collection...")
☐ Deception	• Gene Transfer
☐ Educational/Student Records (e.g., GPA, test scores)	• HIV/AIDS Research (look up "Reportable Diseases/Conditions")
☐ Emergency Use (Single Patient)	• Screening for Reportable Diseases [E2.0000] (PDF)
☐ Gene Transfer	• International Research (look up "International & Non-English Speaking")
☐ Genetic Research	• NIH Genomic Data Sharing (GDS) Policy (PDF)
☐ GWAS (Genome-Wide Association Study) or NIH Genomic Data Sharing (GDS)	• Planned Emergency Research Involving Waiver of Informed Consent* *For Planned Emergency Research Involving Waiver of Informed Consent, also go to the E-IRB Application Informed Consent section, checkmark and complete "Request for Waiver of Informed Consent Process"
☐ Human Cells, Tissues, and Cellular and Tissue Based Products	• Use, storage and disposal of radioactive material and radiation producing devices
☐ Individual Expanded Access or Compassionate Use	
☐ International Research	
☐ Planned Emergency Research Involving Exception from Informed Consent	
☐ Recombinant DNA	
☐ Registry or data repository creation	
☐ Stem Cell Research	
☐ Suicide Ideation or Behavior Research	
☐ Survey Research	
☐ Transplants	
☐ Use, storage and disposal of radioactive material and radiation producing devices	
☐ Vaccine Trials	

FUNDING/SUPPORT

0 unresolved comment(s)

If the research is being submitted to, supported by, or conducted in cooperation with an external or internal agency or funding program, indicate below all the categories that apply.

☐ Not applicable

Check All That Apply

- ☐ Grant application pending
- ☐ (HHS) Dept. of Health & Human Services
  - ☐ (NIH) National Institutes of Health
  - ☐ (CDC) Centers for Disease Control & Prevention
  - ☐ (HRSA) Health Resources and Services Administration
  - ☐ (SAMHSA) Substance Abuse and Mental Health Services Administration
- ☐ (DoJ) Department of Justice or Bureau of Prisons
- ☐ (DoE) Department of Energy
- ☐ (EPA) Environmental Protection Agency
- ☐ Federal Agencies Other Than Those Listed Here
- ☐ Industry (Other than Pharmaceutical Companies)
- ☑ Internal Grant Program w/ proposal
- ☐ Internal Grant Program w/o proposal
- ☐ National Science Foundation
- ☐ Other Institutions of Higher Education
- ☐ Pharmaceutical Company
- ☑ Private Foundation/Association
- ☐ U.S. Department of Education
- ☐ State

Other:

Click applicable listing(s) for additional requirements and information:

- (HHS) Dept. of Health & Human Services
- (NIH) National Institutes of Health
- (CDC) Centers for Disease Control & Prevention
- (HRSA) Health Resources & Services Administration
- (SAMHSA) Substance Abuse & Mental Health Services Administration
- Industry (Other than Pharmaceutical Companies) [IRB Fee Info]
- National Science Foundation
- (DoEd) U.S. Department of Education
- (DoJ) Department of Justice or Bureau of Prisons
- (DoE) Department of Energy Summary and Department of Energy Identifiable Information Compliance Checklist
- (EPA) Environmental Protection Agency

Specify the funding source and/or cooperating organization(s) (e.g., National Cancer Institute, Ford Foundation, Eli Lilly & Company, South Western Oncology Group, Bureau of Prisons, etc.):

- University of Kentucky Center for Clinical and Translational Science grant

- Orthopaedic Trauma Association grant

Add Related Grants

If applicable, please search for and select the OSPA Account number or Electronic Internal Approval Form (eIAF) # (notif #) associated with this IRB application using the "Add Related Grants" button.
If required by your funding agency, upload your grant using the "Grant/Contract Attachments" button.

Add Related Grants

Grant/Contract Attachments

The research involves use of Department of Defense (DoD) funding, military personnel, DoD facilities, or other DoD resources. (See DoD SOP and DoD Summary for details)

○ Yes ◉ No

Using the “attachments” button (below), attach applicable materials addressing the specific processes described in the DoD SOP.

DOD SOP Attachments

Additional Certification: (If your project is federally funded, your funding agency may request an Assurance/ Certification/Declaration of Exemption form.) Check the following if needed:

☐ Protection of Human Subjects Assurance/Certification/Declaration of Exemption (Formerly Optional Form – 310)

Assurance/Certification Attachments

OTHER REVIEW COMMITTEES

0 unresolved comment(s)

If you check any of the below committees, additional materials may be required with your application submission.

