PROTOCOL TITLE:

CHronic nonbacterial Osteomyelitis International Registry (CHOIR)

PRINCIPAL INVESTIGATOR:

Yongdong (Dan) Zhao, MD, PhD
Pediatrics, Division of Rheumatology
206-987-2682
Yongdong.zhao@seattlechildrens.org

Participating Sites Relying on SCH for IRB Review:
University of Washington

Boston Children's Hospital

Table of Contents

1.0 Objectives

Objective

The objective of the study is to establish a prospective disease registry for chronic recurrent multifocal osteomyelitis (CRMO)/chronic nonbacterial osteomyelitis (CNO) in order to investigate the natural history of the disease and the responses of patients to different clinical managements over 5 years.

Aims

Aim 1: To determine the clinical characteristics that are related to prognosis

Aim 2: To compare the effectiveness of various clinical managements in practice setting.

Aim 3: To characterize the long-term outcome of CNO

2.0 Background

Chronic nonbacterial osteomyelitis (CNO) is an autoinflammatory bone disease that mainly affects children and adolescents. Clinical presentations range from mild and sometimes limited unifocal disease to severe, chronically active or recurrent inflammation of multiple bones. The latter is referred to as chronic recurrent multifocal osteomyelitis (CRMO). Here we will use the term "CNO" to refer to the entire spectrum of this disease. CNO can be complicated by vertebral compression fractures, kyphosis, and leg length discrepancy when it is not recognized early or treated adequately. The diagnosis of CNO is made by excluding alternatives in the differential diagnosis including malignancy (leukemia, lymphoma, and primary or metastatic bone tumors), Langerhans cell histiocytosis, and infection. Clinical assessment in conjunction with serum inflammatory parameters and imaging studies, particularly magnetic resonance imaging (MRI), are crucial for the diagnosis and monitoring of disease activity of CNO[1].

Because of significant variation in clinical treatment practices among pediatric rheumatologists, standardized treatment regimens (consensus treatment plans, CTPs) have been developed within the Childhood Arthritis and Rheumatology Research Alliance (CARRA), a North American organization comprised of pediatric rheumatologists and researchers, for CNO patients with an NSAID-refractory course and/or with active spinal lesions[2]. These CTPs provide an opportunity for pediatric rheumatologists to conduct comparative effectiveness research on CNO through prospective data collection. CRMO/CNO workgroup is comprised of pediatric rheumatologists from North America as well as international colleagues who are interested in collaborating in CNO research. Furthermore, risk factors of severe disease have been described by Wipff et al. based on a large retrospective cohort study[3]. Their results may be validated by an independent prospective cohort study. To date, there has been only one prospective study on CNO since its first description in 1972[4]. Therefore, we propose to establish this international registry of patients with CNO to accomplish above goals. Long-term

outcomes of CNO remains unknown due to the lack of prospective study. It has been estimated that at least 50% of CNO patients continue to need medications for CNO during adulthood. Our study will collect the clinical data for up to 20 years and provide valuable data to characterize the long-term outcomes.

3.0 Inclusion and Exclusion Criteria

Potential subjects will be identified by electronic medical record searches, clinic schedules, inpatient lists, and word of mouth recommendation. A member of the study team will review the potential subject's medical records to confirm diagnosis, language, and care plan. If eligible, the caregiver and subject will be approached for participation. Eligibility will be confirmed with the caregiver verbally prior to obtaining informed consent.

Inclusion Criteria

- Presence of bone edema on STIR or T2 fat saturation sequence on MRI within 12 weeks of enrollment (optional)
- Whole body imaging evaluation (either WB MRI or bone scintigraphy) is optional
- Bone biopsy to exclude infection or malignancy when indicated

Exclusion Criteria

- History of or current malignancy
- Current infectious osteomyelitis
- Contraindication to the selected treatment agent

Adults who are unable to consent and lack a legal guardian, wards of the state, and prisoners will be excluded.

Caregivers will be reporting about the subject's medical history therefore they are not considered study subjects.

As this is a multicenter international study, sites will use local language such as Turkish, German, Italian, etc.

4.0 Study-Wide Number of Subjects

This is a multicenter registry with Seattle Children's being the lead site. Due to the rarity of CRMO, we expect to accrue up to 2000 subjects at all sites that gain IRB approval.

5.0 Study-Wide Recruitment Methods

Potential subjects at other sites may be enrolled in a similar manner as those enrolled at Seattle Children's Hospital with subjects being identified by electronic medical record searches, clinic schedules, inpatient lists, and word of mouth recommendation. If local

sites allow, flyers and social media may also be used. The coordinating center, however, does not have control over the recruitment methods used at the participating sites.

