Intranasal Versus Intravenous Ketamine for Procedural Sedation in Children with Non-operative Fractures

Study Protocol & Statistical Analysis Plan

NCT03781817

Date of Last Protocol Approval: 04/02/2021

James Statler, MD, Principal Investigator
University of Alabama at Birmingham
Birmingham, AL 35294

Human Subjects Protocol (HSP)

Form Version: February 1, 2017

- You are applying for IRB review of the research described in this form.
- To avoid delay, respond to all items in order and include all required approvals and documents. For more tips, see the UAB IRB website.
- To complete the form, click the underlined areas and type or paste in your text; double-click checkboxes to check/uncheck.
- All responses should be Times New Roman, Bold, and Underlined.
- Submit all materials to AB 470, 701 20th Street South, Birmingham, AL 35294-0104.

Indicate the type of review you are applying for:

☒ Convened (Full) IRB ***-OR-***

☐ Expedited - See the Expedited Category Review Sheet, and indicate the category(ies) here:

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

1. IRB Protocol Title: Intranasal versus intravenous ketamine for procedural sedation in children with non-operative fractures: A prospective, randomized study.

2. Investigator and Contact Person

a. Name of Principal Investigator: **James Statler**

Degree(s)/Title: **MD** BlazerID: **jstatler**

Dept/Div: **Pediatrics/Pediatric Emergency Medicine**

Mailing Address: **1600 7th ave south, CPP1, Suite 110, Birmingham, AL** UAB ZIP: **35233**

Phone: **205-638-6098** Fax: **205-975-4623** E-mail: jstatler@uabmc.edu

b. Name of Contact Person: **Nipam Shah** Title: **Scientist 1** Phone: **205-638-7431**

E-mail: **nshah@peds.uab.edu** Fax: **205-975-4623**

INVESTIGATOR ASSURANCE STATEMENT & SIGNATURE

By my signature as Principal Investigator, I acknowledge my responsibilities for this Human Subjects Protocol, including:

- Certifying that I and all key personnel comply with reporting requirements of the UAB Conflict of Interest Review Board;
- Certifying that the information, data, and/or specimens collected for the research will be used, disclosed and maintained in accordance with this protocol and UAB policies;
- Following this protocol without modification unless (a) the IRB has approved changes prior to implementation or (b) it is necessary to eliminate an apparent, immediate hazard to a participant(s);
- Verifying that all key personnel listed on the protocol have completed initial IRB training and will complete continuing IRB training as required;
- Verifying that all personnel are licensed/credentialed for the procedures they will be performing, if applicable;
- Certifying that I and all key personnel have read the *UAB Policy/Procedure to Ensure Prompt Reporting of Unanticipated Problems Involving Risks to Subjects or Others to the IRB, Institutional Officials, and Regulatory Agencies* and understand the procedures for reporting;
- Applying for continuing review of the protocol at least annually unless directed by the IRB to apply more frequently;
- Conducting the protocol as represented here and in compliance with IRB determinations and all applicable local, state, and federal law and regulations; providing the IRB with all information necessary to review the protocol; refraining from protocol activities until receipt of initial and continuing formal IRB approval.

Signature of Investigator: _____ **Date:** _____

3. Protocol Personnel

Including the PI, list all key personnel (each individual involved in the design and conduct of this protocol). See the Key Personnel Flowchart.

Complete the UAB (3.a.) and non-UAB (3.b) tables, as applicable. Use the checkboxes to show each individual's role, whether the individual has financial interests as defined by the UAB CIRB, and briefly describe the individual's protocol responsibilities and qualifications to perform those responsibilities. **Insert additional rows as needed.**

FDA: For studies involving investigational drugs, list all investigators who will be listed on FDA Form 1572 and include a copy of the 1572. Send the IRB a copy of Form 1572 any time you update the form with the FDA.

a. UAB Personnel (includes UAB affiliates and Children's of Alabama personnel)

Name, Degree, and Dept.	Blazer ID	Role	Financial Interest?*	Protocol Responsibilities and Qualifications (indicate if this person obtains consent)
Name: **James Statler** Degree: **MD** Department: **PEM**	**jstatler**	Principal Investigator	☒No ☐Yes	Will coordinate all research activities including recruitment, informed consent, data collection, analysis of the data, and reporting of the results and manuscript writing
Name: **Judson Barber** Degree: **MD** Department: **PEM**	**jbarber**	☒Sub-Investigator ☐Other	☒No ☐Yes	Supervise as well as recruitment, informed consent, data collection, analysis of the data, and reporting of the results and manuscript writing
Name: **Nipam Shah** Degree: **MBBS, MPH** Department: **PEM**	**npshah5**	☐Sub-Investigator ☒Other	☒No ☐Yes	recruitment, informed consent, data collection, analysis of the data, and reporting of the results and manuscript writing
Name: **Elle Kaplan** Degree: **MS3** Department: **UAB Medical School**		☒Sub-Investigator ☐Other	☒No ☐Yes	Recruitment, informed consent, data collection, analysis of the data, and reporting of the results and manuscript writing
Name: **Helen Cunningham** Degree: **MS3** Department: **UAB Medical School**		☒Sub-Investigator ☐Other	☒No ☐Yes	Recruitment, informed consent, data collection, analysis of the data, and reporting of the results and manuscript writing
Name: **Adrienne Travis** Degree: **PharmD** Department: **Pharmacy**		☐Sub-Investigator ☒Other	☒No ☐Yes	Randomization and Treatment allocation, will provide prefilled and labelled syringes with placebo and drug (IVK or INK)

b. Non-UAB Personnel Relying on UAB IRB - If you are requesting that the UAB IRB serve as the IRB of record for anyone not affiliated with UAB, list these individuals below.

Name and Degree	From Institution with or without own IRB?	Financial Interest?*	Protocol Responsibilities and Qualifications (indicate if this person obtains consent)
Name: _____ Degree: _____ Institution: _____ Email: _____	☐Has own IRB but requests that UAB IRB serve as IRB of record?***-OR-*** ☐Does not have own IRB and needs to rely on UAB IRB.	☐No ☐Yes	_____

***Financial Interest** – for each individual listed above, answer **Yes** or **No** as to whether the individual or an immediate family member has any of the following:

- An ownership interest, stock options, or other equity interest related to the investigator's institutional responsibilities of any value.
- Compensation greater than $5,000 in the previous two years when aggregated for the immediate family
- Proprietary interest including, but not limited to, a patent, trademark, copyright, or licensing agreement.
- Board of executive relationship, regardless of compensation.
- Any other Financial Interest as defined by the UAB CIRB.

UAB Personnel: If the individual or his/her spouse or dependent child has a Financial Interest, a disclosure has to be made to the UAB CIRB. A completed CIRB evaluation has to be available before the IRB can complete its review.

Non-UAB Personnel: If the individual has a Financial Interest, ***include a copy of the report from his/her own institution's conflict of interest review with this submission to the UAB IRB.***

c. Do the investigators listed above include any students using this research for their thesis or dissertation?	
☒ No, continue with Item 3.d. ☐ Yes, complete the following	
Student Name	**Thesis/Dissertation Title**

d. Is the principal investigator a student, fellow, or resident? ☒Yes ☐No

If Yes, complete items below and obtain signature of faculty advisor or supervisor:

Supervisor's Name: **Judson Barber**
Degree(s) / Job Title: **MD, Professor, Pediatric Emergency Medicine**
Additional Qualifications pertinent to the protocol: _____
Telephone: 205-638-6034
E-Mail: **JBarber@peds.uab.edu**
Signature: _____

e. Describe the principal investigator's activities related to this protocol and provisions made by the PI to devote sufficient time to conduct the protocol: **The principal investigator will be involved in site activation and coordination of all research activities, ensure adherence to study protocol, informed consent, recruitment and data collection, analysis of data, reporting of results and manuscript writing. Sufficient time is allotted on a monthly basis into the schedule of pediatric emergency medicine fellows as to allow for the appropriate balance of clinical and research responsibilities.**

f. Is medical supervision required for this research? ☐Yes ☒No

If Yes, who will provide the medical supervision?

