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Comparative Effectiveness and Complications of Intravenous Ceftriaxone Compared with Oral Doxycycline in Lyme Meningitis in Children (A multi-center prospective cohort study)

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ARTICLE SUMMARY

Introduction:

Lyme disease is the most common vector-borne disease in the Northern hemisphere with more than 400,000 new cases in the U.S annually. Lyme meningitis is an uncommon, but potentially serious clinical manifestation of Lyme disease. Intravenous ceftriaxone had been the first-line treatment for Lyme meningitis, but is associated with a high rate of complications. Although efficacy and effectiveness (or real world evidence) data for oral doxycycline are limited, practice guidelines were recently expanded to recommend either oral doxycycline or ceftriaxone as first-line treatments for Lyme meningitis. Our goal is to compare oral doxycycline to intravenous (IV) ceftriaxone for the treatment of Lyme meningitis on short-term recovery and long-term quality of life.

Methods and analysis:

We are performing a prospective cohort study at twenty U.S. pediatric centers located in diverse geographic range where Lyme disease is endemic. The clinical care team will make all antibiotic treatment decisions for children with Lyme meningitis, as per usual practice. We will follow enrolled children for six months to determine time of acute symptom recovery and impact on quality of life.

Ethics and dissemination:

Boston Children's Hospital, the single Institutional Review Board (sIRB), has approved the study protocol with the other 19 enrolling sites as well as the Utah Data Coordinating Center (DCC) relying on the Boston Children's Hospital sIRB.

Dissemination:

Once the study is completed, we will publish our findings in a peer reviewed medical journal.

The work was supported by NIAID R01A151180-02A1 (Nigrovic).

Strengths and limitations of this study:

-The prospective pragmatic design allows for standardized collection of patient-reported clinical symptoms, treatments and outcomes for children with Lyme meningitis.

- Daily surveys delivered electronically accurately capture symptoms and treatments while allowing remote participation, reducing burden on patients and families.

-Inclusion of 20 centers located in Lyme disease endemic areas in the Northeast, Mid-Atlantic and Upper Midwest regions of the US will capture a clinically and geographically diverse group of children with Lyme meningitis.

- Qualitative interviews will capture patient and parent preferences about Lyme meningitis treatment.

-As antibiotic treatment decisions for Lyme meningitis are likely related to disease severity, we will use propensity score methods to adjust for confounding factors.

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Introduction

With more than 400,000 new cases of Lyme disease each year in the U.S., children are commonly affected.[1,2] Lyme meningitis, an uncommon potentially serious clinical manifestation of acute Lyme disease, presents with headache, fever and fatigue. Previously, an intravenous antibiotic (ceftriaxone) was the recommended first line treatment for Lyme meningitis, but it is associated with a high rate of complications related either to the long-term intravenous catheter placed for medication delivery or to complications from the antibiotic itself.[3] Based on European trials conducted in adults[4,5] and a small observational study of children,[6] some clinicians have begun treating Lyme meningitis in children with oral doxycycline, avoiding the complications associated with intravenous ceftriaxone and reducing health care costs. This comparative effectiveness study will address three critically important clinical questions: *1) How does treatment with oral doxycycline compare with intravenous (IV) ceftriaxone for time to resolution of symptoms in children with Lyme meningitis? 2) Do children have equivalent six-month post-treatment quality of life after treatment with either doxycycline or ceftriaxone? 3) What are patient and parent preferences regarding treatment decisions?*

While previous Lyme disease clinical guidelines recommended intravenous (IV) ceftriaxone as first-line treatment for Lyme meningitis,[7] recent updates (Infectious Disease Society of America (IDSA) guideline, Clinical Infectious Diseases, 2021[8–10] recommend *either* doxycycline *or* ceftriaxone as appropriate first-line treatment. Although most children with Lyme meningitis were previously treated with IV ceftriaxone, clinical experience with oral doxycycline is growing.[6,11] As approximately one quarter of children treated with ceftriaxone have treatment complications,[3] an *equally effective oral antibiotic could lower complication rates, reduce costs, and improve quality of life*.

Oral doxycycline has clear advantages compared with IV ceftriaxone because it avoids use of a peripherally inserted central catheter (PICC) to deliver multiple weeks of treatment. In a previous study, 26% of children with Lyme meningitis treated with ceftriaxone had at least one treatment complication related to either the PICC line (e.g. accidental dislodgment, thrombosis, infection) or an adverse reaction to the parenteral antibiotic.[3] Parenteral therapy is more costly than oral therapy due to the additional costs for IV medication administration either inpatient or at home, as well as additional medical visits for treatment monitoring and complications. The *impact* of demonstrating the effectiveness *of doxycycline for the treatment of Lyme meningitis would be to lower complication rates, improve quality of life, and reduce treatment costs*.

The evidence supporting doxycycline as an oral alternative for the treatment of Lyme meningitis is based on three older efficacy studies, primarily in adults with European strains of *Borrelia* (e.g. *B. garinii* and *B. afzelii*). [4,5,12] A more recent retrospective study of 38 U.S. children with Lyme meningitis treated with oral doxycycline showed resolution of symptoms but lacked a control group.[6] Three systematic reviews of the literature on treatment of pediatric neuroborreliosis concluded that the current evidence is insufficient to recommend doxycycline *instead* of beta-lactam antibiotics.[13–15] Factors limiting the rigor of the previous studies include 1) the small study populations of children with Lyme meningitis, 2) retrospective chart review methods prone to missing data and residual confounding due to unmeasured factors, 3) lack of outcome measures specific to Lyme meningitis, and 4) difficulty assessing resolution of symptoms with granularity. Until rigorous and well-controlled studies demonstrate definitively oral doxycycline is not inferior to IV ceftriaxone, we cannot conclude that doxycycline is as effective as IV ceftriaxone for the treatment of pediatric Lyme meningitis.

We previously captured child and parent preferences about Lyme meningitis treatment.[16] After watching a video about Lyme meningitis treatment choices that included relevant information about

the anticipated benefits and risks of treatment, parent-child dyads were asked a series of questions to understand treatment preferences. Interestingly, 60% of caregivers expressed a strong preference for one treatment option over the other (40% would always prefer IV medication and 20% would always prefer oral medication), despite believing that both treatments were effective and safe. Perceived efficacy and treatment preference were weakly correlated ($r = 0.29$, $p = 0.01$) and perceived safety and treatment preference were moderately correlated ($r = 0.47$, $p < 0.0001$). This observed discordance requires further exploration to inform the shared decision-making process. As such, patient/parent and clinician values around treatment options, including acceptable risks and outcomes, to inform shared decision-making about Lyme meningitis treatments.

To accomplish these goals, we are conducting a comprehensive pediatric Lyme meningitis study, enrolling children at 20 U.S. centers located in regions of the U.S. where Lyme disease is endemic. Treatment decisions will be made by the child's treating clinical team and we will obtain informed consent to collect patient-reported outcomes over the following six months. We will enroll 250 children with Lyme meningitis to determine whether oral doxycycline is non-inferior to intravenous (IV) ceftriaxone for the treatment of Lyme meningitis in children. We will interview patients/parents and clinicians to gain a nuanced understanding of the factors that shape treatment decisions. The overall impact of this study will be to inform best practices for treatment of children with Lyme meningitis, accounting for the preferences of key stakeholders. We propose the following three aims.

Aim 1. Comparative effectiveness for symptom resolution): *To compare oral doxycycline with IV ceftriaxone for time to resolution of symptoms in children with Lyme meningitis using the Pediatric Lyme Meningitis Symptom Measurement instrument.* We hypothesize that oral doxycycline is non-inferior to IV ceftriaxone for time to resolution of Lyme meningitis symptoms.

Aim 2. Comparative effectiveness for six-month post-treatment quality of life): *To compare oral doxycycline with IV ceftriaxone on six-month post-treatment quality of life in children with Lyme meningitis using the Pediatric Quality of Life Inventory.* We hypothesize that oral doxycycline is non-inferior to IV ceftriaxone for 6-month quality of life.

Aim 3. Drivers of treatment decisions and treatment preferences): *To evaluate factors affecting treatment decisions and patient and parent treatment preference using a mixed methods design (pre- and post-treatment surveys as well as exit interviews.* We hypothesize that some patients and parents will prefer doxycycline treatment based on a better side effect profile, but others will prefer IV ceftriaxone because they believe IV medication works better. A nuanced understanding of these differing preferences will allow for Aim 1/2 results to be disseminated and incorporated into clinical practice more effectively.

Methods and Analysis

Study Design

We are conducting a prospective observational study of children with Lyme meningitis at twenty centers located in Lyme disease endemic areas of the Northeast, Mid-Atlantic and Upper Midwest (**Supplemental Figure 1**) using STROBE standards.

Patient Selection and Inclusion/Exclusion Criteria

Study staff started screening for potentially eligible patients on July 2, 2022 (study start date varied by center). Staff screen available medical records as well as laboratory databases. The clinical team will confirm study eligibility. Recruitment will happen over 5 years.

Inclusion criteria are:

1. Age 1 year to ≤ 21 years
2. Definite or probable meningitis:
   - Definite: meningitis defined as cerebrospinal (CSF) white blood cell (WBC) count ≥ 10 cells per high power
   - Probable: Clinical diagnosis of meningitis
3. Positive two-tiered Lyme disease serology obtained within seven days of enrollment:
   - Standard two-tier testing: Positive or equivocal Lyme disease enzyme immunoassay (EIA followed by a positive supplemental immunoblot
   - Modified two-tier testing: Two Lyme disease EIA tests that are positive, equivocal, or a combination of both

Exclusion criteria are:

1. Treatment plan does not include either oral doxycycline or IV ceftriaxone
2. More than 7 days of antibiotic treatment for Lyme meningitis prior to enrollment
3. Conditions that would preclude the assessment of the Pediatric Lyme Meningitis Symptom Survey (i.e. patient/parent reporting of headache, neck pain, sensitivity to light, fever)
4. Inability to complete study activities in either English or Spanish
5. Known pyogenic bacterial meningitis at the time of enrollment

Definition of Primary and Secondary Outcomes

Aim 1 Outcome: The primary outcome is time to resolution of Lyme meningitis symptoms using the Pediatric Lyme Meningitis Symptom Measurement Instrument (**Figure 1**), a five-item daily symptom measurement tool developed for children with Lyme meningitis.[17] We defined symptom resolution as three consecutive days of reported symptom scores of zero with no intermediate non-zero scores.