6.0 Multi-Site Research

Dr. Zhao is the study lead PI and is responsible for verifying that all sites have local IRB approval prior to study work being done. Dr. Zhao and/or his study team will be in charge of sending the most current versions of all regulatory documents to the sites once they are approved by Seattle Children's IRB.

Dr. Zhao will ensure that any study modifications are appropriately justified and receive Seattle Children's IRB approval prior to being implemented. Any study modifications and/or study closure instructions will be outlined in an email that will be sent to all sites. Emails will be sent using the "Delivery Receipt" to ensure that sites receive the emails. Sites will be asked to reply to the email ensuring that they understand the modifications. If there are questions, Dr. Zhao or the study team will be made available for a telephone call.

In addition, Dr. Zhao and his study team may plan to hold monthly phone calls to discuss study progress and interim results with the other sites. If a problem arises at sites, Dr. Zhao and the site PI will communicate via email and/or phone in order to resolve it.

7.0 Study Timelines

Study participation will commence when informed consent is signed and ends 20 years thereafter or sooner, if subject transitions to other practices.

We expect to approach all eligible subjects for participation therefore; recruitment and enrollment will be ongoing.

At this time, we plan to analyze the data periodically per the study aims above. Additional analyses may be added as IRB modifications in the future. Results of de-identified analyses may be shared with the clinical program team for quality improvement.

8.0 Study Endpoints

Primary Endpoint: Determine the effectiveness of commonly used medications in SOP for patients with CNO.

Clinical, laboratory and imaging results as well as PROs will be collected at each clinical visit after enrollment. Enrolled subjects will be stratified based on their past disease course, past treatment. Response to medication will be calculated based on previously described by Beck et al.[5] and Zhao et al.[2] at clinical visits prior to and after starting a new medication for comparison. Clinical disease activity score (CDAS) comprised of patient pain (0-10), patient global disease activity per report (0-10), clinical lesion count by physician, will be used to determine response. >=50% of reduction of CDAS is defined as favorable response.

Secondary Endpoint: Determine the risk factors for patients with NSAID-refractory CNO.

Patients will be classified as NSAID responders (significant improvement of pain, focal exam, ESR, CRP, imaging within 6 months of NSAIDs treatment), NSAID non-responders (requiring >6 weeks of systemic glucocorticoid, disease modifying anti rheumatic drugs, TNF inhibitors, bisphosphonate) based on treating physician's assessment. Baseline demographic, clinical, laboratory, imaging results will be compared between two groups and odds ratio will be calculated. There is no safety endpoint because it is an observational study that does not pose any risk to subjects.

9.0 Procedures Involved

This is a multicenter registry which involves the following procedures:

- Prospective Chart review: will be performed to collect data when subjects and caregivers come to Seattle Children's Hospital or a participating site for a scheduled clinic visit.
- Retrospective Chart review: may also be performed for visits which occurred prior to informed consent, as long as these are already available in the medical record.
- Safety Procedures: The required portions of the study are limited to ongoing review of the subject's medical record, and therefore carry very minimal risk.
- Questionnaires: Subject's will be asked several questions that are not in their medical chart such as their demographics, complete medical history, medications, etc.

No additional visits to the hospital will be requested as all study-related questionnaires will be done when subject comes to the site for a standard of care scheduled clinic visits. At Seattle Children's, subjects typically come to clinic at the every 3-12 months interval after diagnosis, however, this may vary at participating sites.

Access to standard care will not be delayed or precluded by participation in this registry.

The Case Report Forms should be filled out by the participating site study team and data transcribed into the electronic database in a timely manner. Each site will be able to view their own data, while Seattle Children's (coordinating center) will be able to view all of the uploaded limited data, which includes date of birth, partial postal close, date of death, and gender. If needed, for quality review, sites may be asked to send a scan of their completed Case Report Forms to the coordinating center using a secure file sharing systems or secure courier.

10.0 Data and Specimen Banking

All data collected in the data collection sheets for this study will be kept permanently for both the coordinating center and the participating sites. The study data will be stored in

electronic databases secured by password on secure drives. Caregivers and/or subjects may request that data be removed from the database by writing to the principal investigator. Study data will be used for IRB/Ethics Committee-approved research regarding CNO only.

Researchers from academic institutions (either SCH or other institutions) who want to use the de-identified study data (excludes date of birth, partial postal close, date of death, and gender) for other research questions must request the data from Dr. Zhao in writing, and provide proof of IRB approval for their project prior to receiving the data. Coded data without any linkers will be de-identified. Prior to release, a member of the study team will review the de-identified data to verify that no identifiers remain. A copy of any manuscripts, abstracts, or presentations resulting from a release of this kind will be required to be provided to Dr. Zhao. Dr. Zhao may refuse any request due to lack of scientific rigor, absence of appropriate data safeguards, lack of appropriate approvals, or other reasons.