☐ PI will provide ***-OR-***

☐ Other:

Name: _____ Telephone: _____

If other than PI, obtain signature of person providing medical supervision:

Signature _____

g. Describe your process for ensuring all key personnel are adequately informed about the protocol and their research-related duties and functions: **I will discuss in person with each of the key personnel/assistants their duties and responsibilities as well as provide information about the study protocol. I will provide them with a sample copy of the consent and assent forms and I will explain how to obtain informed consent. Each personnel will be allowed to ask questions and to contact me at any time with further questions or concerns. In addition, I will supervise project activities to ensure adherence to protocol.**

4. Funding

Is this protocol funded? ☐Yes ☒No

If No, specify that costs of the protocol will be covered by funds from the UAB department or other source named: **UAB Department of Pediatrics**

If Yes, attach one copy of completed application or request for funding sent to sponsor, and complete a-d.

a. Title of Grant, Contract, or Agreement:

b. UAB PI of Grant, Contract, or Agreement:

c. Office of Sponsored Programs (OSP) Assigned Number: _____
(If not yet available, enter "Pending" and provide upon receipt from OSP.)

d. Sponsor, Funding Route:
(Check and describe all that apply)
(If subaward, list both the funding source and the institution receiving the direct award)

☐ Gov't Agency or Agencies—Agency name(s): _____
☐ Department of Defense (DoD): Identify DoD component: _____
☐ Department of Energy (DOE)
☐ Department of Justice (DOJ)
☐ Department of Education
☐ NIH Cooperative Group Trial - Group name: _____
☐ Private Nonprofit (e.g., Foundation) - Name:
☐ Industry, investigator-initiated - Name: _____
Describe the funding arrangement: _____
NOTE: The UAB IRB typically only reviews industry-sponsored protocols that are investigator initiated or when the protocol qualifies for expedited review or involves gene therapy.
☐ UAB Departmental/Division Funds—Specify: _____

5. Locations Involved

a. Indicate all performance sites that will provide space, services, or facilities for the conduct of this protocol.
☐ UAB Hospital
☐ UAB Hospital - Highlands
☐ The Kirklin Clinic of UAB Hospital
☐ The Kirklin Clinic at Acton Road
☐ UAB Callahan Eye Hospital
☐ UAB Clinical Research Unit
☒ Children's of Alabama
☐ Birmingham Veterans Affairs Medical Center
☐ Jefferson County Department of Health
☐ Other (i.e., any performance site not listed above, including those covered by subawards related to this protocol) - Describe: _____
NOTE: Documentation of IRB approvals from sites receiving subawards must be received by the UAB OIRB before funding will be released for that subaward.

b. Describe the space, service, or facilities available for the conduct of the research in the performance sites listed in Item 5.a (For research on UAB campus, include building names): **Patient screening, enrollment and informed consent will be obtained in the emergency department (ED) of Children's of Alabama (COA). Data collection will take place in the ED as well as in Children's Park Place, Suite 110. The remainder of the research, including data analysis, and collaboration amongst the principal investigator and the sub-investigators, will be conducted in Children's Park Place, Suite 110. The office computer in Suite 110 will be used to store data.**

c. Is this protocol a clinical trial requiring clinical services at one of the performance sites listed in Item 5.a above? ☒Yes ☐No
If Yes, will any of the services be billed to either participants/their insurance or to the study account through the Hospital Billing Office (PFS) or the HSF Billing Office (MSO)? ☒Yes ☐No

If Yes, submit a Full Fiscal Approval Process (FAP)-designated unit submission to s complete a FAP submission and send to fap@uab.edu. For more on the UAB FAP requirements, go to FAP - SiteMinder Processes.

d. Is this a field study? ☐Yes ☒No
If Yes, describe the community and include information about how the community will be involved in the design, implementation and analysis of the research. This would include focus groups, training local facilitators/community health advisors: _____

e. Has this protocol been rejected or disapproved by another review board (another IRB, similar review board, or departmental review committee(s)) that authorizes the use of its patient populations?

☐Yes ☒No

If Yes, provide name(s) of the review board(s) and reason(s) not approved: _____
Attach copies of the disapprovals.
NOTE: If this protocol is subsequently rejected or disapproved by another review board, promptly notify UAB IRB.

f. Will the protocol be conducted at or recruit participants from the Birmingham Veterans Affairs Medical Center (BVAMC)? ☐Yes ☒No
If Yes, describe the involvement of the BVAMC: _____
Attach the VA IRB approval and VA IRB-stamped consent form(s), if applicable.
NOTE: See the BVAMC section of the IRB Guidebook for more information.

g. Will the protocol be conducted at or recruit participants from the Jefferson County Department of Health (JCDH)? ☐Yes ☒No
If Yes, describe the involvement of the JCDH and list the JCDH clinics being used: _____
Attach the JCDH Research Review Panel approval, if applicable.
NOTE: Human subjects research conducted at certain JCDH clinics requires review by the JCDH Research Review Panel. See the JCDH section of the IRB Guidebook for more information.

6. Clinical Trial

Does this protocol meet the following definition of a clinical trial? ☒Yes ☐No
**A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes. For more information, see the full definition of clinical trial here.*
If Yes, you will need to fulfill the following requirements (regardless of funding):

a. All key personnel must complete the Good Clinical Practices (GCP) training. For information on this requirement, visit the IRB website here.

b. This protocol must be registered on ClinicalTrials.gov. Provide the National Clinical Trial (NCT) identifier number: **NCT03781817**
If you have any questions regarding registering a study on ClinicalTrials.gov, email the UAB Center for Clinical and Translational Science at ccts@uab.edu.

7. Multi-Site Studies

a. Is this a multi-site study with the UAB investigator as the lead investigator? ☐Yes ☒No

b. Is this a multi-site study with UAB as a coordinating site? ☐Yes ☒No

c. If Yes to a or b, describe the management of information obtained in multi-site research that might be relevant to the protection of participants. Include, at a minimum, how the following items are managed:

- IRB approvals from other sites
- Unanticipated problems involving risks to participants or others. (For example, if there is an unanticipated problem involving risks to participants or others, which site is responsible for reporting it?)
- Interim results
- Protocol modifications

_____

8. Drugs

Will any drugs or supplements be *used or studied* in this protocol? ☒Yes ☐No
If Yes, attach the completed Drug Review Sheet.

9. Devices

a. Will any devices be *studied* in this protocol? ☐Yes ☒No

b. Will any *not FDA-approved* devices be *used or studied* in this protocol? ☐Yes ☒No

If Yes to a or b, attach the completed Device Review Sheet.

10. Special Approvals

a. Does this protocol involve the use of radioisotopes? ☐Yes ☒No

If Yes, attach documentation of approval from the Radiation Safety Division.

b. Does this protocol include patients with contagious infections (e.g., mumps, measles, chickenpox, TB, meningitis)? ☐Yes ☒No

If Yes, attach documentation of approval from the Infection Control Committee of the appropriate facilities.

c. Does this protocol involve obtaining remnant biopsy or surgical material from the Department of Pathology or any other source? ☐Yes ☒No

If Yes, attach documentation of approval from the entity or individual providing the materials (e.g., the UAB Division of Anatomic Pathology Release of Pathologic Materials).

d. Does this protocol require obtaining any remnant clinical laboratory specimens, body fluids, or microbiological isolates from the Department of Pathology or any other source? ☐Yes ☒No

If Yes, attach documentation of approval from the entity or individual providing the materials (e.g., the UAB Division of Laboratory Medicine Release of Pathologic Materials).

e. Does this protocol use stored (existing) specimens from a repository? ☐Yes ☒No

If Yes, attach documentation of approval for use of specimens, and describe how existing specimens are labeled: _____

11. Use of Specimens

Does this protocol involve the collection of specimens? ☐Yes ☒No

If Yes, complete 11.a-11.h.