Aim 2 Outcome: Quality of life will be measured using the PedsQL™ Pediatric Quality of Life Inventory™ instrument at baseline, 6 weeks, and 6 months after enrollment. The PedsQL™ instrument, validated for many illnesses with neurologic manifestations, includes measures of physical, emotional, social, and school function and takes just a few minutes to complete.

Aim 3 Outcome Aim 3 results will be used to frame recommendations for Lyme meningitis treatment firmly in a shared decision-making model. We will identify themes related to how patients value treatment outcomes and explain discordance among patients/parents and clinicians. These interviews will inform shared decision-making and provide rich contextual data to inform clinicians who care for children with Lyme meningitis.

Data Collection Methods, Assessments, Interventions and Schedule

Study day 0 is the date of consent. At the time of consent, research staff will collect demographic and clinical data including previous medical history as well as severity and duration of symptoms associated with the current illness (**Table 1**). Study staff will abstract current antibiotic and adjunct therapies (e.g., corticosteroids) from the electronic health record at baseline and again 6 months from enrollment. Patients/parents will be asked to complete a baseline treatment preferences survey and the Lyme Meningitis Symptom Score. To compare oral doxycycline with IV ceftriaxone for time to *resolution of symptoms*, we will assess the Pediatric Lyme Meningitis Symptom Measurement instrument (**Figure 1**)[17] daily until symptoms resolve or three consecutive days with no response for up to 30 days from

Table 1: Lyme meningitis schedule of study activities

	Screening	**Baseline**		**Follow-Up**						
	Day -7 up to Day 0	Day 0 = Consent Date	Week 1 (Day 7)	Week 2 (Day 14)	Week 3 (Day 21)	Week 4 (Day 28)	(Day 30)	Week 5 (Day 35)	Week 6 (Day 42) ± 2w	Month 6 (Day180) ±1mo
Screening and eligibility	X									
Consent/Assent		X								
Demographics		X								
Medical history		X								
Medication history		X								
Laboratory results	X									
Electrocardiogram	X									
Treatment preference survey		X								
Clinician survey		X								
Facial palsy pictures (until resolution)		X	X	X	X	X		X	X	X
Qualitative interview									X	
Contact information		X								
History of present illness		X								
Pediatric Lyme Meningitis Symptom Score		Daily until resolution of symptoms or 30 days, whichever occurs first							X	X
Medication usage		Daily until resolution of symptoms or 30 days, whichever occurs first								
Treatment changes/ healthcare use			X	X	X	X				
PedsQL (parent < 18 /self-report ≥ 18 years)		X							X	X
Medical record review										X

enrollment (**Figure 2**). Other information regarding medication usage and complications will also be assessed. Participants will be contacted by research staff if they have missing patient surveys.

For children who have a Lyme disease peripheral facial palsy, we will measure time to resolution using photo documentation weekly for six weeks, biweekly then monthly after 2 months until resolution. Facial photographs will be taken at home, and uploaded to a secure study database (**Supplemental Figure 2**). The study neurologist, blinded to clinical treatment, will assign a House-Brackmann Facial Paralysis scale based on review of the photo uploads (**Table 2**). Study staff will collect health-related quality of life using the PedsQL™ to measure residual sequelae of Lyme meningitis at baseline, 6 weeks, and 6 months via phone, text, email, or through a mailed copy of the survey to the patient/parent.

Table 2: House Brackman score for assessment of peripheral facial palsy

Score	**Overall severity**	**Appearance at rest**	**With motion**			**Abnormal involuntary contraction[a]**
			Forehead wrinkling	*Eye closure*	*Mouth*	
1	Normal	Normal	Normal	Normal	Normal	None
2	Mild	Normal	Slight weakness	Slight weakness	Slight weakness	None
3	Moderate	Normal	Weak; minimum to no movement	Closes only with maximum effort	Moves only with maximum effort	Obvious, but non-disfiguring
4	Mod severe	Normal	None	Incomplete with maximum effort	Droop	Interferes with function
5	Severe	Asymmetry	None	Barely perceptible	Barely perceptible	Usually none
6	Total	Asymmetry	None	None	None	None

[a]Facial muscle spasm, synkinesis or contracture

To assess treatment preferences, patient/parents as well as the treating clinician will be surveyed about treatment preference at baseline. At the 6-weeks follow-up, a trained interviewer will ask open-ended questions of the parent or adult participant (≥ 18 years) to help the research team better understand how treatment decisions were made. Qualitative interviews will be guided by a semi-structured interview format and last approximately 30 minutes. After each interview, a debrief summary will be completed to allow themes to be incorporated into future interviews and monitor data saturation.

Study participants will be compensated real-time using ClinCards[18] for each study activity completed.

Withdrawal from Study

Any time after informed consent has been obtained, a patient and/or their caregiver may request study withdrawal for any reason. No further study data will be collected after the patient is withdrawn, but the previously collected will be retained.

Data Coordinating Center

The Data Coordinating Center (DCC) at the University of Utah provides data coordination and management including a state-of-the-art, energy-efficient data center providing secure, reliable, enterprise-wide infrastructure for delivering mission critical systems and services. The DCC virtual environment provides high availability, data redundancy and encryption, flexible compute infrastructure, and rapid deployment. Critical systems availability has exceeded 99.9% for the past 5 years.

Data Management Methods

Study screening logs will be stored locally in a password protected research drive behind the hospital fire-wall. Study data will be collected using REDCap™. The DCC has developed study instruments to manage data collection.

Protection of Human Subjects

Single Institutional Review Board (sIRB) Approval

Boston Children's Hospital will be the sIRB of record for this multicenter study, responsible for maintaining records related to the reliance agreements and the Communication Plan. The Boston Children's study PI in collaboration with the DCC will manage the collection of site-specific information, submission of site-specific information, and communication between the sIRB and the collaborating sites. The DCC will track IRB approval status at all participating centers and will not permit subject enrollment without documentation of initial sIRB approval and local review sign-off. The DCC will also track the maintenance of that approval throughout subsequent years of the project.

Informed Consent

Waiver of Authorization

Study staff has a waiver of authorization to pre-screen medical and laboratory records in order to establish subject eligibility prior to seeking informed consent.

Parental Permission/Subject Consent

Informed consent from parents or legal guardians will be required for participation of subjects who are eligible for this study and under 18 years of age. Patients 18 and older will consent for themselves. If a child turns 18 in the follow-up period, the participant will be re-consented. After determining that a subject is eligible in consultation with the treating clinical team, the site investigator or designee will approach the patient and/or parent/legal guardian either in person or by telephone to offer study participation. The parent or legal guardian will be informed about the objectives of the study and the potential risks and benefits of participation. Documentation of consent may be either written (in-person) or verbal (remote). All consent documents are available in both English and Spanish.

If a participant is discharged home before Lyme disease serology results are available to confirm eligibility, an information sheet will be given to the participant and family explaining that they may be contacted to participate in an observational study of Lyme meningitis. If positive Lyme disease serology results returns after the patient has been discharged home, trained study staff will consult with the clinical team and seek informed consent over the phone. At the beginning of the qualitative interview, the interviewer will confirm the parent/patient is still willing to participate, explain the purpose of the interview, and inform the interviewee that participation is voluntary in nature will not impact clinical care in any way.

Child Assent

Children who are capable of giving assent will be asked, following an age-appropriate discussion of risks and benefits, to give assent to the study or further study procedures. Assent will be waived for children under 8 years or if the child has a severely reduced mental age, decreased level of consciousness, psychological problems or other legitimate reasons to be unable to provide assent.

Potential Risks

The study protocol has been classified minimal risk. Loss of confidentiality of the subject is a potential risk of the study; however, safeguards described above protect against this. Another possible risk is that questions asked in the qualitative interview could cause emotional discomfort or distress. Although unlikely as most children with Lyme meningitis recover without problems, the interview could cause strong emotions based on the subject's course of care.

Protections against Potential Risks

Regarding loss/breach of privacy and confidentiality, all applicable parties will be responsible for ensuring that appropriate data security procedures are in place. To minimize risks related to discomfort or distress with interview topics and questions, the following will be in place:

- All participants will be informed at the time of screening and consent, and prior to initiating the interview, that they will be asked to discuss their or their child's illness and medical treatment;
- Study staff will fully explain to each participant their right to refuse a question or end the interview anytime; and participants will be provided with contact information for local study investigators for questions or concerns or to report any subsequent discomfort or distress.

Potential Benefits

This research may not help the patient in real-time; however, the information gained from the analysis will lead to further understanding about treatment of Lyme meningitis in children which may help future children with Lyme meningitis.

Quality Control Methods

Standardized data collection forms with built in query systems will help to ensure accuracy of collected data. The DCC will generate reports by site and across the network to track enrollment, follow-up rates and data quality. Study monitoring will be utilized to ensure data quality. The DCC utilizes risk-based methodology to identify and correct problems that may arise at sites. The risk-based approach to monitoring focuses on oversight activities and preventing or mitigating key risks to data quality, as well as to processes critical to human subject protection and integrity of the trial or study.

Site Monitoring

Site monitoring visits will be performed by a trained site monitor either in person or remotely to ensure regulatory compliance, patient safety, and to monitor the quality of data collected. Essential document binders, regulatory documents and data collection forms may be reviewed. The site monitor will provide each site with a written report, and sites will be required to follow up on any deficiencies. We anticipate a virtual site initiation visit (prior to patient enrollment), interim visits, and a close out site visit. The site initiation may take place as group training made up of site investigators and research assistants. Site monitoring visits may be conducted in-person or virtually. This observational study does not have a data safety monitoring board.