Does your research fall under the purview of any of the other review committees listed below? [*If yes, check all that apply and attach applicable materials using the attachment button at the bottom of your screen.*]

○ Yes ◉ No

Additional Information

- ☐ Institutional Biosafety Committee
- ☐ Radiation Safety Committee
- ☐ Radioactive Drug Research Committee
- ☐ Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC)
- ☐ Graduate Medical Education Committee (GME)
- ☐ Office of Medical Education (OME)

- Institutional Biosafety Committee (IBC) - Attach required IBC materials
- Radiation Safety Committee (RSC) - For applicability, see instructions and attach form
- Radioactive Drug Research Committee (RDRC)
- Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC)** - Attach MCC PRMC materials, if any, per instructions.
- Office of Medical Education (OME)
- Graduate Medical Education Committee (GME)

Attachments

**** If your study involves cancer research, be sure to select "Cancer Research" in the "Research Attributes" section.** ORI will send your research protocol to the Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC). The MCC PRMC is responsible for determining whether the study meets the National Cancer Institute (NCI) definition of a clinical trial and for issuing documentation to you (the investigator) which confirms either that PRMC approval has been obtained or that PRMC review is not required. Your IRB application will be processed and reviewed independently from the PRMC review.

ADDITIONAL INFORMATION/MATERIALS

0 unresolved comment(s)

Do you want specific information inserted into your approval letter? ○ Yes ◉ No

Approval Letter Details:

If you wish to have specific language included in your approval letter (e.g., serial #, internal tracking identifier, etc…), type that language in the box below exactly as it should appear in the letter. The text you enter will automatically appear at the top of all approval letters, identical to how you typed it, until you update it. Don't include instructions or questions to ORI staff as those will appear in your approval letter. **If these details need to be changed for any reason, you are responsible for updating the content of this field.**

Additional Materials:

If you have other materials you would like to include for the IRB's consideration, check all that apply and attach the corresponding documents using the Attachments button below.

☐ Detailed protocol
☐ Dept. of Health & Human Services (DHHS) approved protocol (such as NIH sponsored Cooperative Group Clinical Trial)
☑ Other Documents

Protocol/Other Attachments

Attach Type	File Name
Other	Signed Inflammatory Marker Protocol Violation Letter.pdf
Other	Subject Enrollment Memo for IRB.docx
Protocol	CCTS Full Research Proposal.pdf
Protocol	OTA Full Grant Application.pdf
Protocol	IM Study- Protocol Changed- Clean.docx
Protocol	IM AE Risk Mitigation Plan Formal 4.17.20.docx

NOTE: [Instructions for Dept. of Health & Human Services (DHHS)-approved protocol]

If you have password protected documents, that feature should be disabled prior to uploading to ensure access for IRB review.

To view the materials currently attached to your application, click “All Attachments” on the left menu bar.

SIGNATURES (ASSURANCES)

0 unresolved comment(s)

Introduction

All IRB applications require additional assurances by a Department Chairperson or equivalent (DA), and when applicable, a Faculty Advisor or equivalent (FA). This signifies the acceptance of certain responsibilities and that the science is meritorious and deserving of conduct in humans. The person assigned as DA *should not* also be listed in the Study Personnel section, and the individual assigned as FA *should* be listed in the Study Personnel section.

For a list of responsibilities reflected by signing the Assurance Statement, refer to "What does the Department Chairperson's Assurance Statement on the IRB application mean?"

For a detailed illustration of how to complete this section, please review the short online video tutorial "Signatures (Assurance) Section - How to Complete." Otherwise, follow the steps below.

Required Signatures:

First Name	Last Name	Role	Department	Date Signed	
Darren	Johnson	Department Authorization	Orthopaedic Surgery	02/09/2018 10:24 AM	View/Sign
Arun	Aneja	Principal Investigator	Orthopaedic Surgery	02/03/2018 11:57 AM	View/Sign

Department Authorization

☑ This is to certify that I have reviewed this research protocol and that I attest to the scientific validity and importance of this study; to the qualifications of the investigator(s) to conduct the project and their time available for the project; that facilities, equipment, and personnel are adequate to conduct the research; and that continued guidance will be provided as appropriate. When the principal investigator assumes a sponsor function, the investigator has been notified of the additional regulatory requirements of the sponsor and by signing the principal investigator Assurance Statement, confirms he/she can comply with them.

*If the Principal Investigator is also the Chairperson of the department, the Vice Chairperson or equivalent should complete the "Department Authorization".

**IF APPLICABLE FOR RELIANCE: I attest that the principal investigator has been notified of the regulatory requirements of both the Reviewing and Relying IRBs, according to the information provided in the E-IRB application. The attached Reliance Assurance Statement, signed by the principal investigator, confirms that he/she can comply with both sets of IRB requirements.

Principal Investigator's Assurance Statement

I understand the University of Kentucky's policies concerning research involving human subjects and I agree:

1. To comply with all IRB policies, decisions, conditions, and requirements;
2. To accept responsibility for the scientific and ethical conduct of this research study;
3. To obtain prior approval from the Institutional Review Board before amending or altering the research protocol or implementing changes in the approved consent/assent form;
4. To report to the IRB in accord with IRB/IBC policy, any adverse event(s) and/or unanticipated problem(s) involving risks to subjects;
5. To complete, on request by the IRB for Full and Expedited studies, the Continuation/Final Review Forms;
6. To notify the Office of Sponsored Projects Administration (OSPA) and/or the IRB (when applicable) of the development of any financial interest not already disclosed;
7. Each individual listed as study personnel in this application has received the mandatory human research protections education (e.g., CITI);
8. Each individual listed as study personnel in this application possesses the necessary experience for conducting research

activities in the role described for this research study.
9. To recognize and accept additional regulatory responsibilities if serving as both a sponsor and investigator for FDA regulated research.