If No, skip to Item 12.

a. How will specimens be obtained, processed, distributed, and stored? _____

b. How will specimens be labeled (e.g., unique identifier, medical record number, Social Security number, name, date of birth)? _____

c. How will clinical data associated with the specimens be collected and stored? _____

d. What participant-identifying information will be collected and linked to the specimens? _____

e. What steps will be taken to maximize the confidentiality of linked identifiers? For example, procedures could include using a password-protected computer database to link identifiers, with limited personnel knowledgeable of the password, or coded identifiers released without the ability to link to clinical data (also called "stripped" or "anonymized" specimens). _____

f. Is genetic testing planned as part of this protocol? ☐Yes ☐No

If Yes, describe the planned genetic testing here. _____

g. Will specimens be stored for future use? ☐Yes ☐No

If Yes, indicate whether they will be used for the disease under study in this protocol or research on other diseases. _____

h. Will specimens be shared with other investigators in the future? ☐Yes ☐No

If Yes, answer i. and ii.

i. What identifiers, clinical information and demographic information will be shared; or will the specimens be stripped of identifiers (i.e., anonymized)? _____

ii. Outline your procedure for assuring IRB approval for release and use prior to release of specimens.

_____

NOTE: Investigators who receive and/or use these specimens must document approval from the appropriate IRB(s) before the specimens may be released.

12. Gene Therapy

Does this protocol involve gene therapy or administering recombinant materials to humans? ☐Yes ☒No

If Yes, submit the Gene Therapy Project Review Panel Report ***-OR-*** the Protocol Oversight Review Form For Clinical Vaccine Trials, as applicable.

13. HIPAA Privacy and Security

Will the PI or others obtain, review, or make other use of participants' "protected health information" (i.e., information, whether oral or recorded in any form or medium that (a) is created or received by a health care provider and (b) relates to past, present, or future physical or mental health or condition of an individual; or provision of health care; or payment for provision of heath care)? ☒Yes ☐No

If Yes, complete Items 13.a-13.**f.**

If No, skip to 14.

a. Will the data/information be stored or managed electronically (on a computer)?

☒Yes ☐No

b. Is the principal investigator requesting that the UAB IRB waive patient HIPAA authorization from another institution or entity (e.g., insurance company, collaborating institution)? ☐Yes ☒No

If Yes, attach copies of the privacy notices from each institution/entity, and provide the name of each institution/entity: _____

c. Indicate which of the entities would provide health information for this protocol, maintain health information as it was collected for this protocol, and/or store health information after it has been collected for this protocol.

☐ UAB Hospital or UAB Hospital - Highlands
☐ The Kirklin Clinic of UAB Hospital or Acton Road (and/or associated clinics)
☐ UAB Callahan Eye Hospital
☒ Children's of Alabama
☐ Jefferson County Department of Health
☐ School of Dentistry
☐ School of Health Professions
☐ School of Medicine
☐ School of Nursing
☐ School of Optometry
☐ University of Alabama Health Services Foundation
☐ UAB Health Centers
☐ Viva Health
☐ Ophthalmology Services Foundation
☐ Valley Foundation
☐ Medical West - UAB Health System Affiliate
☐ None - **If None, skip to Item 14.**

d. Indicate any information systems that will be the sources of information used for the protocol.

☐ A system maintained centrally by UAB Health System (these include the following: HealthQuest for registration, billing, and patient administration; PowerInsight (clinical data warehouse); Cerner IMPACT for PowerNotes for meds, Lab, Radiology, UED, Surgery

NOTE: If a researcher needs information in a specified format or a specified time, the researcher must confirm with the unit who can supply the information/service that the request can be met before writing the information/service into the research protocol. In addition, the researcher must be aware that these services may have a cost attached that should be considered in the research budget.

To request access to clinical systems for research purposes, visit https://www.oneuabmedicine.org/web/hsis/technical-support, click "Accounts Request" and complete the form indicating access for research purposed.

☒ Another system on a UAB server - Describe: **We will use electronic medical records maintained by COA for extracting clinical data.**

e. Indicate which of the listed identifiers will be accessed, associated and/or linked with the protected health information (PHI) used for this protocol.

☒ Names
☒ Geographic subdivisions smaller than a state
☒ Elements of dates (except year) related to an individual
☐ Telephone numbers
☐ Fax numbers
☐ Email addresses
☒ Social security numbers
☒ Medical record numbers
☐ Health plan beneficiary numbers
☐ Account numbers
☐ Certificate/license numbers
☐ Vehicle identifiers and serial numbers
☐ Device identifiers and serial numbers
☐ Biometric identifiers
☐ Web universal resource locators (URLs)
☐ Internet protocol address numbers
☐ Full-face photographic images
☐ Any other unique identifying number - Describe: _____
NOTE: Codes are not identifying as long as the researcher cannot link the data to an individual
☐ None - **If None, skip to Item 14.**

f. Choose one plan to describe your use of the personal health information:

☐ The data collected meet the specifications for a "limited data set" (LDS)
-If the LDS will leave the covered entity or will be received from another covered entity you will need a Data Use Agreement

☒ Research staff will obtain authorization from each participant to use the information
-Include the HIPAA Authorization form, complete except for participant name and IRB protocol number, as the final page of the consent form

☐ PI requests waiver of authorization to use the information
-Attach Waiver of Authorization and Informed Consent form

PROPOSED RESEARCH

• The IRB will not accept grant applications and/or sponsor's protocols in lieu of the items as outlined below.

- Do not separate responses from items. Instead, insert your response to each item below the item, keeping the information in the order of this form.

14. Purpose - in nontechnical, lay language

a. Summarize the purpose and objectives of this protocol in one short paragraph. **The purpose of this study is to determine if Intranasal Ketamine (INK) is efficacious for Procedural Sedation and Analgesia (PSA) when compared to Intravenous Ketamine (IVK) in children with non-operative fractures. The primary aim is to determine if INK provides non-inferior sedation to IVK as defined by a Modified Ramsay Sedation score of ≥ 4 and also to compare the proportion of successful procedure between two treatment groups. The secondary aim is to compare proportion of adverse events and compare duration of sedation and length of ED stay between treatment groups.**

b. Describe how outcomes will be measured for this protocol. **The outcome measured in this study will be successful sedation as defined by Modified Ramsay Sedation score of ≥ 4. Successful competition of procedure will be defined as completing the procedure with the induction dose and without requiring rescue medication. Any adverse events related to sedation will be documented. Duration of sedation will be the time from administration of induction (first dose) Ketamine to Aldrete score reaching baseline or pre-sedation. . ED length of stay will be defined as time to arrival to ED to time of discharge order from ED physician.**

15. Background - in nontechnical, lay language

a. Summarize in 2-3 paragraphs past experimental and/or clinical findings leading to the design of this protocol. Include any relevant past or current research by the PI. For drug and device studies, summarize the previous results (i.e., Phase I/II or III studies).

Procedural sedation is frequently needed in the pediatric population for a wide range of indications, from imaging studies to painful procedures. Ketamine is commonly used for PSA in the ED due to its unique ability to induce a dissociative state that provides both analgesia and sedation while preserving spontaneous respiratory drive [3, 10]. While ketamine is most commonly administered IV for PSA in children, obtaining IV access can be time-consuming and pain- and anxiety-inducing for children. However, IN administration is relatively non-invasive, requires minimal training, can be administered more expeditiously, and perhaps most importantly, has excellent absorption through the nasal mucosa directly into the systemic circulation, thereby bypassing hepatic "first pass" metabolism [10,15]. This is especially true when using a mucosal atomizer device (MAD), which delivers a fine spray over a broad surface area in the nasal cavity. MADs also reduce sneezing and coughing compared to other devices used for IN medication delivery [3,15].