11.0 Data Analysis/Management

We will use multivariable linear mixed-effects regression models, with each treatment as the dependent variable and person as the random effect, to estimate the average treatment effect, as well as the mean difference between groups, and any interactions as relevant to the particular Aim. The model will adjust for age, gender, lesion number and past medication use. The FDR will be used separately in each Aim to account for multiple pair comparisons, with FDR<0.1 considered significant.

Due to the rarity of CNO, we will enroll as many patients as possible to increase the power of this study to observe difference responses among treatments.

A random percentage of subject visits will be selected throughout the course of the study for data quality checks. A second study team member will review the data for accuracy and address any errors that are identified.

12.0 Confidentiality

Data will be kept in locked cabinets (paper forms) and/or in secure research drives and databases. Data will be identified with study codes and the link between study codes and subject identity will be kept separate from study data. Data being shared with other teams (see section 10) will be shared only as coded data without any linkers to preserve confidentiality.

Local sites will have data that are linked to a person's name, but the coordination center (Seattle Children's) will only receive coded samples without any links. Data (e.g. scans of the Case Report Forms) being sent and shared with the coordinating center will be sent using secure file sharing systems (eg: DropBox, REDCap) or by sending electronic copies via secure courier (eg: password protected CD or USB drive sent via tracked FedEx).

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

Due to the methods used to collect data, we do not expect adverse events related to the registry to occur. However, standardized severe adverse event (SAE) forms will be used to collect data for periodic update to the study group. Because this is an observational study, the medical decision is entirely determined by treating physician and not interfered by this registry.

14.0 Withdrawal of Subjects

Subjects may be withdrawn if they become ineligible for inclusion, such as a mis-diagnosis or subject becomes a foster child or prisoner. For subjects withdrawn for this reason, they (subject and/or caregiver) will be notified of the decision, and data collected prior to the withdrawal will be kept unless the caregiver otherwise requests that the data be removed from the study.

If withdrawn by the study team, further data will not be obtained past the date of withdrawal, but existing data will be kept and analyzed.

If withdrawn at the caregiver or subject's request, they will be asked if they would like for existing data to be removed from the database. If not, then existing study data will be kept and analyzed. If yes, data will be removed from the database at the caregiver and/or subject's request. In either case, additional data will not be collected.

If withdrawn from the study, the decision regarding existing data will be documented and filed with the original source documents. If the data is to be removed from the study, this work will also be documented.

15.0 Risks to Subjects

Rare, temporary, mild risk of emotional distress: It is possible that a subject or caregiver may experience emotional distress when completing the study-related questionnaires. Subjects and caregivers will be informed that they can skip any questions that they do not want to answer. In addition, there is a risk of breach of confidentiality.

The study has no procedures that would carry unforeseeable risk to subject or risks to an embryo or fetus.

16.0 Potential Benefits to Subjects

There is no benefit to participating in the study. This is a registry and does not provide additional treatment beyond what subjects would receive as part of their standard of care regimen.

17.0 Vulnerable Populations

Cognitively Impaired Adults

In the event that a cognitively impaired adult is enrolled, the subject will be withdrawn if they appear to be unduly distressed.

For adult subjects), a provider (MD, ARNP) of the research team will assess whether or not the subject is able to consent for himself/herself. This assessment may include but not be limited to: 1) results of prior educational or cognitive testing performed for medical care or education, 2) clinical assessment from interaction with the adult subject, 3) presence of legal guardianship of another adult or agency on record. If an adult subject lacks a legal guardian, and if his/her capacity to consent is at all unclear, then the subject will not be enrolled. Subjects identified in this situation during the course of screening for the study may be referred to Social Work as part of their routine clinical care, as lack of a legal guardian is an important issue for a subject's safety and well-being during transition to adulthood.

Children

The research presents no more than minimal risk, as the research involves collection and analysis of data collected on paper forms. The information collected will not affect the subject's clinical care.

Pregnant Women

Data collection does not present any particular risk to pregnant women or the fetus, so they will be included in the research.

18.0 Community-Based Participatory Research

N/A

19.0 Sharing of Results with Subjects

Results of analyses performed for study purposes will not be shared with the subject or their caregiver(s).