☑ Furthermore, by checking this box, I also attest that:

- I have appropriate facilities and resources for conducting the study;
- I am aware of and take full responsibility for the accuracy of all materials submitted to the IRB for review;
- If applying for an exemption, I also certify that the only involvement of human subjects in this research study will be in the categories specified in the Protocol Type: Exemption Categories section.
- If applying for an Abbreviated Application (AA) to rely on an external IRB, I understand that certain items above (1, 3, 4, 7-8) may not apply, or may be altered due to external institutional/IRB policies. I document my agreement with the Principal Investigator Reliance Assurance Statement by digitally signing this application.

*You will be able to "sign" your assurance after you have sent your application for signatures (use Submission section). Please notify the personnel required for signing your IRB application after sending for signatures. Once all signatures have been recorded, you will need to return to this section to submit your application to ORI.

SUBMISSION INFORMATION

0 unresolved comment(s)

***** If this Continuation Review entails a change in the scope of your activities to include COVID-19 related research, please insert "COVID19" at the start of your Project and Short Titles.*****

Each Section/Subsection in the menu on the left must have a checkmark beside it (except this Submission section) indicating the Section/Subsection has been completed. Otherwise your submission for IRB review and approval cannot be sent to the Office of Research Integrity/IRB.

If applicable, remember to update the Approval Letter Details text box under the Additional Information section

If your materials require review at a convened IRB meeting which you will be asked to attend, it will be scheduled on the next available agenda and you will receive a message to notify you of the date.

If you are making a change to an attachment, you need to delete the attachment, upload a highlighted version that contains the changes (use Document Type of "Highlighted Changes"), and a version that contains the changes without any highlights (use the appropriate Document Type for the item(s)). Do **not** delete approved attachments that are still in use.

Principal Investigator's Assurance Statement

I understand the University of Kentucky's policies concerning research involving human subjects, and I attest to:

1. Having reviewed all the investigational data from this study, including a compilation of all internal and external unanticipated problems.
2. Having reviewed, if applicable, information from the sponsor including updated investigator brochures and data and safety monitoring board reports.

I also attest that I have reviewed pertinent materials concerning the research and concluded either:

A. The human subject risk/benefit relationship is NOT altered, and that it is not necessary to modify the protocol or the informed consent process,
OR,
B. The human subject risk/benefit relationship has been altered, and have previously submitted or am including with this continuation review submission, a modification of the research protocol and informed consent process.

☑ By checking this box, I am providing assurances for the applicable items listed above.

Your protocol has been submitted.

Download all

	Document Type	File Loaded	Document Description	File Size	Modified By	Mod Date
	ApprovalLetter	ApprovalLetter.pdf		0.079	jlkear0	8/22/2023 8:16:23 AM
	CR_InterimFindings	OTA IM Abstract VAS and MME 2.10.23.docx		0.081	jtgr238	7/31/2023 6:17:19 PM
	CR_EntireConsent	20230731180652481.pdf		0.758	jtgr238	7/31/2023 6:09:08 PM
	CR_EntireConsent	20230731180556007-combined.pdf		0.901	jtgr238	7/31/2023 6:08:53 PM
	AddInfoProduct	Subject Enrollment Memo for IRB.docx	Subject Enrollment Memo	0.050	jafo241	9/9/2022 2:46:26 PM
	AddInfoProtocol	IM AE Risk Mitigation Plan Formal 4.17.20.docx	Risk Mitigation Plan	0.068	ejab226	6/11/2020 11:19:12 AM
	AddInfoProduct	Signed Inflammatory Marker Protocol Violation Letter.pdf	Preventative Action Plan	0.578	ejab226	7/15/2019 7:21:29 PM
	AddInfoProtocol	IM Study- Protocol Changed- Clean.docx	Protocol	0.041	ejab226	7/3/2019 4:23:22 PM
	Waiver	HIPAA-8-2.pdf	HIPAA-Waiver	0.152	smco282	8/2/2018 9:18:21 AM
	AddInfoProtocol	OTA Full Grant Application.pdf	OTA Grant Submission	1.049	smco282	7/24/2018 2:21:34 PM
	AddInfoProtocol	CCTS Full Research Proposal.pdf	CCTS Collaborative Grant-UK/Wake	1.233	smco282	7/24/2018 2:21:06 PM
	StudyDrug	Ketorolac.pdf		0.466	bli255	2/26/2018 12:38:14 PM
	StudyDrug	Form O - Inflammatory Markers.pdf		0.322	bli255	2/26/2018 12:38:03 PM
	StudyDrug	Toradol.pdf	Toradol Prescribing Information	0.115	bli255	1/31/2018 1:25:48 PM

Protocol Changes

Protocol Number: 43611

Click link to sort Changed Date

Project Information IsSubEnrollDataSpecimen changed by jtgr238 on 8/7/2023 9:48:41 AM

~~Y~~N

Project Information ProjectEndDate changed by jtgr238 on 8/7/2023 9:48:41 AM

~~8~~10/31/2023 12:00:00 AM

Risk Level RiskCategory changed by jtgr238 on 8/7/2023 9:48:56 AM

~~2~~1

Study Personnel Changes:

No Changes

There are no recorded changes to study personnel.