Multiple studies have shown that IN pain medications are effective in providing rapid analgesia [4, 9, 12, 14]. In particular, IN ketamine provides adequate sedation, both as monotherapy and in combination with other agents, for imaging studies [23] as well as minor painful procedures such as laceration repair [13] and dental procedures [27, 28]. While the body of existing literature demonstrates that IN ketamine is safe and effective, these studies are limited by small sample sizes (sometimes less than a dozen), and inconsistent end points (e.g. sedation level vs. successful completion of procedure). There are no studies to date that have explored the efficacy of IN ketamine as compared to IV sedatives, and none have examined its use for one of the most common, painful procedures in the pediatric ED such as a closed fracture reduction [3, 8].

Dosing for IN ketamine varies depending on the indication and generally based on the desired effect. Dosing for analgesia, a blend of both analgesia and mild sedation (analgosedation), and moderate-deep sedation varies, and is limited based on the volume delivered, The suggested range for pediatric analgesia is 0.5-3 mg/kg and pediatric PSA is 3-9 mg/kg [3, 10]. In a study using IN ketamine for laceration repair, 3 out of 4 (75%) patients achieved "adequate" sedation using dose of 9 mg/kg. Data safety monitoring committee stopped the study because there were too many failures at doses of 3

mg/kg and 6 mg/kg, suggesting that at 9 mg/kg PSA with IN ketamine alone could be a feasible and efficacious choice for painful procedures [3, 8, 13]. IV ketamine is a commonly employed and validated agent for pediatric PSA in the ED for myriad indications. This study explores the efficacy of IN ketamine as compared to IV ketamine for PSA for the closed reduction of isolated, non-operative fractures in the pediatric ED. We will secondarily compare the duration of sedation, adverse events, and ED length of stay (LOS) between the two groups.

References listed from above:

3. C. Fantacci, G. C. Fabrizio, P. Ferrara, F. Franceschi, A. Chiaretti ***Intranasal drug administration for procedural sedation in children admitted to pediatric Emergency Room***

4. Graudins A, Meek R, Egerton-Warburton D, et al. The PICHFORK (Pain in Children Fentanyl or Ketamine) trial: a randomized controlled trial comparing intranasal ketamine and fentanyl for the relief of moderate to severe pain in children with limb injuries. *Ann Emerg Med*. 2015;65: 248–254.

8. Poonai N, Canton K, Ali S, Hendrikx S, Shah A, Miller M, et al. (2017) Intranasal ketamine for procedural sedation and analgesia in children: A systematic review. PLoS ONE 12(3): e0173253.

9. Quinn, Kellie (07/2018). "Analgesic Efficacy of Intranasal Ketamine Versus Intranasal Fentanyl for Moderate to Severe Pain in Children: A Prospective, Randomized, Double-Blind Study.". *Pediatric emergency care (0749-5161)*, p. 1.

10. Rech, Megan A (08/2017). "When to Pick the Nose: Out-of-Hospital and Emergency Department Intranasal Administration of Medications.". *Annals of emergency medicine(0196-0644)*, 70 (2), p. 203.

12. Reynolds, Stacy L (2017). "Randomized Controlled Feasibility Trial of Intranasal Ketamine Compared to Intranasal Fentanyl for Analgesia in Children with Suspected Extremity Fractures.". *Academic emergency medicine (1069-6563)*, 24 (12), p. 1430.

13. Tsze, D. S., Steele, D. W., Machan, J. T., Akhlaghi, F., & Linakis, J. G. (2012). Intranasal Ketamine for Procedural Sedation in Pediatric Laceration Repair. *Pediatric Emergency Care, 28*(8), 767-770. doi:10.1097/pec.0b013e3182624935

15. Corrigan M, Wilson S, Hampton J. Safety and efficacy of intranasally administered medications in the emergency department and prehospital settings. Am J Health-Syst Pharm. 2015; 72- 1544-1554

23. Gyanesh P, Haldar R, Srivastava D, Agrawal PM, Tiwari AK, Singh PK. Comparison between intranasal dexmedetomidine and intranasal ketamine as premedication for procedural sedation in children undergoing MRI: A double-blind, randomized, placebo-controlled trial. J Anesth. 2013:26.

27. Abrams, R (1993). "Safety and effectiveness of intranasal administration of sedative medications (ketamine, midazolam, or sufentanil) for urgent brief pediatric dental procedures.". *Anesthesia progress (0003-3006)*, 40 (3), p. 63.

28. Bahetwar, S K (2011). "A comparative evaluation of intranasal midazolam, ketamine and their combination for sedation of young uncooperative pediatric dental patients: a triple blind randomized crossover trial.". *The Journal of clinical pediatric dentistry (1053-4628)*, 35 (4), p. 415.

16. Participants (Screening and Selection)

a. How many participants are to be enrolled at UAB (if other sites relying on UAB IRB, list the number for each site)? **70**

If multi-site study, total number at all sites/institutions: _____

b. Describe the characteristics of anticipated or planned participants (if multiple groups, repeat list for each group).

Sex: **Male and Female**

Race/Ethnicity: **All races/ethnicities**

Age: **1- 18 years**

Health status: **All except as noted in exclusion criteria below**

c. From what population(s) will the participants be derived? **Participants will be derived from the population of patients with non-operative fractures presenting to the COA ED requiring reduction.**

Describe your ability to obtain access to the proposed population that will allow recruitment of the necessary number of participants: **We will have full access to the patients attending the COA ED with fractures requiring reduction. All ED physicians will be informed about the study and eligibility criteria and will have PI and research assistant contact information.**

d. Describe the inclusion/exclusion criteria:

Inclusion Criteria:

i. **Children 1-18 years of age**
ii. **Presenting to COA ED and classified as American Society of Anesthesiologists (ASA) I or II non-operative fracture requiring reduction confirmed by X-ray as well as recommended by consulting orthopedic service. ASA I is defined as normal healthy patient and ASA II is defined as a patient with mild systemic disease.**
iii. **Body weight less than or equal to 25 kg as measured by standard weighing scale**

Exclusion criteria:

i. **ASA classification III or above**
ii. **Age less than 1 year**
iii. **History of hypertension, known coronary artery disease or Kawasaki disease, congestive heart failure, acute glaucoma or globe injury, increased intracranial pressure or intracranial mass lesion, acute porphyria, developmental delays, or major psychiatric disorder**
iv. **Currently has any condition that causes increased nasal congestion or runny nose (current upper respiratory infection (URI), allergies, etc.).**
v. **Prior allergy to ketamine**
vi. **Unavailable parent or guardian to provide consent**
vii. **Non-English speaking**

e. If participants will comprise more than one group or stratification, describe each group (e.g., treatment/intervention, placebo, controls, sham treatment) **and** provide the number of participants anticipated in each group.

Participants will comprise two groups: 9mg/kg Intranasal Ketamine (100mg/ml) and 1.5mg/kg Intravenous Ketamine (10mg/ml). Participants will be randomized into one of the two groups. For blinding purposes, patients in both groups will have IV access. Participants randomized to Intranasal Ketamine group will receive Intranasal ketamine and IV normal saline whereas participants randomized to IV ketamine will be receive IV ketamine and Intranasal hypertonic (3%) saline. We anticipate to enroll 35 participants in IV ketamine group and 35 participants in Intranasal Ketamine group.

f. Indicate which, if any, of the special populations listed below will be involved in the protocol. Include the Special Populations Review Form (SPRF) if indicated.