20.0 Setting

The research will take place at Seattle Children's and the following participating sites:

Sites within USA:

Ann & Robert Lurie Children's Hospital of Chicago, Chicago, IL, USA

Boston Children's Hospital, Boston, MA, USA

Children's Healthcare of Atlanta, Emory University, Atlanta, GA, USA

Children's Hospital of Pittsburgh, Pittsburgh, PA, USA

Children's Hospital of The King's Daughters, Norfolk, VA, USA

Children's Mercy Kansas City, MO, USA

Colorado Children's Hospital, CO, USA

Columbia University, New York City, NY, USA

Duke Children's Hospital, Durham, NC, USA

Floating Hospital for Children at Tufts Medical Center, Boston, MA, USA

Goryeb Children's Hospital, Morristown, NJ, USA

Hospital for Special Surgery, New York City, NY, USA

Iowa Children's Hospital, Iowa City, IA, USA

Joseph M Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, NJ, USA

Levine Children's Hospital, Charlotte, NC, USA

Lurie Nationwide Children's Hospital, Columbus, OH, USA

Mattel Children's Hospital UCLA, Los Angeles, CA, USA

Massachusetts General Hospital, Massachusetts, WA, USA

Mayo Clinic, Rochester, WA, USA

Nationwide Children's Hospital, Columbus, OH, USA

Riley Children's Hospital, Indianapolis, IN, USA

Seattle Children's Hospital, Seattle, WA, USA

Stanford Children's Health, Stanford University, Palo Alto, CA, USA

Stony Brook Children's Hospital, Stony Brook, NY, USA

Texas Children's Hospital, Houston, TX, USA

Tufts University, Boston, MA, USA

University of California in San Francisco, San Francisco, CA, USA

University of Iowa Carver College of Medicine, Iowa City, IA, USA

University of Louisville, Louisville, KY, USA

University of North Carolina, Chapel Hill, NC, USA

University of Utah, Salt Lake City, UT, USA

University of Vermont Medical Center, Burlington, VT, USA

International sites:

Asia & Pacific,

Schneider Children's Medical Center of Israel, Petach Tikva Israel and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, **Israel**

Nanjing Children's Hospital, Nanjing, Jingsu State, **China**

Royal Children's Hospital, Melbourne, **Australia**

Sidra Medical & Research Center, Ar-Rayyan, **Qatar**

St. Petersburg State Pediatric Medical University, Saint Petersburg, **Russia**

Africa,

Red Cross Clinic, Cape Town, **South Africa**

Mansoura University, Mansoura City, **Egypt**

Europe,

Palacky University Olomouc Institute of Molecular and Translational Medicine, Olomouc, **Czechia**

Motol University Hospital, Prague, **Czechia**

Bristol Royal Hospital for Children, Bristol, UK

Hacettepe University, Ankara, **Turkey**

Sağlık Bilimleri Üniversitesi Ümraniye Eğitim ve Araştırma Hastanesi, Istanbul, **Turkey**

Children's Hospital Dresden, University Medical Center Carl Gustav Carus, TU Dresden, Dresden, **Germany**

Dr. von Hauner Children's Hospital, Ludwig-Maximilians-University, Munich, **Germany**

Pediatric Rheumatology, Olgahospital, Bismarckstr. 8, Stuttgart, **Germany**

Vivantes Children's Hospital in Friedrichshain, Berlin, **Germany**

Anna Meyer Children's Hospital, University of Florence, **Italy**

Bambino Gesù Children's Hospital, Rome, **Italy**

Clinica Pediatrica, Università degli Studi di Brescia, **Italy**

Dept. of Woman and Child Health, Padua, **Italy**

Division of Rheumatology, Ospedale Pediatrico Bambino Gesù IRCCS, Rome, **Italy**

Gaetano Pini Hopital in Milano, Milan, **Italy**

University of Genoa and Istituto Giannina Gaslini, Genoa, **Italy**

University of Palermo, Palermo, **Italy**

Bristol Royal Hospital for Children & Royal National Hospital for Rheumatic Diseases, **UK**

Central and North West London NHS Foundation Trust, **UK**

Great Ormond Street Hospital, London, **UK**

Institute of Translational Medicine, University of Liverpool, Liverpool, **UK**

Alder Hey Children's NHS Foundation Trust Hospital, Liverpool, **UK**

Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle, **UK**

Oxford University Hospitals NHS Foundation Trust, Oxford, **UK**

Latin America,

Departamento de Enfermedades Infecciosas e Inmunología Pediátrica

Escuela de Medicina, **Pontificia Universidad Católica de Chile**

North America,

McMaster Children's Hospital, Hamilton, Ontario, **Canada**

The Hospital for Sick Children and University of Toronto, Toronto, ON, **Canada**

University of British Columbia, Vancouver, BC, **Canada**

University of Calgary, Calgary, Alberta, **Canada**

21.0 Resources Available

The study team will be comprised of a clinician who is involved in the provision of the routine clinical care of patients with CNO, and researchers who are involved in the collection of data for the study. The study team has dedicated office space at Seattle Children's which may be used for the study data collection and analysis. Additional statistician support may be obtained to support future study analyses and these people would be added to the IRB staff list as a modification.

Chart reviews may be performed by any member of the study team after they receive appropriate study training. In addition, clinician members of the study team will be available to any chart reviewer who has questions or needs additional support for data collection.

Study team members are already in clinic and obtaining informed consent for this study will present a small increase in work over existing efforts.