Data Analysis Plan

Statistical analysis plan for Aims 1 and 2: Data elements will be assessed to identify potentially confounding baseline characteristics that may differ between the doxycycline and ceftriaxone groups. Site-specific characteristics will also be compared, including baseline utilization rates of doxycycline and ceftriaxone in Lyme meningitis, volume, quality measures, and case mix. Categorical data will be analyzed using either a Chi-square or Fisher's exact test and continuous data with a Student's t-test or Mann-Whitney U test. We will compare the primary outcome, the number of days to resolution of symptoms, using linear regression adjusting for propensity scores with treatment group (oral doxycycline versus IV ceftriaxone) as the primary predictor.

For *Aim 1*, if the upper bound on the 95% confidence interval for the increase in propensity score adjusted mean time to resolution of symptoms for patients treated with oral doxycycline compared to IV ceftriaxone is three days or less, then we will consider oral doxycycline non-inferior to IV ceftriaxone. We identified the three-day threshold as a meaningful cut-off in a previous parental study survey.[16] As only a minority of children with Lyme meningitis are expected to have a peripheral facial palsy, we are not adequately powered to compare time to facial palsy resolution. For *Aim 2*, if the upper bound of the propensity score adjusted PedsQL™ at 6 months for patients treated with oral doxycycline compared to IV ceftriaxone is $\leq$ 4.5,[19] then we will consider oral doxycycline non-inferior to IV ceftriaxone.

Statistical analysis plan for Aim 3: Each interview will be audio-recorded, transcribed, reviewed by the study team for accuracy, and de-identified. Debrief summaries will be reviewed regularly to monitor data collection and saturation. Content analysis[20] will be used to analyze exit interview data. Passages of the transcript that represent areas of particular interest are identified with codes (e.g., time to symptom resolution). Initial codes will be based on the study aims and areas of inquiry as outlined in the qualitative interview agenda. Codes may be added as new themes emerge from the interviews. The study coding team will all independently code transcripts, compare codes, and discuss and resolve any discrepancies. Transcripts will be coded by at least two members of the coding team until inter-coder concordance is ≥ 85%. The remaining transcripts will be assigned to individual coders and approximately 20% of those transcripts will be coded by two members of the team to ensure concordance. After all interviews and content analysis have been completed, data-driven themes will be reviewed and summarized. In the event that direct quotations or statements are disseminated, care will be taken to ensure that readers are not able to identify the individual from the content of their statement.

Statistical Power and Sample Considerations

Aim 1 power analysis: The primary analysis will compare the time (days) to resolution of symptoms for oral doxycycline versus IV ceftriaxone using a non-inferiority design. We will start to count days of symptoms from the time of study enrollment. Based on our Delphi survey, we estimate that children with Lyme meningitis average 5 days to resolution of symptoms with a standard deviation of 3.5 days. We anticipate that approximately 80% of children with Lyme meningitis at the study sites will be treated with oral doxycycline first-line during the planned study period. We estimate a 25% loss to follow-up rate, a conservative estimate given the 10% loss to follow-up rate achieved for a recent study.[21] Using our non-inferiority point estimate of 1-day with an upper bound of 3-day delay in symptom resolution for children with Lyme meningitis treated with oral doxycycline compared to IV ceftriaxone, a sample size of 250 patients (n = 200 in oral doxycycline group and n = 50 in IV ceftriaxone group) will obtain 93% power assuming a 5% Type I error rate (**Table 3**).

Table 3: Sensitivity analysis showing power across a range of patients receiving doxycycline and loss to follow-up rates.

Proportion of children who receive oral doxycycline	*Loss to follow-up rates*				
	10%	*15%*	*20%*	*25%*	*30%*
90%	81%	78%	76%	74%	72%
80%	96%	95%	94%	93%	91%
70%	99%	98%	98%	97%	96%

Aim 2 power analysis: Health-related quality of life will be assessed with propensity score stratified linear regression, to calculate adjusted mean differences in scores between the treatment groups. Assuming that the 80% of patients who receive oral antibiotics will have the same quality of life as the 20% of patients who receive IV antibiotics. With 250 patients enrolled and 25% dropout, we would be able to identify differences in the PedsQL™ quality of life instrument greater than 4.6 with 80% power assuming a standard deviation of 10 with a 5% Type I error rate. This 4.6 score difference is close to the 4.5-unit difference often cited as a clinically meaningful difference.[19]

Aim 3 power analysis: We did not conduct a formal power calculation for this exploratory aim. Data will be collected until saturation is achieved, meaning that – upon regular iterative data review – similar themes are consistently being identified and new themes are no longer emerging.[22]

Study Training

We held a formal training program for investigators and research staff prior to the start of enrollment which covered study procedures, clinical care, data entry procedures, quality assurance, site monitoring, and the informed consent process supplemented by a manual of operations which provides details about the study procedures, regulatory information, and other necessary information.

Patient and Public Involvement statement

Qualitative methods – by their very nature – engage the patient and caregiver in sharing their experiences and expertise with the research community. Research scientists then organize and share those experiences with clinicians, other scientists, and the public to inform practice and policy. In this study, participants engage in a qualitative interview to share their experiences with diagnosis and treatment of pediatric Lyme meningitis, including feedback on study methods and assessment to address the aims and inform future iterations of this work.

Data Statement Section

The study dataset stripped of all identifiers will be made available without cost to interested researchers as soon as possible but no later than one year after completion of data collection. Data access will require an agreement to the conditions of use governing access to the public release data, including restrictions against attempting to identify study participants, destruction of the data after analyses are completed, reporting responsibilities, restrictions on redistribution of the data to third parties, and proper acknowledgment of the data resource.

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Figure Legends

Figure 1: Pediatric Lyme Meningitis Symptom Measurement Instrument

Figure 2: Stopping rules for the daily Lyme Meningitis Symptom Score survey

Supplemental Figures

Supplemental Figure 1: Study organizational structure

Supplemental Figure 1: Instructions for the patient/parent upload of facial pictures

Consent Documents Included (English version)

Informed consent (Boston Children's Hospital)

Child assent document (Boston Children's Hospital)

Study information sheet (Boston Children's Hospital)

Contributorship statement

LEN conceived of the study, led study design, drafted the protocol and led study implementation. THC contributed to study design and led study implementation. ARC designed propensity matching strategy, contributed to overall study design and critically reviewed the study protocol. SEV designed qualitative methods and contributed to study design. JJH designed facial palsy assessment methods. JAR contributed to statistical analysis plan and contributed to study implementation. UO and BLM contributed to study design and implementation. BJF designed data collection instruments and contributed to study design and implementation. JMB led study design, designed the statistical analysis plan, drafted the protocol and contributed to study implementation. All authors contributed to refinement of the study protocol and approved the final protocol manuscript.

Competing interests

None of the protocol co-authors have any relevant financial conflicts of interest to declare.

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Figure 1: Pediatric Lyme meningitis symptom score (range 0-6 points)

Pediatric Lyme Meningitis Symptom Measurement Instrument			
1. How bad was your headache today?			
0 None	0 Mild	1 Moderate	2 Severe
2. How bad was your neck pain?			
0 None	0 Mild	1 Moderate	2 Severe
3. Do you have a fever today (temperature ≥ 100.4° F or 38.0° C)?			
0 No		1 Yes	
4. Did you have any sensitivity to light?			
0 No		2 Yes	
5. Did you have any problems with their vision, such as double vision?			
0 No		1 Yes	

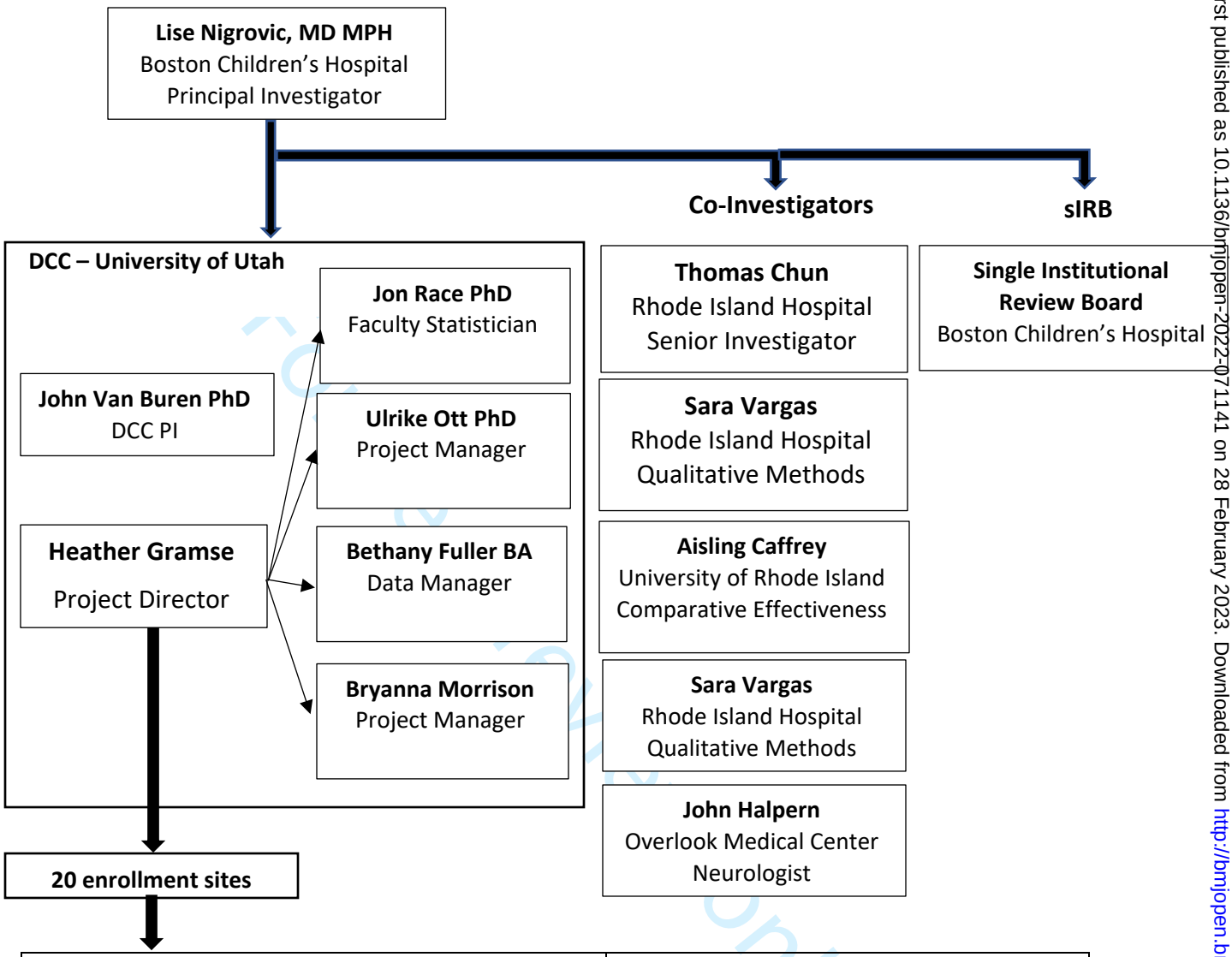
Figure 2: Stopping rules for the daily Lyme Meningitis Symptom Score survey

Stopping Rules

1) If subject has 3 missing days in a row, then stop. Subject is considered censored.
2) If subject has 3 days with a score = 0, without any days with a score > 0 inbetween, then stop. Subject is considered resolved.
3) If subject hits Day 30 without resolution, then stop. Subject is considered censored.