☐ Pregnant Women: Attach SPRF—Pregnant Women, Fetuses, Neonates/Nonviable Neonates
☐ Fetuses: Attach SPRF—Pregnant Women, Fetuses, Neonates/Nonviable Neonates
☐ Neonates/Nonviable Neonates: SPRF—Pregnant Women, Fetuses, Neonates/Nonviable Neonates
☐ Prisoners: Attach SPRF—Prisoners
☒ Minors (<18 years old): Attach SPRF—Minors
☐ Employees or students at institution where research conducted
☐ Persons who are temporarily decisionally impaired
☐ Persons who are permanently decisionally impaired
☐ Non-English Speakers

For each box checked, describe why the group is included **and** the additional protections provided to protect the rights and welfare of these participants who are vulnerable to coercion: **The research question is focused on children less than 25 kg of body weight. We will ensure participant protection through informed consent process. Parents/legal guardian will provide consent if patient is 7-13 years of age and assent will be obtained from the child. For patients less than 7 years of age, informed consent will be provided by the parent/legal guardian. We do not anticipate to have patients 14 years or greater in the study but if there are patients 14 or greater we will obtain consent from parent/legal guardian as well as patient.**

g. List any persons other than those directly involved in the protocol who will be at risk. If none, enter "None": **None**

h. Describe the recruitment process (e.g., medical record review, referrals, letter of invitation, existing patients) that will be used to seek potential participants (e.g., individuals, records, specimens). Research recruitment by non-treating physicians/staff may require completion of Partial Waiver of Authorization for Recruitment/Screening. **Patients will be initially identified by monitoring the ED tracker board and further screening for study eligibility will be done on discussion with ED physician treating the patient. In addition, on duty ED physician (Attending/Fellow/Resident/NP) or staff nurse will contact study PI or study personnel if there is a potential patient in the ED. When there is a potential patient eligible for the study, PI or study personnel will approach the patient and/or parent/legal guardian, provide information about the study and obtain informed consent.**

i. If you will use recruitment materials (e.g., advertisements, flyers, letters) to reach potential participants, attach a copy of each item. If not, identify the source (e.g., IRB Protocol Number for approved databases) from which you will recruit participants. **We will post study recruitment flyer (Attached) at different locations in the ED. Flyer will list study eligibility criteria and contact information of the PI as well as research assistant and study coordinator.**

j. Describe the screening process/procedures for potential participants. **No further screening will take place other than described above.**

17. Protocol Procedures, Methods, and Duration - in nontechnical, lay language

a. Describe the procedures for all aspects of your protocol. Tell us what you are doing.

Recruitment and Enrollment

The study investigators will initially screen for participants based on eligibility criteria listed above. Eligible patients will be given information about the study and informed consent and /or assent will be obtained using appropriate forms based on patient's age. Patient will then be randomized by unblinded research pharmacist to receive either 9 mg/kg IN ketamine (100 mg/mL) (maximum 1 mL/naris) or 1.5 mg/kg IV ketamine (10 mg/mL) as an optimal IV induction dose for sedation.

Randomization and Blinding:

Patients will be randomized 1:1 into Intranasal or Intravenous Ketamine using simple randomization. Study group allocation will be concealed by unblinded study pharmacist using sealed envelopes. All Patients, ED staff, including physicians, bedside nurse, study personnel, and any additional staff involved in bedside care will be blinded to the randomization and group assignments. Only research pharmacist will remain unblinded and will not be present during enrollment or patient care. For blinding purposes, and per our center's current practice, all patients will have IV access established. Per hospital protocol, sedation and procedural consents will be obtained, and sedation safety and equipment checklists and procedure "timeout" will be performed prior to initiation of sedation. In our institution, the emergency department physician administering sedation medications and monitoring the patient is uninvolved in the fracture reduction. Research pharmacist will maintain prefilled syringes loaded with the study drug, intravenous normal saline, or intranasal hypertonic (3%) saline. Study drugs will be stored in a

dedicated automated medication dispensing system in the ED. These syringes will be pre-labelled by a color code without identifying the drug inside. Color code indicates the route of administration (Intranasal or Intravenous). Treatment allocated to the patient will only be known to the research pharmacist. Research pharmacist will maintain a log of randomization ID and patient identifier. Study drugs will be discarded at the conclusion of the sedation per our ED protocol. Sedating physician will document randomization ID in their sedation record. Study pharmacist will use pyxis data entry and documentation to verify drug administration and drug dosage.

Breaking the blinded code:
We do not anticipate any serious adverse events and need for premature code breaking. After all patients are enrolled and data entry is complete, we will break the blinded code just before data analysis.

Sedation induction and monitoring:
Subject randomized to the IN ketamine will receive IN Ketamine. After 8 minutes, IV Normal Saline (NS) will be given over 30 seconds. Subjects randomized to IV Ketamine will first receive IN hypertonic (3%) saline. After 8 minutes, IV Ketamine will be given over 20-30 seconds.

The study personnel will assess the level of sedation at 5-minute intervals, per our ED protocol, after IN medication administration (induction dose) using the modified Ramsay sedation scale until a score of ≥ 4 is achieved, which will serve as our definition of adequate sedation. Modified Ramsay Sedation scale scores range from 1-8 based on wakefulness of the patient. Score of 1 indicates fully awake and alert whereas score of 8 indicates unresponsive to external stimuli including pain. This scoring will be done by trained study personnel. Sedation scoring will be continued at 5-minute intervals until the reduction is completed. Failure of sedation will be defined as not achieving adequate sedation by Ramsay score of < 4 within 10 minutes of IN administration.

Patients who fail sedation at 10 minutes will receive 0.5 mg/kg IV ketamine or more, with additional IV doses as deemed necessary by treating physician. No subsequent IN medications will be given after the induction dose. Duration of successful sedation will be defined as induction dose time to when the patient is appropriate for discharge from sedation as noted by sedating ED physician. Discharge criteria includes patient said to have reached baseline/pre-sedation modified Aldrete Score.

Procedure: **Once sedation is achieved, orthopedic surgeon will start the fracture reduction. Depending on the type of fracture, length of reduction varies from 5-60 minutes. This includes cast placement and molding which can be painful and is to be included as part of the procedure. Successful completion of procedure will be defined as completed reduction and casting as deemed necessary by orthopedist using only the first 2 drug doses that include the induction intranasal drug and IV drug given at the 8-minute mark. For our purposes, a failed sedation will be described as modified Ramsay sedation score of < 4 by 10 minutes from induction dose or where the patient requires a rescue dose of IV Ketamine at any time throughout the procedure as deemed necessary by sedating physician. Rescue doses are often needed and are not generally documented or referred as "failed" sedation. However, we are directly comparing the induction dose of IN Ketamine to induction dose of IV ketamine. The treating ED physician will assess the outcome and either conclude the sedation as failed or successful. After the procedure is completed, the ED physician will assess and deem the patient appropriate for discharge once the patient has been said to have reached baseline/pre-sedation modified Aldrete Score.**

Data collection:
We will collect clinical and demographic variables (Attached Data collection sheet).

Clinical variables collected will include patient age, patient weight, imaging obtained, the type of fracture, mechanism of fracture, location of fracture, time of injury, NPO status, prior pain medication administration and time, other associated presenting symptoms, medical history, surgical history, allergies, time to sedation, sedation scores and vital signs at each interval set by ED protocol, whether rescue medication was needed, type of casting placed, adverse events, non-sedation-related delays (c-arm/radiology, casting supplies, nursing, ortho, etc), reduction failure not related to a sedation complication, duration of sedation, sedation discharge score, ED length of stay. Demographic information such as age, gender, race/ethnicity, ED arrival date/time.