Recruitment may take up to 6 hours per week and chart review/data collection may be done over approximately 20 hours per month.

Existing study team member work stations, printers, and phones will be used to support the study. Additional materials may be purchased as needed.

Training materials (eg: slide deck, handouts) will be provided with a copy of this protocol to study team members to review, either in self-directed learning or by individual or group training sessions.

22.0 Prior Approvals

N/A

23.0 Recruitment Methods

Potential subjects will be identified by electronic medical record searches, clinic schedules, inpatient lists, and word of mouth recommendation. Once identified, the study team member will review the medical record (if available) to confirm diagnosis, care plan, and language. If the subject seems eligible, then the subject and caregiver(s) will be approached for participation via phone, mail, email, or at their next clinic visit.

In addition, potential subjects may self-identify through flyers posted on patient advocacy groups on social media (e.g. Facebook, Instagram, Twitter), and Seattle Children's current research studies website and e-newsletters.

Medical Chart

Once a potential subject is identified, they may be mailed or emailed an introduction packet consisting of an introduction letter, consent and/or assent, and a response form before their next scheduled visit. If they do NOT want to be approached about the study at their next scheduled visit or via phone follow-up, the caregiver can indicate as such on the response form and can mail it back to the study team or respond via email. If the study team does not receive a response, a study team member may give the caregiver and potential subject a call to determine whether the subject and caregiver would like to hear more about the study, and will abide by the response given. If not reached via phone, the study team member will approach the potential subject and caregiver(s) in-person at the next scheduled clinic visit or inpatient visit.

Via mail/e-mail

If possible, Seattle Children's may send potential subjects and their caregivers an introduction letter, consent and/or assent forms, and a response form prior to a clinic visit, to allow the caregiver and subject to take time to consider the study. This would include study team contact information so the potential subject and caregiver(s) would have the choice of doing nothing, calling us, or sending the response form back via mail or e-mail to indicate their interest in the registry.

If interested, we may call the family to ask if there are questions and confirm their next scheduled visit appointment.

Via in-person

A member of the care team (eg: MD, ARNP, RN, etc.) will ask the family if they would like to speak to research. If yes, then the study team member will tell the family more about the research and complete the informed consent process if they are interested. If the family would like more time, they may complete the consent process by mail and return copies by fax, email, or mail to the study team. Please see section 29.0 below for details about the consent process.

Via social media

An information flyer will be posted on patient advocacy groups on social media which would include the phone number and email an interested subject could use to get in touch with the study team. We would then follow similar steps as those listed above.

Subjects will not be paid for participation in the study.

24.0 Use of Social Media

Study flyers on social media, such as Facebook, will be used as recruiting methods for the registry. The use of social media offers some key advantages compared to traditional recruitment methods (e.g. physician referral, TV and radio advertisement, etc) as it provides the ability to reach a diverse and broad audience, in particular, patients with CNO due to its rarity.

To protect the privacy and confidentiality, a phone number and email will be provided for interested subjects to get in touch with the study team. In the posting, potential subjects will be encouraged to contact the study team rather than replying directly to the post.

The materials used in social media as well as verbiage will be submitted to the IRB prior to implementation.

25.0 Local Number of Subjects

Due to the rarity of CNO, we expect to accrue as many subjects as possible at Seattle Children's with a minimum of at least 5 subjects.

26.0 Provisions to Protect the Privacy Interests of Subjects

When approaching subject's in-person, the study team will ask the caregiver and/or their caregiver if they would be interested in hearing about research. If yes, the study team will review the consent form with them. If no, the study team will thank the subject and/or caregiver for their time. The subject and their caregiver will be provided with the consent form in case they would like to read over it at their own pace at home.

It will be stressed that study participation is voluntary and they can say agree or disagree to take part in the registry without any repercussions to their care.

27.0 Compensation for Research-Related Injury

The standard language for compensation applies; this study does not provide direct benefit to subjects.

28.0 Economic Burden to Subjects

There are no costs to participating in this study.

29.0 Consent Process

Whenever possible, informed consent/assent will be obtained when the subject expresses interest or attends a clinically scheduled telephone, telehealth, outpatient visit or inpatient stay. Consent/assent will be obtained in a private outpatient exam room, inpatient room, conference room, consultation room, or a setting where the subject is ensured privacy and is free from potential coercive influences. The study team member presenting the study to a potential subject will give the subject the opportunity to ask questions either in private or in the presence of their caregiver(s). The study team member will allow enough time to make an informed assessment of the subject's comprehension of the details of the study. Caregivers and subjects may take as much time as they need to decide if they would like to participate and may request a later follow up telephone conference with a member of the study team to provide informed consent.

We will be following SOP HRP – 090 to conduct the consent conference. If a member of the study team who is obtaining informed consent is also the subject's treating provider, then the provider will remind the family of the voluntary nature of the research, and will specifically indicate that whether or not the subject participates in the study, it will not affect the subject's care.