Protocol Type Comment by Samuel Bell - ORI to PI on 8/7/2023 9:25:12 AM
A few screening comments. Please see the following sections of the protocol for specifics:

- Project Information
- Risk Level
- Study Personnel

Additionally, as the study is closed to new enrollment, please remove the approved version of the informed consent as it will no longer be needed and thus does not need a new IRB approval stamp.

Project Information Comment by Samuel Bell - ORI to PI on 8/7/2023 9:18:59 AM
Please also update the anticipated end date of the research project.

Project Information Comment by Samuel Bell - ORI to PI on 8/7/2023 9:18:43 AM
As study is closed to new enrollment, please check "no" for "...will study be open to enrollment of new subjects..."

Risk Level Comment by Samuel Bell - ORI to PI on 8/7/2023 9:19:27 AM
As the study is closed to enrollment, please reduce the risk level to risk level 1: not greater than minimal risk.

Study Personnel Comment by Samuel Bell - ORI to PI on 8/7/2023 9:21:04 AM
Daniel Primm's human subject protection training is set to expire in early September, 2023. While this may not affect the CR approval, they should plan to complete HSP refresher training as soon as possible to remain on the study. More information on HSP refresher training can be found at the following link: https://www.research.uky.edu/office-research-integrity/three-year-refresher-hsp-training-faqs

07-3-2019

1. Title

Inflammatory Response to Trauma – Does Early Cytokine Modulation Improve Patient Outcome?

2. Study Design

Primary Purpose: Treatment
Allocation: Randomized
Interventional Mode: Parallel Assignment
Interventional Model Description: Compare the effectiveness of a NSAID to placebo in acute trauma setting.
Masking: Triple (Participant, Care Provider, Investigator)
Masking Description: Participant medical team will be blinded to the treatment or placebo intervention.

3. Outcome Measures

Primary Outcome: Length of Hospital Stay

Secondary Outcomes:

- Daily Concentrations of IL-1, IL-6, IL-10, and PGE2
- Incidence of Post-Traumatic Complications (e.g., bacterial pneumonia, SIRS, MODS, ARDS, and AKI)
- Mortality
- Visual Analogue Pain Scores
- Inpatient Morphine Milligram Equivalents
- Change in Inpatient Subjective Pain Reports
- Change in Outpatient Subjective Pain Reports

4. Background

Accidental trauma is the 4th leading cause of death in the United States, and it is associated with a complex inflammatory response. This response is associated with post-traumatic complications such as multi-organ dysfunction syndrome (MODS), bacterial pneumonia, acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS), and post traumatic pain (PTP). It is unknown whether early modulation of inflammatory cytokines is associated with improved patient outcomes, reduced narcotic requirements, and improved patient subjective pain after hospital discharge.

Our preliminary data has shown: (1) elevated blood cytokine concentrations during the acute phase of trauma are correlated with the development of fatal post-traumatic complications, (2) that early administration of a non-steroidal anti-inflammatory drug (NSAID) resulted in decreased blood serum levels of IL-6, Prostaglandin E2 (PGE2), improved pulmonary edema, and enhanced arterioles ability to vasoconstrict in response to hemorrhage in animal models, and (3) that the addition of the internal physiologic parameters (inflammatory cytokines) to New Injury Severity Score (NISS – a marker of the external anatomical insult) significantly improves the ability to predict hospital length of stay of trauma patients when compared to NISS alone. Our group is the first to use an integrative approach that combines the external anatomic injury data with the internal physiologic response for accurate prediction of patient's clinical outcome. Therefore, if we apply this same mindset to treatment, we can improve the trauma patients' care by addressing both parameters as opposed to solely focusing on the external injury as done in the past. Our ability to modify post-traumatic physiologic response via short-term administration of a NSAID may lead to improved patient outcome.

Over the last decade, clinicians remain puzzled over the safety of NSAID administration after fracture in terms of bone union. In addition, given the current landscape for opioid epidemic in the United States, alternative non-opioid pain management during acute trauma has the potential to reduce opioid consumption and represents a pivotal component of multimodal analgesia strategy.

5. Inclusion and Exclusion Criteria

Inclusion Criteria

- Patient aged 18-75

a. Patient or legally authorized representative (LAR) able to provide consent.
b. Patient with New Injury Severity Score (NISS) > 9 at time of admission determined by trauma staff.
c. Anticipated admission ≥5 days

Exclusion Criteria

d. Patient age < 18 or > 75
e. Patients with injury more than 24 hours prior to evaluation
f. Hemorrhagic shock or risk of significant hemorrhage.
g. Patients with preexisting inflammatory medical condition such as inflammatory arthropathy or inflammatory bowel disease
h. Patients with acquired immunodeficiency syndrome (AIDS)
i. Patients who are pregnant
j. Patients with active GI bleed or ulceration
k. Patients with chronic use of steroids or immune modulating drugs or history of organ transplantation
l. Patients with preexisting chronic renal, liver, or lung disease
m. Patients with history of myocardial infarctions
n. Patients with chronic heart failure
o. Patients with allergy to NSAID
p. Patients with coagulation defects (e.g., clotting factor deficiencies, thrombophilia, or any bleeding disorder)
q. Patients receiving chronic opioid therapy or treatment for opioid use disorder.