Subject	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 30	Notes	Status
1	Score > 0	Score > 0	Score = 0	Score = 0	Score = 0	END							Resolved
2	Score > 0	Score > 0	Score = 0	Score = 0	Missing	Score = 0	END					Send Day 6	Resolved
3	Score > 0	Score > 0	Score = 0	Score = 0	Missing	Missing	Missing	END				Send texts for up to 3 missings in a row	Censored
4	Score > 0	Score > 0	Score = 0	Missing	Missing	Score = 0	Missing	Missing	Missing	END			Censored
5	Score > 0	Score = 0	Score > 0	Score = 0	Missing	Score = 0	Missing	Score = 0	END				Resolved
6	Score > 0	Score = 0	Score = 0	Score > 0	Score = 0	Score > 0	Score > 0	Score > 0	Score > 0	Score > 0	Score > 0	Everyone will be asked again at 6 weeks and 6 months	Censored
7	Score = 0	Score = 0	Score = 0	END									Resolved

Supplemental Figure 1: Study organizational structure



Enrollment site	Site investigators
Boston Children's Hospital	Dr. Lise Nigrovic (PI)
Hasbro Children's Hospital	Dr. Thomas Chun (Senior Investigator)
Baystate Medical Center	Dr. Katie Harer
Children's Hospital of Philadelphia	Drs. Frances Balamuth, Rebecca Green
Children's Hospital of Wisconsin	Dr. Anna Huppler, Michael Levas
Children's Minnesota	Dr. Anupam Kharbanda
Children's National Medical Center	Drs. Roberta DeBiasi, Alexandra Yonts
Cohen Children's Medical Center	Dr. Sunil Sood
Connecticut Children's Medical Center	Dr. Mariann Nocera-Kelley
Dartmouth Medical Center	Dr. Mia Rutman
Goryeb Children's Hospital	Dr. Christina Gagliardo
Nemours Children's Health	Dr. Amy Thompson
Massachusetts General Hospital	Dr. Margaret Samuels-Kalow

Nationwide Children's Hospital	Drs. Daniel Cohen, Courtney Coyle
Pennsylvania State University Hershey Medical Center	Dr. Kathryn Kasmire
Stony Brook Children's Hospital	Drs. Andrew Handel, Sharon Nachman
UPMC Children's Hospital of Pittsburgh	Dr. Desiree Neville
University of Massachusetts	Dr. Christina Hermos
Westchester Medical Center	Dr. Sheila Nolan
Yale New Haven Children's Hospital	Dr. Paul Aronson

Facial Droop Photo Upload Instruction Sheet

It is determined that you/your child has Facial Palsy or a facial droop. The term facial palsy generally refers to weakness of the facial muscles, mainly resulting from temporary damage to the facial nerve. When a facial nerve is either non-functioning or missing, the muscles in the face do not receive the necessary signals in order to function properly.

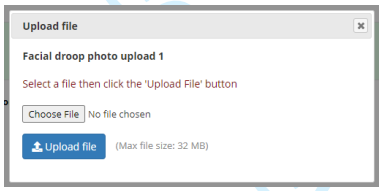
You have been asked to take 5 pictures of you/your child weekly until symptoms of droop resolve. If you/your child continue to have symptoms past 6 weeks, you will only need to take pictures once per month until symptoms go away or for 6 months. We will not be collecting any photos after 6 months.

If you are still in the hospital, the Research Coordinator at your hospital may help you take the first set of pictures and may show you how to upload to the REDCap database. This sheet has been created to help you with your weekly photos.

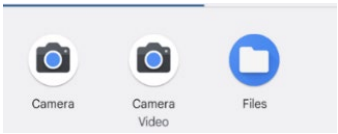
If you are at home, please follow these instructions for uploading photos:

To Upload:

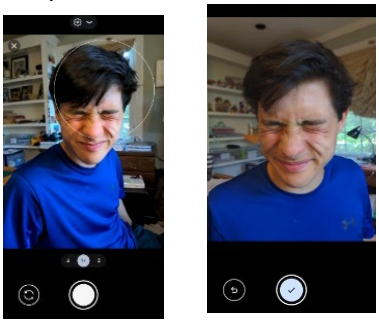
1. Click on the "Upload file" link.
2. A pop-up window will appear as shown:



3. When you select “Upload file", you will have multiple options:
    1) To take the picture directly in REDCap, the option to use your camera will appear. Select “camera” button

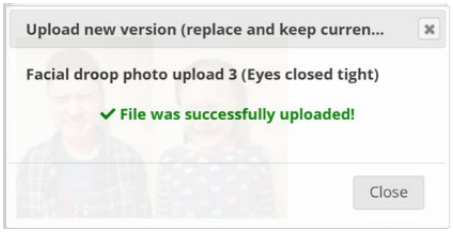


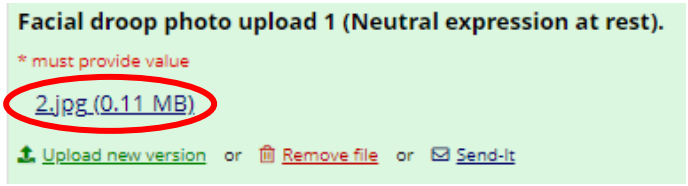
- Frame the person’s face in your camera’s viewfinder, then press the camera’s shutter button as you normally would.
- If you are happy with the picture, press the camera’s shutter button, which now has a check mark in it.



    2) If you have previously taken the picture, select the "Browse" icon (or “Choose File”).
        - After selecting the file, the name of the file will appear next to the "Browse" icon.
        - In the same pop-up window, under the "Browse" icon you will click on the blue icon labeled "Upload file" (different from the link).

4. “File was successfully uploaded!” will pop-up, select the “Close” button.
5. The file upload is now complete.





Please Take the following pictures of your/your child’s face:

1. Neutral expression at rest (think passport photo).

2. Smile

3. Close eyes tight.

4. Wrinkle forehead by lifting eyebrows.

5. Pretend to blow up a balloon with puffed cheeks.

Boston Children's Hospital

Lyme Meningitis Study

With more than 300,000 new cases of Lyme disease each year in the U.S., approximately half of new cases occur in children. Children with Lyme meningitis usually have a headache, fever and fatigue. Children diagnosed with Lyme meningitis are treated with either oral or intravenous antibiotics.

We are conducting a study to evaluate 2 things:

1. Compare the two medications usually used to treat Lyme Meningitis to determine if one has better outcomes or is more manageable for families.
2. Determine patient, parent and clinician preferences for the treatment of Lyme meningitis to inform future decision-making

To do this, we will be enrolling 250 children at 20 U.S. medical centers where Lyme disease is endemic. Treatment decisions will be made by you and your child's medical team. **This study will not affect in any way how you/your child are treated for Lyme meningitis. We seek simply to learn how quickly your treatment works for you.** You may be in this study if you:

- ✓ Are between 1 and 21 years old
- ✓ Have been recently diagnosed with Lyme Meningitis
- ✓ Treatment plan includes oral doxycycline or IV ceftriaxone/cefotaxime

If you decide to join this research study, we will collect the following information:

- Current symptoms and treatment preferences
- Daily symptoms until improved (30 days maximum)
- Phone interview at 6 weeks
- If your child has peripheral facial palsy, weekly facial photos until resolution

If you are discharged today, without knowing all of your test results, you may be called within the next week to provide verbal consent for the study and to begin the above study procedures. Participation in this study will not benefit you directly. Participation will inform the best treatment for children with Lyme meningitis in the future. It will take you about 6 months to complete this study. The most likely risk is accidental disclosure of confidential medical information. Many measures have been taken to prevent this risk.

Your clinical care will be covered by your health insurer as your treatment will not change by taking part in this research. **You will receive between $50 and $110 in gift cards for the completion of study activities.**

If you have any questions about this study, please contact the Principal Investigator at Boston Children's Hospital by calling: 617-355-5862 or Email: lymemeningitis@childrens.harvard.edu.