Duration of study:
The total duration of the study will be 2 years including enrollment, data collection, and data analysis and writing report.

b. What is the probable length of time required for the entire protocol (i.e., recruitment through data analysis to study closure)? **24 months**

c. What is the total amount of time each participant will be involved? **Participant will be involved until discharge from the ED. This is variable for each patient depending on the medical condition. On average, total time should be less than 6 hours accounting for the entire duration of ED stay.**

d. If different phases are involved, what is the duration of each phase in which the participants will be involved? If no phases are involved, enter "None." **None**

e. List the procedures, the length of time the procedure takes, the total # of times the procedure is performed, and indicate whether each is performed solely for research or would already be performed for treatment or diagnostic purposes (routine care) for the population.
-Insert additional table rows as needed.
-If procedure is sometimes research and sometimes routine care, include on separate lines with number of times as each.

Procedure	Length of Time Required of Participants	Total # of Times the Procedure is Performed	Research (Res) –OR- Routine Care
Enrollment/Informed Consent	**10-15minutes**	**Once**	☒Res ☐Routine
Sedation and Procedural consent	**5 minutes**	**Once**	☐Res ☒Routine
Sedation induction (IV or IN Ketamine)	**8 minutes**	**Once**	☒Res ☐Routine
Sedation induction		**Once**	☐Res ☒Routine
Rescue medications	**Over the length of reduction procedure**	**Repeated as needed**	☒Res ☒Routine
Reduction procedure	**5-60 minutes**	**Once**	☐Res ☒Routine
Sedation monitoring	**From induction dose to ED discharge**	**Once**	☐Res ☒Routine
Sedation monitoring	**From induction dose to ED discharge**	**Once**	☒Res ☐Routine

f. Will an interview script or questionnaire be used? ☐Yes ☒No
If Yes, attach a copy.

g. Will participants incur any costs as a result of their participation? ☐Yes ☒No
If Yes, describe the reason for and amount of each foreseeable cost. _____

h. Will participants be compensated? ☒Yes ☐No
If Yes, complete i-v.
i. Type: (e.g., cash, check, gift card, merchandise): **Greenphire Clincard**

ii. Amount or Value: **$10**
iii. Method (e.g., mail, at visit): **At visit**
iv. Timing of Payments: (e.g., every visit, each month): **only at the ED visit on day of enrollment. There will be no follow up visits.**
v. Maximum Amount of Compensation per Participant: **$10**

18. Benefits

a. Describe the potential benefits of the research. **Study will lead to better insight into the potential IN ketamine provides for PSA to achieve successful fracture reductions obviating the need for IV access.**

19. Risks - in nontechnical, lay language

a. List the known risks for participants as a result of participation in the research. This should not include the minimal risk of loss of confidentiality. However, it should include any physical, psychological, social, economic, and/or legal risks. If there is a greater than minimal risk of loss of confidentiality describe why this is so. Do not list risks associated with the standard-of-care procedures.
NOTE: Risks included here should be included in the consent form or information sheet, as applicable.
There is a risk of compromising confidentiality and patient's personal health information. Otherwise, study will not lead to any additional risks or discomforts other than the normal, standard risks and discomforts associated with procedure. Ketamine is associated with some well-known side effects and giving the study drug intranasal is not known to increase the risk or severity of side effects. There may also be risks that are unknown at this time. The known side effects of Ketamine are: Vomiting, Drooling, Allergic reaction, Agitation, Decreased oxygen levels.

b. Estimate the frequency, severity, and reversibility of each risk listed. **It is highly unlikely that the patients' health information and/or confidentiality will be compromised. We will put in place multiple safeguards (as detailed in section 23) to minimize any potential risk to the patients' health information and/or confidentiality.**

c. Is this a therapeutic study or intervention? ☒Yes ☐No
If Yes, complete i.-iii.
i. Describe the standard of care in the setting where the research will be conducted: _____
ii. Describe any other alternative treatments or interventions: _____
iii. Describe any withholding of, delay in, or washout period for standard of care or alternative treatment that participants may be currently using: _____

d. Do you foresee that participants might need additional medical or psychological resources as a result of the research procedures/interventions? ☐Yes ☒No
If Yes, describe the provisions that have been made to make these resources available. _____

e. Do the benefits or knowledge to be gained outweigh the risks to participants? ☒Yes ☐No
If No, provide justification for performing the research: _____

20. Precautions/Minimization of Risks

a. Describe precautions that will be taken to avoid risks and the means for monitoring to detect risks.
There is a risk of compromising the patients' health information and/or confidentiality. However, we will minimize this risk through the following measures:

When enrolled, the patient's information will be entered into a spreadsheet housed solely on Children's of Alabama and/or UAB operated, encrypted, password-protected computers. To maintain confidentiality, the electronic and printed information will only be viewed by the IRB-approved UAB personnel and never left open in an unsecured location. Any printed documents containing identifiers will be destroyed as soon as information has been transferred from print to the patient's secure electronic medical record or to the online spreadsheet. The printed documents will be destroyed using Children's of Alabama and/or UAB-issued paper shredding bins. At the

completion of the project, all patient identifiers will be destroyed through the deletion of the data from the Children's of Alabama and/or UAB operated, encrypted, password-protected computers.

Patients will be monitored for any unknown side effects relevant to intranasal administration and appropriate treatment will be given based on the side effect.

If the protocol involves drugs or devices skip Items 20.b. and 20.c. and go to Item 21. Instead include this information in the Drug Review Sheet or Device Review Sheet, as applicable.

b. If hazards occur to an individual participant, describe (i) the criteria that will be used to decide whether that participant should be removed from the protocol; (ii) the procedure for removing such participants when necessary to protect their rights and welfare; and (iii) any special procedures, precautions, or follow-up that will be used to ensure the safety of other currently enrolled participants. **If any personal health information or confidentiality is compromised, then we will notify all patient's caregivers enrolled in the study in order to alert them to the issue. At that point, the study will be stopped until further investigation and evaluation can be performed to ascertain if in fact a breach of personal health information or confidentiality has occurred. If in fact it has occurred, the Institutional Review Board will be notified and all aspects of the study will be postponed until the situation has been resolved. While we do not anticipate serious adverse events, in the unlikely event they do occur, they will be immediately reported to IRB.**

c. If hazards occur that might make the risks of participation outweigh the benefits for all participants, describe (i) the criteria that will be used to stop or end the entire protocol and (ii) any special procedures, precautions, or follow-up that will be used to ensure the safety of currently enrolled participants. **Not Applicable**

21. Informed Consent

a. Do you plan to obtain informed consent for this protocol? ☒Yes ☐No

If Yes, complete the items below.

If No, complete and include the Waiver of Informed Consent or Waiver of Authorization and Informed Consent, as applicable.

b. Do you plan to document informed consent (obtain signatures) for this protocol? ☒Yes ☐No

If Yes, complete the items below.

If No, complete the items below **and** include the Waiver of Informed Consent Documentation.

c. How will consent be obtained? **Study investigators/study coordinator/research assistant will obtain informed consent in the emergency department once potential patients are identified.**

d. Who will conduct the consent interview? **Study key personnel as listed in section 3.**

e. Who are the persons who will provide consent, permission, and/or assent? **If patient is less than 7 years of age, parent/legal guardian will provide consent. If patient is 7-13 years, patient will provide assent and parent/legal guardian will provide consent. If patient is 14 years but less than 18 years, patient and parent/legal guardian will sign the consent form.**

f. What steps will be taken to minimize the possibility of coercion or undue influence? **We will adhere strictly to our consent and assent forms and if a patient or caregiver expresses discomfort with participation (beyond having further questions), the study staff will be instructed to thank them for their time and document them as having refused participation.**

g. What language will the prospective participant and the legally authorized representative understand? **They will not be expected to understand anything more than an 8th grade reading level.**

h. What language will be used to obtain consent? **English will be used. Strictly for purposes of convenience for the Emergency Department and Children's of Alabama Interpreter Services any non-english speaking caregivers will be excluded from the study.**

i. If any potential participants will be, or will have been, in a stressful, painful, or drugged condition before or during the consent process, describe the precautions proposed to overcome the effect of the condition on the consent process. If not, enter "None." **In such situations, the treating physician will stabilize patients before informed consent process. Additionally, the person obtaining consent we will allow enough time for patients to understand the study and ask questions than a patient who is otherwise normal before they will sign the consent form.**

j. If any protocol-specific instruments will be used in the consenting process, such as supplemental handouts, videos, or websites, describe these here and provide a copy of each. If not, enter "None." **None**

k. How long will participants have between the time they are told about the protocol and the time they must decide whether to enroll? If not 24 hours or more, describe the proposed time interval and why the 24-hour minimum is neither feasible nor practical. **The patient's/parent/legal guardian will have approximately 10 minutes to decide whether to enroll. Due to the constraint of enrolling patients prior to them undergoing the reduction procedure in the ED, we cannot allow for a 24-hour time period to decide whether to enroll. Since enrolling will not affect the care the patient will receive a ten-minute window to decide about enrollment is sufficient.**