6. Sample Size Calculation

Pretrial sample size calculations were performed regarding LOS because this will be the primary outcome measure of the clinical trial. Using a significance level of 0.05 and an assumed SD of 1.5 days, a sample size of 42 patients per group (84 total) would yield 80% power to detect a difference of 0.928 days in average LOS between the placebo and ketorolac groups. Allowing for a dropout rate up to 25%, the target enrollment will be 112 patients total, with 56 patients per group. Power calculations were performed using nQuery 8.5 (Statistical Solutions Ltd; Cork, Ireland).

7. Statistical Analysis Plan

Group-level summary statistics will be calculated for demographic and clinical variables, and differences between the 2 groups will be evaluated using two-sample t-tests for quantitative measures and Fisher exact tests for categorical measures, as appropriate. LOS and MME values will be summarized using medians and interquartile ranges for each group. Group-level VAS pain scores will be summarized using means and standard deviations. An analysis of variance model will be fit to compare log-transformed LOS between the 2 groups. Linear mixed models will be used to estimate differences in VAS pain scores and log-transformed MME values over time between the 2 groups. Time and group comparisons for each cytokine will be made using linear mixed models, with and without adjusting for selected covariates. Patient demographic variables and will be considered for inclusion as covariates in each model but will only be retained if they significantly improve the model. Linear mixed models may be log-transformed, double-log-transformed, or square-root-transformed to correct for right skewness, as appropriate. Likelihood ratio testing and Akaike information criterion will be used to select appropriate covariance structures in each case. A Kenward–Roger adjustment will be used to correct for negative bias in the standard errors and degrees of freedom calculations. Throughout the study, a P value of less than 0.05 will be considered significant. All analyses will be completed in SAS 9.4 (SAS Institute Inc.; Cary, NC).

8. Study-Wide Recruitment Methods

Potential patients will be prospectively identified either at the time of the initial consultation, at the morning fracture conference, based on the orthopaedic injury diagnosis (inclusion criteria noted above). Patients will be screened by their inclusion and exclusion criteria and will be considered for enrollment in the study should they meet study criteria.

9. Study Timeline

After arrival, patient screening and enrollment is expected within 12 hours of arrival to ensure initial blood draw. Further participation of subjects will include blood draws and ketorolac administration through day 5. Patient participation will continue through to their follow-up visits and conclude with their 6 weeks post discharge clinic visit. Detailed project timeline and schedule of activities is listed in Table 1.

Tentative time table of the proposed project

	Inpatient							Outpatient				
Procedures	Enrollment	Day 1	Day 2	Day 3	Day 4	Day 5	Discharge	2 Week	6 Week	3 Month	6 Month	12 Month
Inclusion/Exclusion Review	X											
Informed Consent	X											
Blood Sample		X	X	X	X	X						
Ketorolac Intervention		X	X	X	X	X						
MME		X	X	X	X	X	X					
VAS		X	X	X	X	X	X	X	X	X	X	X
Post-Traumatic Complications		X	X	X	X	X	X	X	X	X	X	X

10. Procedures Involved

a. **Patient identification**: Patients will be identified on morning intake rounds by the trauma team and the research staff who are present daily to screen and enroll patients.

b. **Screening/Enrollment**: Study population will consist of 112 patients (56 control, 56 treatment) admitted to the inpatient surgical service at University of Kentucky (UK) level I trauma center for management of trauma care. Trauma patients that are between the ages of 18-75 and with NISS > 9 (moderate injury) with anticipated admission of ≥5 days (to ensure completion of the treatment) will be enrolled (Grisoni et al., 2001; Stevenson, Segui-Gomez, Lescohier, Di Scala, & McDonald-Smith, 2001). All patients will be initially treated according to the standard Advance Trauma Life Support (ATLS) protocol and standard ICU protocols (if applicable). Experienced clinical research staff will prospectively identify patients who meet the inclusion criteria and none of the exclusion criteria detailed in table 2.

c. **Randomization:** Consented patients will be randomized using a computer-generated algorithm to the control group (1-2 mL of intravenous saline every 6 hours for 5 days after admission) or treatment group (15 mg of intravenous ketorolac every 6 hours for 5 days after admission).

d. **Treatment:** Ketorolac (15 mg) has been chosen as the treatment of choice for several reasons:

(1) Ketorolac has a similar pharmacodynamics profile as indomethacin, which was used

in our previous animal model (Xiang et al., 2012).
(2) It is readily available intravenously obviating limitations of oral intake.
(3) In numerous prospective clinical studies, ketorolac infusion produced no change in cardiac or hemodynamic parameters in patients undergoing major vascular surgery (Camu, Van Overberge, Bullingham, & Lloyd, 1990; Peirce, Fragen, & Pemberton, 1990).
(4) 30 mg is the approved dose that is consistent with United States Food and Drug Administration (FDA) labeling per the package
(5) Ketorolac is part of the routine trauma acute pain protocol