PEDILYMENET MENINGITIS STUDY

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5 Supplemental Table 1
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6 Table 1
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	*
		(*d*) If applicable, explain how loss to follow-up was addressed	*
		(*e*) Describe any sensitivity analyses	n/a
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	n/a Study protocol only
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	n/a
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (e.g., average and total amount)	n/a
Outcome data	15*	Report numbers of outcome events or summary measures over time	n/a
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	n/a
		(*b*) Report category boundaries when continuous variables were categorized	n/a
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	n/a
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	n/a
Generalisability	21	Discuss the generalisability (external validity) of the study results	n/a
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1-2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Comparative Effectiveness and Complications of Intravenous Ceftriaxone Compared with Oral Doxycycline in Lyme Meningitis in Children (A multi-center prospective cohort study)

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Keywords:	PAEDIATRICS, ACCIDENT & EMERGENCY MEDICINE, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

Comparative Effectiveness and Complications of Intravenous Ceftriaxone Compared with Oral Doxycycline in Lyme Meningitis in Children (A multi-center prospective cohort study)

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Key words: Lyme disease, meningitis, children, doxycycline, ceftriaxone, comparative-effectiveness, patient preference

ABSTRACT

Introduction:

Lyme disease is the most common vector-borne disease in the Northern hemisphere with more than 400,000 new cases in the U.S annually. Lyme meningitis is an uncommon, but potentially serious clinical manifestation of Lyme disease. Intravenous ceftriaxone had been the first-line treatment for Lyme meningitis, but is associated with a high rate of complications. Although efficacy and effectiveness (or real world evidence) data for oral doxycycline are limited, practice guidelines were recently expanded to recommend either oral doxycycline or ceftriaxone as first-line treatments for Lyme meningitis. Our goal is to compare oral doxycycline to intravenous (IV) ceftriaxone for the treatment of Lyme meningitis on short-term recovery and long-term quality of life.

Methods and analysis:

We are performing a prospective cohort study at twenty U.S. pediatric centers located in diverse geographic range where Lyme disease is endemic. The clinical care team will make all antibiotic treatment decisions for children with Lyme meningitis, as per usual practice. We will follow enrolled children for six months to determine time of acute symptom recovery and impact on quality of life.

Ethics and dissemination:

Boston Children's Hospital, the single Institutional Review Board (sIRB), has approved the study protocol with the other 19 enrolling sites as well as the Utah Data Coordinating Center (DCC) relying on the Boston Children's Hospital sIRB. Once the study is completed, we will publish our findings in a peer reviewed medical journal.

Strengths and limitations of this study:

- Inclusion of 20 centers located in Lyme disease endemic areas in the Northeast, Mid-Atlantic and Upper Midwest regions of the US will capture a clinically and geographically diverse group of children with Lyme meningitis.
-The prospective pragmatic design allows for standardized collection of patient-reported clinical symptoms, treatments and outcomes for children with Lyme meningitis.
- Daily surveys delivered electronically accurately capture symptoms and treatments while allowing remote participation, reducing burden on patients and families.
- Qualitative interviews will capture patient and parent preferences about Lyme meningitis treatment.
- As treatment decisions are made by the clinical team, we cannot control the antibiotic selection for children with Lyme meningitis.

Word count: 3,849

Introduction

With more than 400,000 new cases of Lyme disease each year in the U.S., children are commonly affected.[1,2] Lyme meningitis, an uncommon potentially serious clinical manifestation of acute Lyme disease, presents with headache, fever and fatigue. Intravenous ceftriaxone was previously the recommended first line treatment for Lyme meningitis,[3] but is associated with a high rate of complications related either to the long-term intravenous catheter placed for medication delivery or to complications from the antibiotic itself.[4] Based on European trials conducted in adults[5,6] and a small observational study of children,[7] some clinicians have begun treating Lyme meningitis in children with oral doxycycline, avoiding the complications associated with intravenous ceftriaxone and reducing health care costs. This comparative effectiveness study will address three critically important clinical questions: *1) How does treatment with oral doxycycline compare with intravenous ceftriaxone for time to resolution of symptoms in children with Lyme meningitis? 2) Do children have equivalent six-month post-treatment quality of life after treatment with either doxycycline or ceftriaxone? 3) What are patient and parent preferences regarding treatment decisions?*

Recent updates to the Infectious Disease Society of America (IDSA) guideline[8–10] recommend *either* doxycycline *or* ceftriaxone as appropriate first-line treatment. Although previously most children with Lyme meningitis were treated with intravenous ceftriaxone, clinical experience with oral doxycycline is growing.[7,11] As approximately one quarter of children treated with ceftriaxone have treatment complications,[4] an equally effective oral antibiotic could lower complication rates, reduce costs and improve quality of life.

Oral doxycycline has clear advantages compared with intravenous ceftriaxone because it avoids use of a peripherally inserted central catheter (PICC) to deliver multiple weeks of treatment. In a previous study, 26% of children with Lyme meningitis treated with ceftriaxone had at least one treatment complication related to either the PICC line (e.g. accidental dislodgment, thrombosis, infection) or an adverse reaction to the parenteral antibiotic.[4] Parenteral therapy is more costly than oral therapy due to the additional costs for IV medication administration either inpatient or at home, as well as additional medical visits for treatment monitoring and complications. The *impact* of demonstrating the effectiveness *of doxycycline for the treatment of Lyme meningitis would be to lower complication rates, improve quality of life, and reduce treatment costs*.

The evidence supporting doxycycline as an oral alternative for the treatment of Lyme meningitis is based on three efficacy studies conducted in adults from Europe where the predominate *Borrelia* strain differ (i.e.. *B. garinii* and *B. afzelii*).[5,6,12] A more recent retrospective study of 38 U.S. children with Lyme meningitis treated with oral doxycycline showed resolution of symptoms but lacked a control group.[7] Three systematic reviews of the literature on treatment of pediatric neuroborreliosis concluded that the current evidence is insufficient to recommend doxycycline *instead* of beta-lactam antibiotics.[13–15] Factors limiting the rigor of the previous studies include 1) the small study populations of children with Lyme meningitis, 2) retrospective chart review methods prone to missing data and residual confounding due to unmeasured factors, 3) lack of outcome measures specific to Lyme meningitis, and 4) difficulty assessing resolution of symptoms with granularity. Until rigorous and well-controlled studies demonstrate definitively oral doxycycline is not inferior to intravenous ceftriaxone, we cannot conclude that doxycycline is as effective as ceftriaxone for the treatment of pediatric Lyme meningitis.

We previously captured child and parent preferences about Lyme meningitis treatment.[16] After watching a video about Lyme meningitis treatment choices that included relevant information about the anticipated benefits and risks of treatment, parent-child dyads were asked a series of questions to

understand treatment preferences. Interestingly, 60% of caregivers expressed a strong preference for one treatment option over the other (40% would always prefer intravenous medication and 20% would always prefer oral medication), despite believing that both treatments were effective and safe. Perceived efficacy and treatment preference were weakly correlated ($r = 0.29$, $p = 0.01$) and perceived safety and treatment preference were moderately correlated ($r = 0.47$, $p < 0.0001$). This observed discordance requires further exploration to inform the shared decision-making process to better understand patient/parent and clinician values around treatment options, including acceptable risks and outcomes.

To accomplish these goals, we are conducting a comprehensive pediatric Lyme meningitis study, enrolling children at 20 U.S. centers located in regions of the U.S. where Lyme disease is endemic. Treatment decisions will be made by the child's treating clinical team and we will obtain informed consent to collect patient-reported outcomes over the following six months. We will enroll 250 children with Lyme meningitis to determine whether oral doxycycline is non-inferior to intravenous ceftriaxone for the treatment of Lyme meningitis in children. We will interview patients/parents and clinicians to gain a nuanced understanding of the factors that shape treatment decisions. The overall impact of this study will be to inform best practices for treatment of children with Lyme meningitis, accounting for the preferences of key stakeholders. We propose the following three aims.

Aim 1. Comparative effectiveness for symptom resolution): *To compare oral doxycycline with intravenous ceftriaxone for time to resolution of symptoms in children with Lyme meningitis using the Pediatric Lyme Meningitis Symptom Measurement instrument.* We hypothesize that oral doxycycline is non-inferior to IV ceftriaxone for time to resolution of Lyme meningitis symptoms.

Aim 2. Comparative effectiveness for six-month post-treatment quality of life): *To compare oral doxycycline with intravenous ceftriaxone on six-month post-treatment quality of life in children with Lyme meningitis using the Pediatric Quality of Life Inventory.* We hypothesize that doxycycline is non-inferior to ceftriaxone for 6-month quality of life.

Aim 3. Drivers of treatment decisions and treatment preferences): *To evaluate factors affecting treatment decisions and patient and parent treatment preference using a mixed methods design (pre- and post-treatment surveys as well as exit interviews.* We hypothesize that some patients and parents will prefer doxycycline treatment based on a better side effect profile, but others will prefer ceftriaxone because they believe intravenous medication works better. A nuanced understanding of these differing preferences will allow for *Aims 1/2* results to be disseminated and incorporated into clinical practice more effectively.

Methods and analysis

Study Design

We are conducting a prospective observational study of children with Lyme meningitis at twenty centers located in Lyme disease endemic areas of the Northeast, Mid-Atlantic and Upper Midwest (**Supplemental Figure 1**) using STROBE standards.

Patient selection and inclusion/exclusion criteria

Study staff started screening for potentially eligible patients on July 2, 2022 (study start date varied by center). Staff screen available medical records as well as laboratory databases. The clinical team will confirm study eligibility. Recruitment will happen over 5 years.

Inclusion criteria are:

1. Age 1 year to ≤ 21 years
2. Definite or probable meningitis:
   - Definite: meningitis defined as cerebrospinal (CSF) white blood cell (WBC) count ≥ 10 cells per high power
   - Probable: Clinical diagnosis of meningitis
3. Positive two-tiered Lyme disease serology obtained within seven days of enrollment:
   - Standard two-tier testing: Positive or equivocal Lyme disease enzyme immunoassay (EIA followed by a positive supplemental immunoblot
   - Modified two-tier testing: Two Lyme disease EIA tests that are positive, equivocal, or a combination of both

Exclusion criteria are:

1. Treatment plan does not include either oral doxycycline or intravenous ceftriaxone
2. More than 7 days of antibiotic treatment for Lyme meningitis prior to enrollment
3. Conditions that would preclude the assessment of the Pediatric Lyme Meningitis Symptom Survey (i.e. patient/parent reporting of headache, neck pain, sensitivity to light, fever)
4. Inability to complete study activities in either English or Spanish
5. Known pyogenic bacterial meningitis at the time of enrollment

Definition of primary and secondary outcomes

Aim 1 Outcome: The primary outcome is time to resolution of Lyme meningitis symptoms using the Pediatric Lyme Meningitis Symptom Measurement Instrument (**Figure 1**), a five-item daily symptom measurement tool developed for children with Lyme meningitis.[17] We defined symptom resolution as three consecutive days of reported symptom scores of zero with no intermediate non-zero scores.