Consent discussions will take approximately 20 minutes to complete, but more time is available should the family need it. Follow-up to the consent discussion could be conducted remotely over the telephone, should the family need more time to think about participation.

Non-provider members of the study team are available to obtain informed consent should any conflicts arise that may make it difficult for a family to decline participation in the study.

Methods to confirm understanding will vary depending on the family's preferences and skills, and may include verbal summaries, pictures, asking questions, repeat back of the content, and other methods.

Participating sites will be responsible for their own consent documents. The coordinating center will not provide templates.

When consenting remotely, every effort will be made to deliver the consent/assent forms to the individual by mail, fax, email well ahead of the scheduled conference so they have the opportunity to review the consent prior to the consent conference. The study team will verify the identities via the display of picture ID or the date of the subject's last clinic/hospital visit and verify that the consent conference location is private to help ensure privacy and confidentiality. Next, the study team will review the consent/assent forms with the subject and/or legal guardian and will provide opportunities for questions to ensure comprehension of the details of the study. If the subject agrees to participate, the study team will ask the subject if they would like to electronically or physically sign the consent/assent form which are both identical in content.

If the subject and/or legal guardian decides to electronically sign the consent/assent form, they may either use 1) DocuSign or 2) REDCap e-consent. An electronic copy of consent/assent forms will be saved under password-protected sharedrive. If there are addition information (i.e. new risk information), forms will be updated and existing subjects will be re-consented for continuous participation.

To conform to the federal eSIGN law, the following will be added.
Consent/Permission form statement:
"If using electronic documentation: You agree this form and any later updates to this form and notices provided in connection with this study may be provided to you in an electronic version. You agree that you are able to electronically receive, review, and save a printed or electronic copy of this form containing your signature. We and you agree to electronically sign this form. We and you agree that our actions to electronically sign this form document your informed consent. We and you agree that our electronic signatures have the same meaning and effect as handwritten signatures. You understand that you can request a paper form if you would prefer to use a paper consent form."

Assent form statement:
"If using electronic documentation (this means using something like a computer or phone instead of paper): You agree this form and any later updates to this form and notices provided in connection with this study may be provided to you in an electronic version. You agree that you are able to electronically receive, review, and save a printed or electronic copy of this form containing your signature. We and you agree to electronically sign this form. We and you agree that our actions to electronically sign this form document your assent. We and you agree that our electronic signatures have the same meaning and effect as handwritten signatures. You understand that you can request a paper form if you would prefer to use a paper assent form."

1) the study team will sign into Seattle Children's DocuSign account through Seattle Children's web portal. The study team will subsequently type in the emails of the study team, subject and/or legal guardian and assign the portions of the document to be signed by each party. After submitting this form, an email will be sent to the designated individual(s). The process of transmitting, receiving, and signing the consent/assent forms via DocuSign may take 5-10 minutes and no audio and/or video will be recorded.

The individuals receiving the email may sign the consent/assent form at the time of reception or save these documents to sign at a later time. The sent email will contain a link, which will allow individuals to navigate to the consent/assent form on DocuSign's website. No sign up is required to sign the document. When signing the document, the individuals receiving the email are required to fill in their portions, which includes typing in their full name, current date, current time, and their signature. Computers or smartphones can be used to do this process. No additional or advanced knowledge besides knowing how to use a computer or smartphone is required to use DocuSign. Many young children may have their own smartphones and may use computers for portions of their school curriculum, thus young children and adults should have no difficulty with this process. The study team will be present for questions about signing the document(s) if the participant and/or legal guardian is signing the document(s) immediately. If the subject and/or legal guardian is signing the document later, the study team will be available by email or phone. After the subject and/or legal guardian have signed the consent/assent forms, the study team will fill out their assigned portions of the document and make a note on the consent form of when the consent conference took place and that it was by phone or video conference (so as to explain the difference in dates). After all parties have signed the document, DocuSign will provide a copy of the signed document to all parties. The study team will saved the copy of the signed document into the study's directory in Seattle Children's file share. 2) The REDCap e-Consent Framework provides standardized tools to obtain consent and store consent documentation with a certification screen and a storage function which automatically generates a PDF of the signed form stored within the project. The 'Auto-Archiver + e-Consent Framework' survey option adds two things to the typical survey-taking process. Before a participant completes the survey, an extra certification page is added to the end of the survey that displays an in-line PDF copy of the document in which they will be asked to confirm that all information in the document is correct. The survey will not be considered complete until they fulfill the certification step. Upon completion of the survey, a static copy of their responses in the form of a consent-specific PDF will be stored in the project's File Repository. The consent-specific PDF will have the values of the e-Consent Framework Options inserted at the bottom of each page in the PDF.