Patients with pre-existing medical co-morbidities and contraindications to ketorolac will be excluded from the study (see 5 for detailed exclusion criteria)
Patients in the treatment group will receive 15 mg IV ketorolac every 6 hours for 5 days after admission.

e. **Post-operative inpatient care**: Enrolled patients will have daily blood samples (10 cc) will be collected post-admission and at 24 hours intervals for 5 days by blinded health care personnel. The initial blood sample will be collected within 12 hours of initial injury and before the first scheduled administration of ketorolac to establish baseline cytokine profile. Subsequent blood sample collection will be 24 hours apart. Medication compliance and monitoring will be performed daily by the same research coordinators.

Sandwich ELISA with be used to determine the concentrations of IL-1, IL-6, IL-10, and PGE2 in obtained blood samples. Blinded quality control samples will be included in every batch for each ELISA assay. This will allow for the calculation of coefficient of variation (CV) within and across patient cohorts. In the present study, the CV will be calculated for IL-1, IL-6, IL-10, and PGE2. If wide variations are observed among the analytes during the analysis, we will restrict our analysis to analytes in which the CV is less than 20%.

In addition to the standard trauma labs (Sodium, Potassium, Creatinine, Lactic acid, Glucose, Platelet, blood urea nitrogen (BUN), hematocrit, and white blood cell count), patient demographics (sex, age, and BMI), injury data (mechanism of injury, NISS, and types of surgical/procedural interventions), posttraumatic complications (occurrence of bacterial pneumonia, ARDS, SIRS, MODS), complications defined in the National Trauma Dataset, and inflammatory data will be collected. This data will be maintained in our clinical database (REDCap) by a full-time Clinical Study Coordinator.

Enrolled patients will be monitored daily by research staff throughout their hospital stay and routine outpatient clinic visits. Patient's subjective pain scores will be assessed and documented by the trained nursing staff using Visual Analogue Scale (VAS) daily. Pre-injury narcotics use along with other pain modulating medication intake will be recorded per day in morphine milligram equivalent (MME) for the duration of ketorolac or placebo therapy in our password protected database. Patients' clinical course will be monitored closely and daily by research staff to ensure no NSAIDs will be administered to the control cohort to ensure consistency and protocol adherence. After patient discharge, various patient surveys will be used to assess patient pain, function, and quality of life. Opioid and pain modulating medication prescription refills will be monitored using State Scheduled Prescription Electronic Reporting System. Patient narcotic requirement will be assessed during all the routine follow up visits by the same research staff to maintain consistency.

11. Data and Specimen Banking

Blood sample specimens obtained from the research subjects will be labeled with the patient's unique study ID number and will be stored in the CCTS lab until analysis. Following analysis, the specimens will be disposed of in accordance with UK policies. No specimens will be retained for future studies. The stored de-identified data from the study will be kept for a minimum of 6 years for records in the event follow- up studies are pursued and will remain protected and encrypted. Data will be permanently

deleted following this time period. The banked data will be stored on a password-protected research drive. Upon conclusion of the study, the data will be stored in a password encrypted file that only the PI has access to.

12. Data Management

Following initial enrollment, each patient will be assigned a unique patient identifier. All electronic documentation containing total morphine equivalents, specimen results, and all other medical information will be associated with this unique patient identifier during analysis. All protected health information will be stored in a separate, password-protected research file that will not be accessed regularly. Following our secondary analysis, all personal health information will be removed from our electronic files and destroyed in accordance with patient privacy guidelines.

Data obtained at the UK during the study will be recorded and stored using password protected spreadsheet on the department's secure drive and will be maintained at the hospital by the research staff. Final analysis will be conducted using Excel spreadsheets. All documents will be stored on a password-protected research drive and only research personnel will have access to its content. Paper documents, including consent forms, will be stored in a locked cabinet in a secure research room in the Kentucky Clinic Suite K434.

All study personnel have completed human subject protection, responsible conduct of research, and patient confidentiality training. Only IRB-approved research personnel will administer consents and perform phone surveys. All efforts will be made to maintain the confidentiality of the patient reported data. Only study personnel listed in eIRB will have access to identified study data.

13. Provisions to Monitor the Data to Ensure the Safety of Subjects

Subjects in this study will be exposed to greater than minimal risk but presenting the prospect of direct benefit to individual in the study. The patients will be monitored continuously as inpatients post-operatively and any issues with medication effects, wound healing, or other medical complications will be logged as adverse events. Blinding will only be broken for unexpected complications potentially relating to ketorolac administration and the research study. The research team will meet monthly to monitor data collection and handling. During this time, study staff will also review adverse events logs.

14. Withdrawal of Subjects

We do not anticipate any situation in which a subject would be withdrawn from the study by the researchers should they wish to remain. We anticipate analyzing the data via an intention to treat analysis and thus would include data from all subjects initially enrolled, even if they developed an intolerance or medical contraindication to continuing the study.