Aim 2 Outcome: Quality of life will be measured using the PedsQL™ Pediatric Quality of Life Inventory™ instrument at baseline, 6 weeks, and 6 months after enrollment. The PedsQL™ instrument, validated for many illnesses with neurologic manifestations, includes measures of physical, emotional, social, and school function and takes just a few minutes to complete.

Aim 3 Outcome Aim 3 results will be used to frame recommendations for Lyme meningitis treatment firmly in a shared decision-making model. We will identify themes related to how patients value treatment outcomes and explain discordance among patients/parents and clinicians. These interviews will inform shared decision-making and provide rich contextual data to inform clinicians who care for children with Lyme meningitis.

Data collection methods, assessments, interventions and schedule

Study day 0 is the date of consent. At the time of consent, research staff will collect demographic and clinical data including previous medical history as well as severity and duration of symptoms associated with the current illness (**Table 1**). Study staff will abstract current antibiotic and adjunct therapies (e.g.,

Table 1: Lyme meningitis schedule of study activities

	Screening	Baseline		Follow-Up						
	Day -7 up to Day 0	Day 0 = Consent Date	Week 1 (Day 7)	Week 2 (Day 14)	Week 3 (Day 21)	Week 4 (Day 28)	(Day 30)	Week 5 (Day 35)	Week 6 (Day 42) ± 2w	Month 6 (Day180) ±1mo
Screening and eligibility	X									
Consent/Assent		X								
Demographics		X								
Medical history		X								
Medication history		X								
Laboratory results	X									
Electrocardiogram	X									
Treatment preference survey		X								
Clinician survey		X								
Facial palsy pictures (until resolution)		X	X	X	X	X		X	X	X
Qualitative interview									X	
Contact information		X								
History of present illness		X								
Pediatric Lyme Meningitis Symptom Score		Daily until resolution of symptoms or 30 days, whichever occurs first							X	X
Medication usage		Daily until resolution of symptoms or 30 days, whichever occurs first								
Treatment changes/ healthcare use			X	X	X	X				
PedsQL (parent < 18 /self-report ≥ 18 years)		X							X	X
Medical record review										X

corticosteroids) from the electronic health record at baseline and again 6 months from enrollment. Patients/parents will be asked to complete a baseline treatment preferences survey and the Lyme Meningitis Symptom Score. To compare oral doxycycline with intravenous ceftriaxone for time to *resolution of symptoms*, we will assess the Pediatric Lyme Meningitis Symptom Measurement instrument (**Figure 1**)[17] daily until symptoms resolve for three consecutive days up to 30 days from enrollment (**Figure 2**). Additional electronic surveys will assess medication usage and complications.. Participants will be contacted by research staff if they have missing patient surveys.

For children who have a Lyme disease peripheral facial palsy, we will measure time to resolution using photo documentation weekly for six weeks, biweekly then monthly after 2 months until resolution. Facial photographs will be taken at home, and uploaded to a secure study database (**Supplemental Figure 2**). The study neurologist, blinded to clinical treatment, will assign a House-Brackmann Facial Paralysis scale based on review of the photo uploads (**Table 2**). Study staff will collect health-related quality of life using the PedsQL™ to measure residual sequelae of Lyme meningitis at baseline, 6 weeks, and 6 months via phone, text, email, or through a mailed copy of the survey to the patient/parent.

Table 2: House Brackman score for assessment of peripheral facial palsy

Score	**Overall severity**	**Appearance at rest**	**With motion**			**Abnormal involuntary contraction**[a]
			Forehead wrinkling	*Eye closure*	*Mouth*	
1	Normal	Normal	Normal	Normal	Normal	None
2	Mild	Normal	Slight weakness	Slight weakness	Slight weakness	None
3	Moderate	Normal	Weak; minimum to no movement	Closes only with maximum effort	Moves only with maximum effort	Obvious, but non-disfiguring
4	Mod severe	Normal	None	Incomplete with maximum effort	Droop	Interferes with function
5	Severe	Asymmetry	None	Barely perceptible	Barely perceptible	Usually none
6	Total	Asymmetry	None	None	None	None

[a]Facial muscle spasm, synkinesis or contracture

To assess treatment preferences, we will survey patient/parents as well as the treating clinician about baseline treatment preferences. At the 6-weeks follow-up, a trained interviewer will ask open-ended questions of the parent or adult participant ($\geq$ 18 years) to help the research team better understand how treatment decisions were made. Qualitative interviews will be guided by a semi-structured interview format and last approximately 30 minutes. After each interview, a debrief summary will be completed to allow themes to be incorporated into future interviews and monitor data saturation.

Study participants will be compensated real-time using ClinCards[18] for each study activity completed.

Withdrawal from study

Any time after informed consent has been obtained, a patient and/or their caregiver may request study withdrawal for any reason. No further study data will be collected after the patient is withdrawn, but the previously collected will be retained.

Data coordinating center

The Data Coordinating Center (DCC) at the University of Utah provides data coordination and management including a state-of-the-art, energy-efficient data center providing secure, reliable, enterprise-wide infrastructure for delivering mission critical systems and services. The DCC virtual environment provides high availability, data redundancy and encryption, flexible compute infrastructure, and rapid deployment. Critical systems availability has exceeded 99.9% for the past 5 years.

Data management methods

Study screening logs will be stored locally in a password protected research drive behind the hospital firewall. Study data will be collected using REDCap™. The DCC has developed study instruments to manage data collection. Standardized data collection forms with built in query systems will help to ensure accuracy of collected data. The DCC will generate reports by site and across the network to track enrollment, follow-up rates and data quality. Study monitoring will be utilized to ensure data quality. The DCC utilizes risk-based methodology to identify and correct problems that may arise at sites. The risk-based approach to monitoring focuses on oversight activities and preventing or mitigating key risks to data quality, as well as to processes critical to human subject protection and integrity of the trial or study.

Site monitoring

Site monitoring visits will be performed by a trained site monitor either in person or remotely to ensure regulatory compliance, patient safety, and to monitor the quality of data collected. Essential document binders, regulatory documents and data collection forms will be reviewed. The site monitor will provide each site with a written report, and sites will be required to follow up on any deficiencies. We anticipate a virtual site initiation visit (prior to patient enrollment), interim visits, and a close out site visit. The site initiation may take place as group training made up of site investigators and research assistants. Site monitoring visits may be conducted in-person or virtually. This observational study does not have a data safety monitoring board.

Study training

We held a formal training program for investigators and research staff prior to the start of enrollment which covered study procedures, clinical care, data entry procedures, quality assurance, site monitoring, and the informed consent process supplemented by a manual of operations which provides details about the study procedures, regulatory information, and other necessary information.

Data analysis plan

Statistical analysis plan for Aims 1 and 2: Data elements will be assessed to identify potentially confounding baseline characteristics that may differ between the doxycycline and ceftriaxone groups. Site-specific characteristics will also be compared, including baseline utilization rates of doxycycline and ceftriaxone in Lyme meningitis, volume, quality measures, and case mix. Categorical data will be analyzed using either a Chi-square (or Fisher's exact test) and continuous data with a Student's t-test (or Mann-Whitney U test). We will compare the primary outcome, the number of days to resolution of

symptoms, using linear regression adjusting for propensity scores with treatment group (oral doxycycline versus intravenous ceftriaxone) as the primary predictor.

For *Aim 1*, if the upper bound on the 95% confidence interval for the increase in propensity score adjusted mean time to resolution of symptoms for patients treated with oral doxycycline compared to intravenous ceftriaxone is three days or less, then we will consider doxycycline non-inferior to ceftriaxone. We identified the three-day threshold as a meaningful cut-off in a previous parental study survey.[16] As only a minority of children with Lyme meningitis are expected to have a peripheral facial palsy, we are not adequately powered to compare time to facial palsy resolution. For *Aim 2*, if the upper bound of the propensity score adjusted PedsQL™ at 6 months for patients treated with doxycycline compared to ceftriaxone is ≤ 4.5,[19] then we will consider oral doxycycline non-inferior to ceftriaxone.

Statistical analysis plan for Aim 3: Each interview will be audio-recorded, transcribed, reviewed by the study team for accuracy, and de-identified. Debrief summaries will be reviewed regularly to monitor data collection and saturation. Content analysis[20] will be used to analyze exit interview data. Passages of the transcript that represent areas of particular interest are identified with codes (e.g., time to symptom resolution). Initial codes will be based on the study aims and areas of inquiry as outlined in the qualitative interview agenda. Codes may be added as new themes emerge from the interviews. The study coding team will all independently code transcripts, compare codes, and discuss and resolve any discrepancies. Transcripts will be coded by at least two members of the coding team until inter-coder concordance is ≥ 85%. The remaining transcripts will be assigned to individual coders and approximately 20% of those transcripts will be coded by two members of the team to ensure concordance. After all interviews and content analysis have been completed, data-driven themes will be reviewed and summarized. In the event that direct quotations or statements are disseminated, care will be taken to ensure that readers are not able to identify the individual from the content of their statement.

Statistical power and sample considerations

Aim 1 power analysis: The primary analysis will compare the time (days) to resolution of symptoms for oral doxycycline versus intravenous ceftriaxone using a non-inferiority design. We will start to count days of symptoms from the time of study enrollment. Based on our Delphi survey, we estimate that children with Lyme meningitis average 5 days to resolution of symptoms with a standard deviation of 3.5 days. We anticipate that approximately 80% of children with Lyme meningitis at the study sites will be treated with oral doxycycline first-line during the planned study period. We estimate a 25% loss to follow-up rate, a conservative estimate given the 10% loss to follow-up rate achieved for a recent study.[21] Using our non-inferiority point estimate of 1-day with an upper bound of 3-day delay in symptom resolution for children with Lyme meningitis treated with oral doxycycline compared to intravenous ceftriaxone, a sample size of 250 patients (n = 200 in oral doxycycline group and n = 50 in IV ceftriaxone group) will obtain 93% power assuming a 5% Type I error rate (**Table 3**).