These values (i.e., name, etc.) are added to the PDF as extra documentation of the identity of the person who is consenting. The participant will open the survey and read through the consent form. When they get to the bottom, they will have the opportunity to fill in their information and sign their name if they agree to participate. They will select "Next Page" and a read-only copy of the consent will be generated that they can review, download, and/or print. At the bottom of the page, they will need to select "I certify that all the information in the document above is correct, and I understand that signing this form electronically is the equivalent of signing a physical document." Once this is selected they will be able to submit the survey/consent/assent.

The study team will use REDCap survey composition function and type in the emails of the subject and/or legal guardian and assign the portions of the document to be signed by each party. After submitting this form, an email will be sent to the designated individual(s). The process of transmitting, receiving, and signing the consent/assent forms via REDCap may take 5-10 minutes and no audio and/or video will be recorded. The individuals receiving the email may sign the consent/assent form at the time of reception or save these documents to sign at a later time. The sent email will contain a link, which will allow individuals to navigate to the consent/assent form on REDCap website. No sign up is required to sign the document. When signing the document, the individuals receiving the email are required to fill in their portions, which includes typing in their full name, current date, and their signature. Computers or smartphones can be used to do this process. The study team will be present for questions about signing the document(s) if the participant and/or legal guardian is signing the document(s) immediately. If the subject and/or legal guardian is signing the document later, the study team will be available by email or phone. After the subject and/or legal guardian have signed the consent/assent forms, REDCap will automatically save a copy of the signed document to the project. The study team will saved the copy of the signed document into the study's directory in Seattle Children's file share.

If the subject and/or legal guardian decides to physically sign the consent/assent forms, the study team will either send the forms by mail to the designated physical address or by email to the provided email addresses. After signing the forms, the subject and/or legal guardian will send it back to the study team via mail or scan/photograph the signed form to forward by email attachment. *The research team member will sign the form on the day that it is received and make a note on the consent form of when the consent conference took place and that it was by phone or video conference (so as to explain the difference in dates).*

Non-English Speaking Subjects

At Seattle Children's, subjects who speak other languages will be approached for the study. Some subject-facing study materials have been translated into Spanish, Arabic, Bengali, Russian and simplified Chinese and submitted as a study modification following initial IRB approval of English documents. Additional subject-facing study materials will be translated and submitted as study modifications when available. An interpreter (in-person, phone, or tablet) will be made available during the visit. External sites will be responsible for obtaining their own translations.

Partial Waiver of HIPAA

We are requesting a waiver HIPAA for pre-screening purposes only. This waiver would allow us to review the medical record prior to approaching potentially eligible subjects for participation to confirm diagnosis, language, and care plan. This approach would allow us to only approach subjects for participation who are likely to be eligible, and

would prevent the study team from causing an unnecessary burden for families who are not eligible for the study.

Identifiable screening data will only be kept intact until the eligibility has been confirmed. If ineligible, the reason for ineligibility will be retained as coded data for analysis purposes, but will not be identifiable (eg: coded without any linkers). If eligible, this data will be incorporated into data collected on the data collection form. Electronic screening data will be kept on secure research shared drives which are accessible to the study team and/or on secure electronic databases (eg REDCap) which limits access by username and password. Paper screening data will be kept in secured offices in secure cabinets. Paper screening data for ineligible subjects will not have any identifiers on the worksheet, only study codes. PHI accessed or collected during screening will not be reused nor disclosed to other people or entities except as required by law or research regulations. Without the PHI (medical record number and name), we would be unable to access the information needed to confirm eligibility. Without the waiver of HIPAA, completing the HIPAA authorization would confer a larger burden to families of ineligible subjects than the eligibility review itself.

Waiver of consents for adults who have transitioned care out of Seattle Children's Hospital

Due to the rarity of this disease, we need to maximize data collection on all eligible patients including those we may have not been able to consent during their care within Seattle Children's. Criteria for this group are: age of 18 or older at the time of data collection, never consented to CHOIR, and confirmed transition as documented in clinical or other note. No patient contact will be initiated, and no questionnaire will be administered. The research could NOT practicably be carried out without the waiver or alteration because this group of patients might have moved or not reachable due to outdated contact information within our system. All eligible patients must also be included in the study for the results to be meaningful. Obtaining consent from patients whose data will be analyzed is impracticable due to the number of patients involved, the timespan over which the data was generated, and the subsequent movement of those patients. The waiver or alteration will NOT adversely affect the rights and welfare of the subjects because there is no intervention or patient contact required. Only de-identified data will be collected from previous care notes. Information that could put subjects or their families at harm (e.g., affect eligibility for insurance, employability, stigmatization) or that would alter or affect the subject's care will not be collected. Any publication of presentation of research results would be done in a manner that would never reveal an individual's identity either directly or indirectly.