However, a subject may choose to withdraw from the study on their own accord, at any time, for any reason. Contact information and instructions detailing how to withdraw from the study will be provided in the consent form and will involve contacting the principal investigator directly. If a subject chooses to withdraw, any and all data that was previously collected will be included in the analysis; however, we will cease any further data collection. All personal health information collected prior to a patient's withdrawal from the study will be destroyed in accordance with patient privacy laws. In addition, any paper documents obtained will be destroyed in accordance with standard HIPPA guidelines. Upon being notified of a patient's decision to withdraw from the study, researchers will no longer contact the patient via phone, administer in-office surveys, or access their medical information online.

15. Risks to Subjects

Long-term non-steroidal anti-inflammatory drug (NSAID) intake has been correlated with impaired or delayed fracture healing in animal and clinical studies with a dose dependent response. However, the evidence in animal studies is conflicting, and there are few retrospective clinical studies and even fewer large scale prospective randomized trials. A recent meta-analysis demonstrated that higher quality studies found no evidence of negative effect of NSAIDs on bone-healing. To our knowledge, the present study will be the largest prospective randomized clinical trial to evaluate the effect of short term and low dose administration of NSAID on trauma patient outcomes, opioid consumption, and fracture union rates.

Surgical risks are described to the patient prior to surgery and are part of standard of care procedures for hip fracture surgery. There are no additional surgical risks to patients who participate in this study.

Although the treatment arm in this study involves randomization to ketorolac, standard ketorolac is commonly used as part of the acute trauma pain protocol. Risks commonly associated with ketorolac are listed in attachments to the eIRB.

There is also a risk of a breach of confidentiality. All research team members are appropriately trained and understand the importance of confidentiality.

16. Potential Benefits to Subjects

The use of ketorolac in the acute period could potentially decreasing the inflammatory cascade leading to a decrease in severe posttraumatic complications such as multi-organ dysfunction syndrome, bacterial pneumonia, acute respiratory distress syndrome, systemic inflammatory response syndrome, and post traumatic pain. Additionally this could result in decreased ICU stay and better postoperative pain control (decreasing opioid dependence/usage).

17. Vulnerable Populations

At high energy trauma centers such as those participating in the study, some percentage of the patients will be eligible for the study but will not be able to consent due to traumatic brain injuries, or for other reasons related to their injury. We will consent these patients using the individuals' legally authorized representative. The process for obtaining consent for surgery or study participation varies based upon the state the patient is being treated within, and as such the details of this process will be guided by the standard practice of the local IRB.

Whenever possible, we will also discuss involvement in the study with the patient's family (provided the patient gives permission for us to discuss with them) to ensure that the decision to participate in the study is made with appropriate consideration and that the entire family is comfortable with involvement.

18. Sharing of Results with Subjects

To maintain the blinded nature of the study, the subjects will not be aware of which treatment group a subject has been randomly assigned to. At the conclusion of the study, following de-identification and data analysis, results of this data collection may be shared with patients who have participated in this research as it becomes available, if they request it verbally or in writing. This will only occur after final data analysis if a subject inquires.

19. Setting

Research subjects will be identified, recruited, and followed post-operatively as inpatients at the

University of Kentucky Chandler Hospital. They will be followed post-discharge at the Kentucky Clinic. Data analysis will primarily occur in locked, private offices at in one of two secure research offices located at the Kentucky Clinic.

20. Resources Available

The University of Kentucky Chandler Hospital is a large level-1 Trauma center in eastern Kentucky. The Orthopedics Department has locations within the Kentucky clinic that serve as a dedicated research space, which contain computers with access to password-protected research drives.

The Principle Investigator (PI) will be responsible for overseeing the study and ensuring consistency throughout the project. The orthopedic PI will serve as the research coordinator and assist in data collection and analysis. Recruitment and consent will be performed by the PI or the research assistant. Each member of the research staff has passed the CITI exam on ethical conduct of research and have received training and supervision regarding patient confidentiality and study protocol. The PI will meet with all research staff periodically to review each role and ensure adequate training for the respective positions. Upon enrollment of each patient, the corresponding surgical team will be counseled concerning the details of the study and their role, prior to admitting the patient into the OR.

The PI and research assistant will be responsible for institutional /IRB communication as well as data review and assistance with follow-up patient coordination as needed. There are no anticipated adverse consequences associated with this study, however, the principal investigator and research assistant will both be available should any unexpected medical or psychological problems arise. The research subjects will be provided with appropriate contact information in the consent form and will be provided with the PIs contact information at the time of enrollment as well.

21. Recruitment Methods

No formal external recruitment methods will be used for this study, as acute trauma patients that are moderately to severe injured are universally admitted to the hospital after injury while awaiting surgery. Patients will be identified, screened, and approached for enrollment in the study as noted above (see 8. Study Timeline). After review and screening, the patient will be given the opportunity to ask researchers questions about the study. There will be no financial compensation in return for participation in this study.