Table 3: Sensitivity analysis showing power across a range of patients receiving doxycycline and loss to follow-up rates.

Proportion of children who receive oral doxycycline	*Loss to follow-up rates*				
	10%	*15%*	*20%*	*25%*	*30%*
90%	81%	78%	76%	74%	72%
80%	96%	95%	94%	93%	91%
70%	99%	98%	98%	97%	96%

Aim 2 power analysis: Health-related quality of life will be assessed with propensity score stratified linear regression, to calculate adjusted mean differences in scores between the treatment groups. Assuming that the 80% of patients who receive oral doxycycline will have the same quality of life as the 20% of patients who receive intravenous ceftriaxone. With 250 patients enrolled and 25% dropout, we would be able to identify differences in the PedsQL™ quality of life instrument greater than 4.6 with 80% power assuming a standard deviation of 10 with a 5% Type I error rate. This 4.6 score difference is close to the 4.5-unit difference often cited as a clinically meaningful difference.[19]

Aim 3 power analysis: We did not conduct a formal power calculation for this exploratory aim. Data will be collected until saturation is achieved, meaning that upon regular iterative data review, similar themes are consistently being identified and new themes are no longer emerging.[22]

Ethics and dissemination

Single Institutional Review Board (sIRB) Approval

Boston Children's Hospital will be the sIRB of record for this multicenter study, responsible for maintaining records related to the reliance agreements and the communication plan. The Boston Children's study PI in collaboration with the DCC will manage the collection of site-specific information, submission of site-specific information, and communication between the sIRB and the collaborating sites. The DCC will track IRB approval status at all participating centers and will not permit subject enrollment without documentation of initial sIRB approval and local review sign-off. The DCC will also track the maintenance of that approval throughout subsequent years of the project.

Informed Consent

Waiver of authorization

Study staff has a waiver of authorization to pre-screen medical and laboratory records in order to establish subject eligibility prior to seeking informed consent.

Parental permission/Subject consent

We will obtained informed consent from parents or legal guardians of eligible children under 18 years of age (**Supplemental Figure 3**). Patients 18 and older will consent for themselves. If a child turns 18 in the follow-up period, the participant will be re-consented. After determining that a subject is eligible in consultation with the treating clinical team, the site investigator or designee will approach the patient and/or parent/legal guardian either in person or by telephone to offer study participation. The parent or legal guardian will be informed about the objectives of the study and the potential risks and benefits of participation. Documentation of consent may be either written (in-person) or verbal (remote). All consent documents are available in both English and Spanish.

If a participant is discharged home before Lyme disease serology results are available to confirm eligibility, an information sheet will be given to the participant and family explaining that they may be contacted in the future to participate in Lyme meningitis study (**Supplemental Figure 4**). If positive Lyme disease serology results returns after the patient has been discharged, trained study staff will consult with the clinical team and seek informed consent over the phone if eligible. At the start of the qualitative interview, the interviewer will confirm the parent/patient is still willing to participate, explain the purpose of the interview, and inform the interviewee that participation is voluntary in nature will not impact clinical care in any way.

Child assent

Children who are capable of giving assent will be asked, following an age-appropriate discussion of risks and benefits, to give assent to the study or further study procedures (**Supplemental Figure 3**). Assent will be waived for children under 8 years or if the child has a severely reduced mental age, decreased level of consciousness, psychological problems or other legitimate reasons to be unable to provide assent.

Potential risks

The study protocol has been classified minimal risk. Loss of confidentiality of the subject is a potential risk of the study; however, safeguards described above protect against this. Another possible risk is that questions asked in the qualitative interview could cause emotional discomfort or distress. Although unlikely as most children with Lyme meningitis recover without problems, the interview could cause strong emotions based on the subject's course of care.

Protections against potential risks

Regarding loss/breach of privacy and confidentiality, all applicable parties will be responsible for ensuring that appropriate data security procedures are in place. To minimize risks related to discomfort or distress with interview topics and questions, the following will be in place:

- All participants will be informed at the time of screening and consent, and prior to initiating the interview, that they will be asked to discuss their or their child's illness and medical treatment;
- Study staff will fully explain to each participant their right to refuse a question or end the interview anytime; and participants will be provided with contact information for local study investigators for questions or concerns or to report any subsequent discomfort or distress.

Potential benefits

This research may not help the patient in real-time; however, the information gained from the analysis will lead to further understanding about treatment of Lyme meningitis in children which may help future children with Lyme meningitis.

Patient and public involvement statement

We first involved the public in our previously published survey of patient/parent dyads about Lyme meningitis treatment preferences, [16] which informed the selection of the outcome measures and defined our minimally important differences for the non-inferiority analysis. Our study uses qualitative interviews to engage the patient and caregiver in sharing their experiences and expertise with researchers. These interviews will include feedback on study methods and assessment to understand the burdens of participation and to inform future iterations of this work. Investigators will organize and disseminate those experiences with clinicians, other scientists, and the public to inform future practice for children with Lyme meningitis.

Data statement section

We will make the study dataset stripped of all identifiers available without cost to interested researchers as soon as possible, but no later than one year after completion of data collection. Data access will require an agreement to the conditions of use governing access to the public release data, including restrictions against attempting to identify study participants, destruction of the data after analyses are completed, reporting responsibilities, restrictions on redistribution of the data to third parties, and proper acknowledgment of the data resource.

Contributorship statement

LEN conceived of the study, led study design, drafted the protocol and led study implementation. THC contributed to study design and led study implementation. ARC designed propensity matching strategy, contributed to overall study design and critically reviewed the study protocol. SEV designed qualitative methods and contributed to study design. JJH designed facial palsy assessment methods. JAR contributed to statistical analysis plan and contributed to study implementation. UO and BLM contributed to study design and implementation. BJF designed data collection instruments and contributed to study design and implementation. JMB led study design, designed the statistical analysis plan, drafted the protocol and contributed to study implementation. Pedi Lyme Net study group members contributed to study design, protocol development and study implementation. All authors contributed to refinement of the study protocol and approved the final protocol manuscript.

Competing interests

None of the protocol co-authors have any relevant financial conflicts of interest to declare.

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Figure Legends

Figure 1: Pediatric Lyme Meningitis Symptom Measurement Instrument

Figure 2: Stopping rules for the daily Lyme Meningitis Symptom Score survey

Supplemental Figures

Supplemental Figure 1: Study organizational structure

Supplemental Figure 2: Instructions for the patient/parent upload of facial pictures

Supplemental Figure 3: Informed consent and assent (Boston Children's Hospital)

Supplemental Figure 4: Study information sheet (Boston Children's Hospital)

Figure 1: Pediatric Lyme meningitis symptom score (range 0-6 points)

Pediatric Lyme Meningitis Symptom Measurement Instrument			
1. How bad was your headache today?			
0 None	0 Mild	1 Moderate	2 Severe
2. How bad was your neck pain?			
0 None	0 Mild	1 Moderate	2 Severe
3. Do you have a fever today (temperature ≥ 100.4° F or 38.0° C)?			
0 No		1 Yes	
4. Did you have any sensitivity to light?			
0 No		2 Yes	
5. Did you have any problems with their vision, such as double vision?			
0 No		1 Yes	

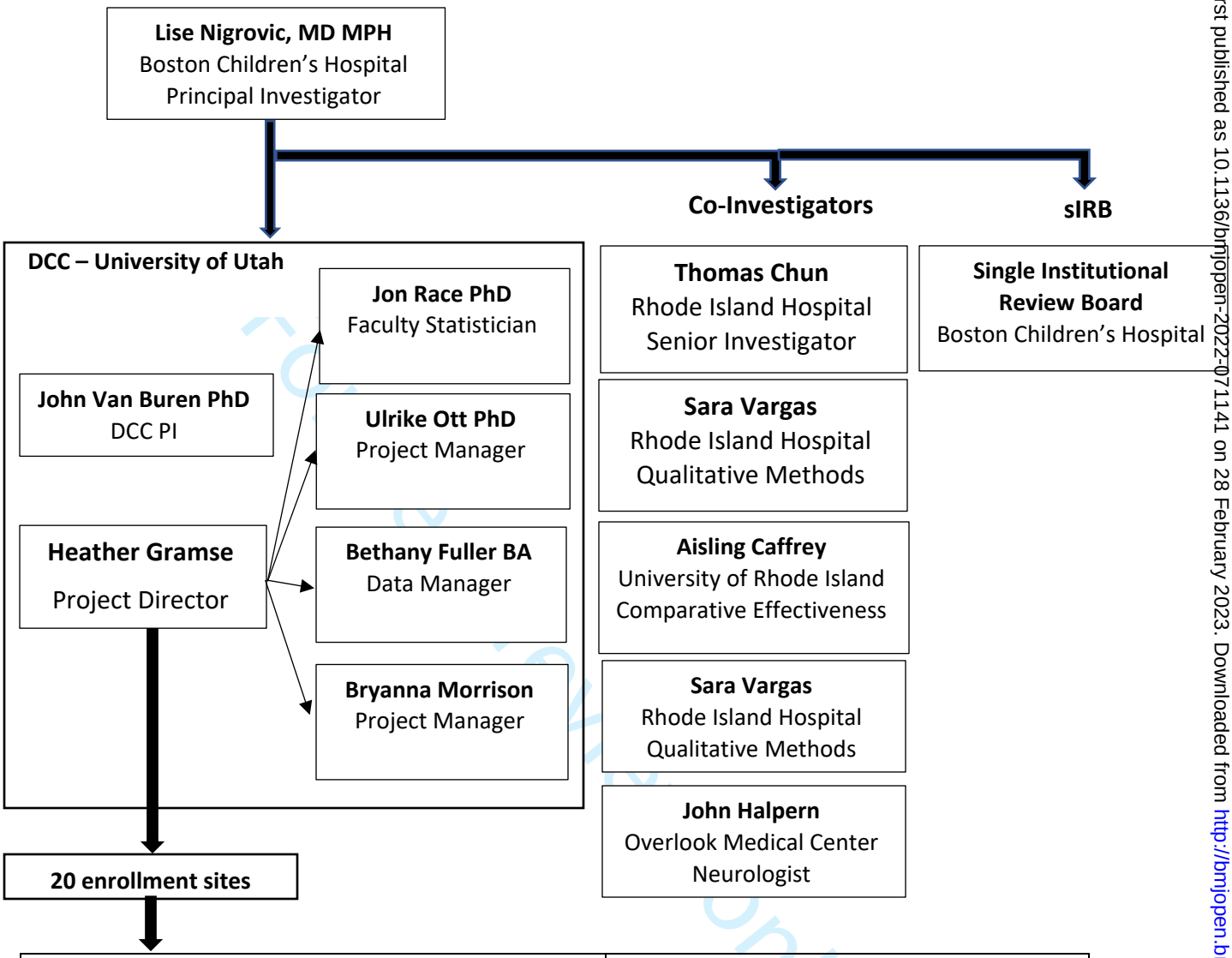
Figure 2: Stopping rules for the daily Lyme Meningitis Symptom Score survey

Stopping Rules

1) If subject has 3 missing days in a row, then stop. Subject is considered censored.
2) If subject has 3 days with a score = 0, without any days with a score > 0 inbetween, then stop. Subject is considered resolved.
3) If subject hits Day 30 without resolution, then stop. Subject is considered censored.