Subjects who are not yet adults (infants, children, teenagers)

Subjects enrolled at Seattle Children's Hospital under the age of 18 will be considered minors for this study and must have a legal caregiver provide informed consent in order

to participate. Parental permission will be obtained by one caregiver, as this is a minimal risk study without prospect of benefit. At all other participating sites, the local site PI will document consent, assent, and parental permission based on their local laws and regulations.

Assent will be obtained from subjects who are age 7 years or greater and have cognitive function and decision making skills function equivalent to a 7 year old or better. Therefore, a subject older than 7 years who has a developmental delay, but is still functioning on par with a typically developing 7 year old will still be approached for assent. Functional level will be assessed by the caregiver(s) and investigator if this is in question. If there is not consensus between caregiver(s) and investigator in this regard, then the subject will be approached for assent. Assessment may be done using different sources of information, including caregiver(s)' report of subject's typical ability at home, available testing performed for medical or educational care, provider's assessment of the subject's ability.

For subjects age 7 – 12, assent will be documented by the subject signing his/her name on the simple assent form. Subjects age 13 – 17, will sign the assent/consent form. If cognitively able to assent but physically unable to sign, then assent will be obtained verbally or by the subject's usual communication method, and witnessed by an adult person who is not the study team member obtaining consent (eg: other Children's staff member). The witness shall sign their name on the assent form.

For all subjects who are eligible to provide assent, the study team member will review the assent form in person with the subject. This may include reading portions of the form aloud, summarizing portions of the form, or other methods to explain the decision to the subject. If the subject agrees to participate, then the assent form will be signed as above.

Subjects who reach the age of majority and are their own legal guardian as of the 18th birthday will be re-approached for consent. If they decline ongoing participation, their existing information will be kept, but further data collection will be stopped.

Subjects who reach of the age of majority and are not their own legal guardian will be re-consented by their legal guardian unless the legal guardian has a court order that extends their guardianship past the age of majority.

If the child who reaches the age of majority is legally their own guardian, but is cognitively unable to provide informed consent, then they will not be eligible to continue in the study, and their participation will be complete. In this case, existing data will be kept, but further data collection will be stopped.

Cognitively Impaired Adults

Cognitively impaired adults are eligible to participate only if they have a legal guardian who is able to provide informed consent. People who are unable to provide informed

consent but lack another legal guardian will not be enrolled. If a cognitively impaired adult is functioning at the level of a typical 7 year old or better, then assent will be obtained and documented as above.

Caregivers of eligible children who themselves have cognitive impairment who are still their child's legal guardian will be able to provide consent if they are able to understand the consent process and make a decision. If this is at all unclear, then the child will be considered ineligible and the child will not be enrolled.

Adults Unable to Consent

HRP-013 will be followed when enrolling adults who are unable to consent.

Consent for use of HUD

N/A

30.0 Process to Document Consent in Writing

We will be following "SOP: Written Documentation of Consent (HRP-091)."

31.0 Drugs or Devices

N/A

32.0 Good Clinical Practice

N/A

33.0 References

1. Hofmann SR, Schnabel A, Rosen-Wolff A, Morbach H, Girschick HJ, Hedrich CM. Chronic Nonbacterial Osteomyelitis: Pathophysiological Concepts and Current Treatment Strategies. *J Rheumatol* 2016.
2. Zhao Y, Wu EY, Oliver MS, Cooper AM, Basiaga ML, Vora SS, Lee TC, Fox E, Amarilyo G, Stern SM, Dvergsten JA, Haines KA, Rouster-Stevens KA, Onel KB, Cherian J, Hausmann JS, Miettunen P, Cellucci T, Nuruzzaman F, Taneja A, Barron KS, Hollander MC, Lapidus S, Li SC, Ozen S, Girschick H, Laxer RM, Dedeoglu F, et al. Consensus Treatment Plans for Chronic Nonbacterial Osteomyelitis Refractory to Nonsteroidal Anti-Inflammatory Drugs and/or with Active Spinal Lesions. *Arthritis Care Res (Hoboken)* 2017;Nov 7:doi: 10.1002/acr.23462. [Epub ahead of print].
3. Wipff J, Costantino F, Lemelle I, Pajot C, Duquesne A, Lorrot M, et al. A large national cohort of French patients with chronic recurrent multifocal osteitis. *Arthritis Rheumatol* 2015;67:1128–1137.
4. Giedion A, Holthusen W, Masel LF VD. Subacute and chronic "symmetrical" osteomyelitis. *Ann Radiol (Paris)* 1972;15:329–42.

5. Beck C, Morbach H, Beer M, Stenzel M, Tappe D, Gattenlöhner S, et al. Chronic nonbacterial osteomyelitis in childhood: prospective follow-up during the first year of anti-inflammatory treatment. Arthritis Res Ther 2010;12:R74