22. Confidentiality

As part of our design, researchers will have access to patients' names and phone numbers in order to collect the required data. Upon enrollment, each patient will also be assigned a unique identifier. All patient personal information will be stored in a master list that links the patient's identifying information to their medical record number, which will be maintained in a separate, locked file that only approved research personnel will have access to. During the data collection period, researchers will not directly use this master list and, instead, will draw upon information from a separate that contains only the patient's first name, phone number, and unique patient identifier

All paper data collection documents are kept in locked file cabinets within locked offices that are accessible only to the project investigators and staff. All online databases are password protected to guard against unauthorized access and only approved research personnel will be granted access.

23. Provisions to Protect the Privacy Interests of Subjects (HIPAA)

All eligible subjects will identified by orthopedic trauma team and researchers during morning fracture conference or upon presentation to the ED. After this point, only approved research personnel will have access to patients' private health information. All research will be stored electronically on secure research drives or locked offices as described above.

Only health information related to their orthopedic injury and surgery will be reviewed for the purposes of this study. Other unrelated personal health information will not be accessed or used in any way. All subjects will sign a HIPAA authorization form for use of any protected health information to be used for research purposes, as stated above.

24. Compensation for Research-Related Injury

There will be no additional compensation for research related injury as all treatments/medications are approved for postoperative pain management. Patients would be treated for any complications of surgery including non-union or fractures that may be slow to heal using approved methods by their treating surgeon consistent with standard of care. The patient would be responsible for all costs associated with this treatment.

25. Economic Burden to Subjects

Although ketorolac is part of the routine trauma acute pain protocol, the cost of the study medication (ketorolac) will be paid for by either an internal or external grant. All other treatment costs are within the standard of care and the expenses will be paid for by the patient and their health insurance. There is no additional post-operative follow-up required for this study beyond the surgeon's standard follow-up routine. There will be no financial compensation in return for participation in this study. The cost to analyze and collect the specimens for analysis will also be covered by the internal or external grant.

26. Consent Process

Consent and/or Authorization by a Legally Authorized Representative (LAR)

Eligible patients will be approached for their consent to participate. Informed consent will be obtained prior to the collection of any study related data. To encourage a high level of participation from eligible patients, the attending surgeon may be involved in the consent conversation. The research coordinator and surgeon may initiate the conversation together.

By virtue of the types of injuries studied (resulting from high energy mechanisms such as high-speed motor vehicle crashes, high falls, and blast injuries) it is expected that a large proportion (> 30%) to have an associated traumatic brain injury which my render them unable to provide consent for the study. It will be important not to exclude these patients from the study, as it would significantly reduce our ability to produce generalizable knowledge. These patients are at no greater risk of adverse consequences by virtue of their participation in the study and should be given the same opportunity to participate.

Consistent with Kentucky health care decision statutes for choosing a legally authorized representative for adult subjects unable to consent, one of the following responsible parties, in the following order of priority (if no individual in a prior class is reasonably available, willing, and competent to act), is authorized to make research participation decisions on behalf of the person: (a) the judicially-appointed guardian of the person, if the guardian has been appointed and if the decisions to be made under the consent are within the scope of the guardianship; (b) the attorney-in-fact named in a durable power of attorney, if the durable power of attorney specifically includes authority for the decisions to be made under the consent; (c) the spouse of the person; (d) an adult child of the person, or if the person has more than one (1) child, the majority of the adult children who are reasonably available for consultation; (e) the parents of the subject; (f) the nearest living relative, or if more than one of the same relation, a majority of the nearest living relatives.

Consent by a legally authorized representative should involve all the same considerations that informed consent from a competent subject involves.

Guidance will be provided to assist the LAR in making the consent decision. They will advised to base the decision on the participant's expressed wishes, or, if these are not known, what they believe the participant would have desired under the circumstances of the injury, their beliefs and values. If the LAR does not know what the participant would have wanted, the LAR will advised to base the decision with the participant's best interest in mind. They will be asked to carefully consider how much leeway the participant would likely give the LAR in making the choice about participation in the study.

Recognizing that consent is an ongoing process, the study team will encourage the participants to ask additional questions that may arise during their participation in the study.

27. Process to Document Consent in Writing

The consent will be documented in accordance with the guidelines set forth by the IRB and ORI at UK. The patient will receive a copy of this consent for their personal records during the enrollment process.

The consent template provided by the IRB was used in the creation of the consent for this study and provides answers to many anticipated questions. Each signed consent will be stored in a locked cabinet in Kentucky clinic room k434 and only approved study personnel are able to access this.

28. Drugs or Devices

Ketorolac is FDA approved, with a labeled indication for short-term (up to 5 days in adults), management of moderately sever acute pain that requires analgesia at the opioid level. As such, this study represents on-label use of the medication, but with investigation of potential additional benefits. Use of Toradol in this patient population does not involve a novel route or dosage, and is not being used in a patient population that would increase the risks. Toradol is used as part of the Acute Trauma pain protocol.

Placebo will consist of normal saline. Additional treatment done by the surgical teams are determined by the attending surgeon based on the injury characteristics and are independent of involvement in this study.

29. References

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