22. Procedures to Protect Privacy

a. Describe how you will protect the privacy interest of the participants. Include how you will make sure others cannot overhear your conversation with potential participants and that individuals will not be publicly identified or embarrassed. **All discussions will remain private between research personnel, the patient, and their guardian(s). Individuals will not be publically identified in any way and thus will not be subject to embarrassment.**

23. Procedures to Maintain Confidentiality

a. Describe how you will store research data to maintain confidentiality (both paper records and electronic data), including how access is limited. If data will be stored electronically anywhere other than a server maintained centrally by UAB, identify the department and all computer systems used to store protocol-related data. **When enrolled, the patient's information will be entered into a spreadsheet housed solely on Children's of Alabama and/or UAB operated, encrypted, password-protected computers. To maintain confidentiality, the electronic and printed information will only be viewed by the IRB-approved UAB personnel and never left open in an unsecured location. Any printed documents containing identifiers will be destroyed as soon as information has been transferred from print to the patient's secure electronic medical record or to the online spreadsheet. The printed documents will be destroyed using Children's of Alabama and/or UAB-issued paper shredding bins. At the completion of the project, all patient identifiers will be destroyed through the deletion of the data from the Children's of Alabama and/or UAB operated, encrypted, password-protected computers.**

b. Will any data from this protocol be given to any person, including the subject, or any group, including coordinating centers and sponsors? ☐Yes ☒No

If Yes, complete i-iii.

i. Who will receive the data? _____

ii. What data will be shared? _____

iii. How will the data be identified, coded, etc.? _____

24. Genomic Data Sharing (GDS)

Researchers who collect genomic data as part of a NIH grant funded after January 25, 2008 may be required to submit those data to a NIH database for broad scientific sharing. See Genomic Data Sharing in the IRB Guidebook for more information.

a. Does this protocol involve the proposed submission of genetic data into genomic repositories created to share genetic information for research purposes? ☐Yes ☒No

b. Will UAB be uploading the final genomic data to the central repository (e.g., dbGaP)? ☐Yes ☐No

If Yes to both a and b, submit a Detailed Data Sharing Plan to the IRB for review. This plan should include any known data use limitations and indicate whether aggregate-level data are appropriate for general research use. For guidance see the NIH Genomic Data Sharing Policy.

c. Submit a copy of the NIH Institutional Certification Form.

To determine which certification form to include, answer i-ii.

i. Was this protocol funded prior to January 25, 2015? ☐Yes ☐No

- **If yes,** and consent will be obtained, submit the Extramural Institutional Certification - Before January 25 - With Consent.
- **If yes,** and consent will not be obtained, submit the Extramural Institutional Certification - Before January 25 - Without Consent.

ii. Was this protocol funded after January 25, 2015? ☐Yes ☐No

- **If yes,** submit the Extramural Institutional Certification - After January 25.

25. Additional Information

In the space below, provide any additional information that you believe may help the IRB review the proposed research, or enter "None." **None**

CONSENT FORM

Title of Research: Intranasal versus intravenous ketamine for procedural sedation in children with non-operative fractures: A prospective, randomized study.

UAB IRB Protocol #: **IRB-300002731**

Principal Investigator: James Statler, M.D.

Sponsor: Society for Pediatric Sedation

General Information	You are being asked to take part in a research study. This research study is voluntary, meaning you do not have to take part in it. The procedures, risks, and benefits are fully described further in the consent form.
Purpose	The purpose of the study is to determine whether a medicine we commonly give for painful procedures through an intravenous (IV) line is just as effective or better when given through a nasal spray.
Duration & Visits	You will be in this study for the duration of this emergency department visit. Your participation in the study will end once you are discharged from the emergency department.
Overview of Procedures	We will give your child medicine either through the IV or by nose spray to help with pain and provide sedation (decreased level of awareness) during the procedure.
Risks	The most common side effects from the medication include vision changes, drooling, nausea, vomiting, and agitation. Severe effects may include allergic reaction, apnea, hallucinations, laryngospasm, or decrease in oxygen level.
Benefits	You will not benefit directly from taking part in this study.
Alternatives	If you do not want to take part in the study, the care and treatment you and your child will receive during this emergency department visit will not change. You and your child will receive the normal standard of care based on the doctor that is assigned to you.

Purpose of the Research Study

We are asking you to take part in a research study. You and your child are being asked to participate because you have indicated that your child may have a broken bone. Based on your physicians' assessment, your child may not need surgery but short procedure to reset the bone in place. This is a painful procedure and physicians often use an FDA (Food and Drug Administration) approved drug called Ketamine to help with pain and also put them to sleep (or make them unaware) during this procedure.

Traditionally, Ketamine is given through an intravenous (IV) line. An IV is performed by a medical professional when they insert a needle into the child's arm or hand to pass a plastic tube into a vein and then taking the needle out leaving the plastic tube in place. However, we now have the option to give children the same medication through a nasal spray.

The purpose of this research study is to test how well the study drug (Ketamine) when given through nasal spray compares to IV for painful broken bone procedures. This comparison has not been done before and could show that we could avoid the painful step of getting an IV. We are planning to enroll 70 patients in this study. Children must weigh 55 pounds or less to participate in this study.

Study Participation & Procedures

Your child will be randomly picked by a computer (like the flip of a coin) to be placed in one of two groups. One group will receive the study drug, Ketamine, through the IV and the other through the nasal spray for the first dose. Every child will have an IV line; this is our standard practice and will allow us to give more medication through the IV, if it is needed. We will not give additional doses of the nasal spray. We will monitor and grade the level of your child's sedation (awakeness) using a scoring system. We will not begin the procedure unless your child is under adequate sedation. If your child is not sedated enough, we will give additional study drug through the IV. We will monitor the level of sedation through the entirety of the procedure as well as after the procedure is completed until your child is ready to be discharged from Emergency department. We will record required health information on your child during this visit. Participating in this study should not increase the time you and your child will spend in the emergency department.

This is a double-blinded study. This means neither you nor your doctors and nurses will know whether the study drug is given through nasal spray or IV. If we give your child the study drug through the nose, we will give them sterile saline through the IV. If we give your child the study drug through the IV, we will give them sterile saline through the nose. We will do this in order to not reveal how the study drug was given.

Your de-identified private information (private information with all identifiers removed) may be used for future research studies or distributed to another researcher for future research studies without additional informed consent. **This is only when there are no identifiers associated with the data.** The clinical results (including individual research results) will not be returned to you.

Risks and Discomforts

By participating in this research study, there is a risk of compromising confidentiality and your child's personal health information. However, we minimize this risk by only recording your child's personal health information on Children's of Alabama and/or UAB operated, encrypted, password-protected computers.

Otherwise, participation in this research study will not cause you or your child to be subject to any additional risks or discomforts other than the normal, standard risks and discomforts associated with procedure. Your child may have some side effects from taking the study drug that occur occasionally. These side affects are well known. Giving the study drug through the nose is not known to increase the risk or severity of side effects. There may also be risks that are unknown at this time. You will be given more information if other risks are found.

The known side effects of Ketamine are:

- Vomiting
- Drooling
- Allergic reaction
- Agitation
- Decreased oxygen levels

Benefits

You will not benefit directly from taking part in this study. However, this study may help us better evaluate how well the study drug given through nasal spray works for children with broken bones. This study could show that it works just as well as when it is given through the IV which would help future children avoid the need for an IV.

Alternatives

The alternative to participating in this research study is to not participate. If you choose to not participate, your child will still receive the normal, standard of care for your child's illness.

Confidentiality and Authorization to Use and Disclose Information for Research Purposes

Federal regulations give you certain rights related to your health information. These include the right to know who will be able to get the information and why they may be able to get it. The study doctor must get your authorization (permission) to use or give out any health information that might identify you.

What protected health information may be used and/or given to others?

All medical information, including but not limited to information and/or records of any diagnosis or treatment of disease or condition, which may include sexually transmitted diseases (e.g., HIV, etc.) or communicable diseases, drug/alcohol dependency, etc.; all

personal identifiers, including but not limited to your name, social security number, medical record number, date of birth, dates of service, etc.; any past, present, and future history, examinations, laboratory results, imaging studies and reports and treatments of any kind, including but not limited to drug/alcohol treatment, psychiatric/psychological treatment; financial/billing information, including but not limited to copies of your medical bills; any other information related to or collected for use in the research study, regardless of whether the information was collected for research or non-research (e.g., treatment) purposes; records about any study drug you received or about study devices used; and consent forms from past studies that might be in your medical record.

Your consent form will be placed in your medical record at UAB Health System or Children's of Alabama. This may include either a paper medical record or electronic medical record (EMR). An EMR is an electronic version of a paper medical record of your care within this health system. Your EMR may indicate that you are on a clinical trial and provide the name and contact information for the principal investigator.

If you are receiving care or have received care within this health system (outpatient or inpatient), results of research tests or procedures (i.e. laboratory tests, imaging studies and clinical procedures) may be placed in your existing medical record.

If you have never received care within this health system (outpatient or inpatient), a medical record will be created for you to maintain results of research tests or procedures.

Results of research tests or procedures may be placed in your medical record. All information within your medical record can be viewed by individuals authorized to access the record.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Who may use and give out information about you?

Information about your health may be used and given to others by the study doctor and staff. They might see the research information during and after the study.

Who might get this information?

All Individuals/entities listed in the informed consent document(s), including but not limited to, the physicians, nurses and staff and others performing services related to the research (whether at UAB or elsewhere). Your information may also be given to the sponsor of this research. "Sponsor" includes any persons or companies that are working for or with the sponsor, or are owned by the sponsor, or are providing support to the sponsor (e.g., contract research organization).

Information about you and your health, which might identify you, may be given to:

- the Office for Human Research Protections (OHRP)
- the U.S. Food and Drug Administration (FDA)
- Department of Health and Human Services (DHHS) agencies
- Governmental agencies in other countries
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- the University of Alabama at Birmingham - the physicians, nurses and staff working on the research study (whether at UAB or elsewhere); other operating units of UAB, UAB Hospital, UAB Highlands Hospital, University of Alabama Health Services Foundation, Children's of Alabama, Eye Foundation Hospital, and the Jefferson County Department of Health, as necessary for their operations; the UAB IRB and its staff
- the billing offices of UAB and UAB Health Systems affiliates and/or Children's of Alabama and its billing agents

Why will this information be used and/or given to others?

Information about you and your health that might identify you may be given to others to carry out the research study. The sponsor will analyze and evaluate the results of the study. In addition, people from the sponsor and its consultants will be visiting the research site. They will follow how the study is done, and they will be reviewing your information for this purpose.

What if I decide not to give permission to use and give out my health information?

By signing this consent form, you are giving permission to use and give out the health information listed above for the purposes described above. If you refuse to give permission, you will not be able to be in this research.

May I review or copy the information obtained from me or created about me?

You have the right to review and copy your health information. However, if you decide to be in this study and sign this permission form, you will not be allowed to look at or copy your information until after the research is completed.

May I withdraw or revoke (cancel) my permission?

Yes, but this permission will not stop automatically. The use of your personal health information will continue until you cancel your permission.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to continue being in this study.

When you withdraw your permission, no new health information which might identify you will be gathered after that date. Information that has already been gathered may still be

used and given to others. This would be done if it were necessary for the research to be reliable.

Is my health information protected after it has been given to others?

If you give permission to give your identifiable health information to a person or business, the information may no longer be protected. There is a risk that your information will be released to others. Including others outside of UAB, without your permission.

Voluntary Participation and Withdrawal

Whether or not you take part in this study is your choice. There will be no penalty if you decide not to be in the study. If you decide not to be in the study, you will not lose any benefits you are otherwise owed.

You are free to withdraw from this research study at any time. Your choice to leave the study will not affect your relationship with this institution. However, you should return to see the study doctor for safety reasons so you can be taken off the study drug and referred for follow-up care. Contact the study doctor if you want to withdraw from the study.

Cost of Participation

There will be no study drug cost to you for taking part in this study. The costs of your standard medical care will be billed to you and/or your insurance company in the usual manner.

Payment for Participation in Research

You will be paid $10 for participating in the form of cash. Ask the study staff about the method of payment that will be used for this study (e.g., check, cash, gift card, direct deposit).

Payment for Research-Related Injuries

UAB and Society for Pediatric Sedation have not provided for any payment if you are harmed as a result of taking part in this study. If such harm occurs, treatment will be provided. However, this treatment will not be provided free of charge.

Optional Research

We would like your permission to keep your private information (data containing personal information) collected in this study for future research. The future research may be similar to this study or may be completely different. Your private information will be stored indefinitely or until used.

Your private information will be labeled with a code that only the study doctor can link back to you. Results of any future research will not be given to you or your doctor.

You can take part in this study even if you decide not to let us keep your private information for future research.

If you give us permission now to keep your private information, you can change your mind later and ask us to destroy it. However, once we have analyzed your private information, we may not be able to take it out of our future research.

We may share your private information, so that others can use it in their research. Their research may be similar to this study or may be completely different. Once we have shared your private information with other researchers, we will not be able to get it back.

Future research use of your private information will be conducted in compliance with applicable regulatory requirements.

You will not find out the results of future research on your private information Allowing us to do future research on your private information will not benefit you directly.

The private information used for future research may be used for commercial profit. There are no plans to provide financial compensation to you should this occur.

Initial your choice below:

___ I agree to allow my private information to be kept and used for future research on sedation.

___ I do not agree to allow my private information to be kept and used for future research on sedation.

Questions

If you have any questions, concerns, or complaints about the research or a research-related injury including available treatments, please contact the study doctor. You may contact Dr. James Statler at 205-638-6098 or after hours by calling 205-638-9100 and asking to page Dr. Statler by name.

If you have questions about your rights as a research participant, or concerns or complaints about the research, you may contact the UAB Office of the IRB (OIRB) at (205) 934-3789 or toll free at 1-855-860-3789. Regular hours for the OIRB are 8:00 a.m. to 5:00 p.m. CT, Monday through Friday.

Legal Rights

You are not waiving any of your legal rights by signing this consent form.

Signatures

You are making a decision whether or not to have you and your child participate in this study. Your signature below indicates that you have read (or been read) the information provided above and agree to participate in this study. You will receive a copy of this signed consent form.

_____

Signature of Parent or Guardian Date

_____

Signature of Participant (Ages 14-18) Date

_____

Signature of Person Obtaining Consent Date

Reviewed by:

_____

Signature of Principal Investigator Reviewing Consent Document Date

Waiver of Assent

The assent of _____ (name of child/minor) was waived because of:
Age _____ Maturity _____ Psychological state of the child _____