Subject	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 30	Notes	Status
1	Score > 0	Score > 0	Score = 0	Score = 0	Score = 0	END							Resolved
2	Score > 0	Score > 0	Score = 0	Score = 0	Missing	Score = 0	END					Send Day 6	Resolved
3	Score > 0	Score > 0	Score = 0	Score = 0	Missing	Missing	Missing	END				Send texts for up to 3 missings in a row	Censored
4	Score > 0	Score > 0	Score = 0	Missing	Missing	Score = 0	Missing	Missing	Missing	END			Censored
5	Score > 0	Score = 0	Score > 0	Score = 0	Missing	Score = 0	Missing	Score = 0	END				Resolved
6	Score > 0	Score = 0	Score = 0	Score > 0	Score = 0	Score > 0	Score > 0	Score > 0	Score > 0	Score > 0	Score > 0	Everyone will be asked again at 6 weeks and 6 months	Censored
7	Score = 0	Score = 0	Score = 0	END									Resolved

Supplemental Figure 1: Study organizational structure



Enrollment site	Site investigators
Boston Children's Hospital	Dr. Lise Nigrovic (PI)
Hasbro Children's Hospital	Dr. Thomas Chun (Senior Investigator)
Baystate Medical Center	Dr. Katie Harer
Children's Hospital of Philadelphia	Drs. Frances Balamuth, Rebecca Green
Children's Hospital of Wisconsin	Dr. Anna Huppler, Michael Levas
Children's Minnesota	Dr. Anupam Kharbanda
Children's National Medical Center	Drs. Roberta DeBiasi, Alexandra Yonts
Cohen Children's Medical Center	Dr. Sunil Sood
Connecticut Children's Medical Center	Dr. Mariann Nocera-Kelley
Dartmouth Medical Center	Dr. Mia Rutman
Goryeb Children's Hospital	Dr. Christina Gagliardo
Nemours Children's Health	Dr. Amy Thompson
Massachusetts General Hospital	Dr. Margaret Samuels-Kalow

Nationwide Children's Hospital	Drs. Daniel Cohen, Courtney Coyle
Pennsylvania State University Hershey Medical Center	Dr. Kathryn Kasmire
Stony Brook Children's Hospital	Drs. Andrew Handel, Sharon Nachman
UPMC Children's Hospital of Pittsburgh	Dr. Desiree Neville
University of Massachusetts	Dr. Christina Hermos
Westchester Medical Center	Dr. Sheila Nolan
Yale New Haven Children's Hospital	Dr. Paul Aronson

Facial Droop Photo Upload Instruction Sheet

It is determined that you/your child has Facial Palsy or a facial droop. The term facial palsy generally refers to weakness of the facial muscles, mainly resulting from temporary damage to the facial nerve. When a facial nerve is either non-functioning or missing, the muscles in the face do not receive the necessary signals in order to function properly.

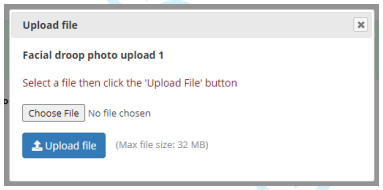
You have been asked to take 5 pictures of you/your child weekly until symptoms of droop resolve. If you/your child continue to have symptoms past 6 weeks, you will only need to take pictures once per month until symptoms go away or for 6 months. We will not be collecting any photos after 6 months.

If you are still in the hospital, the Research Coordinator at your hospital may help you take the first set of pictures and may show you how to upload to the REDCap database. This sheet has been created to help you with your weekly photos.

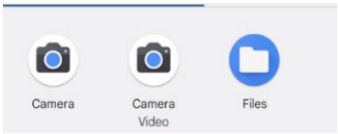
If you are at home, please follow these instructions for uploading photos:

To Upload:

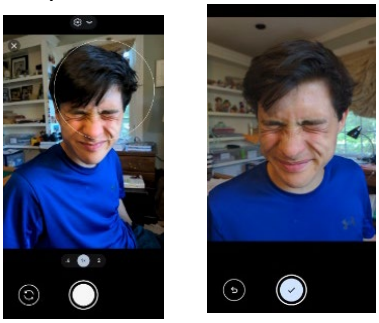
1. Click on the "Upload file" link.
2. A pop-up window will appear as shown:



3. When you select “Upload file", you will have multiple options:
    1) To take the picture directly in REDCap, the option to use your camera will appear. Select “camera” button

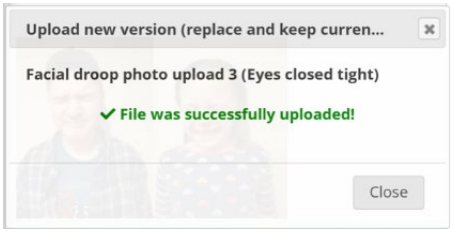


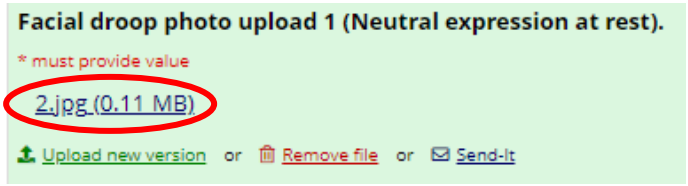
- Frame the person’s face in your camera’s viewfinder, then press the camera’s shutter button as you normally would.
- If you are happy with the picture, press the camera’s shutter button, which now has a check mark in it.



    2) If you have previously taken the picture, select the "Browse" icon (or “Choose File”).
        - After selecting the file, the name of the file will appear next to the "Browse" icon.
        - In the same pop-up window, under the "Browse" icon you will click on the blue icon labeled "Upload file" (different from the link).

4. “File was successfully uploaded!” will pop-up, select the “Close” button.
5. The file upload is now complete.





Please Take the following pictures of your/your child’s face:

1. Neutral expression at rest (think passport photo).

2. Smile

3. Close eyes tight.

4. Wrinkle forehead by lifting eyebrows.

5. Pretend to blow up a balloon with puffed cheeks.

Boston Children's Hospital

RESEARCH CONSENT FORM

Protocol Title: Comparative effectiveness and complications of intravenous ceftriaxone compared with oral doxycycline in Lyme meningitis

Principal Investigator: Lise Nigrovic, MD MPH

This consent form gives you important information about a research study. A research study helps scientists and doctors learn new information to improve medical practice and patient care.

Please read this consent form carefully and take your time making a decision. The first section gives you an overview of the key information you should know about the research study. More detailed information about these topics may be found in the pages that follow.

The form may contain words that you do not understand. Please ask questions about anything you do not understand. We encourage you to talk to others (for example, your friends, family, or other doctors) before you decide to participate in this research study.

Please check one of the following:

_____You are an adult participant in this study.

_____You are the parent or guardian granting permission for a child in this study.

If the participant is a child the use of "you" refers to "your child"

Summary of Important Information

We are asking you to participate in this research study. Participation in this research study is voluntary. You may choose not to take part in this research study or may choose to leave the research study at any time. Your decision will not impact the clinical care you receive at Boston Children's Hospital.

In this research study we want to learn more about Lyme meningitis. We want to understand how different antibiotics impact how quickly your symptoms resolve.

It is important to consider reasons why you would or would not want to participate in this research.

Boston Children's Hospital

RESEARCH CONSENT FORM

If you decide to join this research study, the following things will happen: We will collect information about your current symptoms and treatment preferences. We will collect information about your symptoms daily for 30 days and then measure your overall health in 6 weeks and 6 months. Your clinical care will be decided upon by your doctors using their best judgement and in consultation with you. **This study will not affect in any way how you are treated for Lyme meningitis. We seek simply to learn how quickly your treatment works for you.**

The most important risk is accidental disclosure of confidential medical information. Many measures have been taken to prevent this risk.

The most important potential benefits to know about are: Participation in this study will not benefit you directly. Participation will inform the best treatment for children with Lyme meningitis in the future.

It will take you about 6 months to complete this study. During this time, we will ask you to complete brief symptom surveys daily until your symptoms resolve and then to complete phone follow-up 6 week and 6 months after enrollment.

Your clinical care will be covered by your health insurer as your treatment will not change by taking part in this research. You will receive up to $110 in gift cards for the completion of the study activities.

How are individuals selected for this research study?

You are being asked to participate in this research study because you have Lyme meningitis.

Why is this research study being conducted?

The goal of this research is to understand whether oral doxycycline works about as well as IV ceftriaxone in children with Lyme meningitis.

Who is conducting this research study, and where is it being conducted?

A grant from the National Institute of Allergy and Infectious Diseases (N.I.A.I.D.) will provide funding for this study.

How many people will participate in this research study?

Approximately 250 people will take part in this study at 20 different hospitals and medical facilities, including approximately 20 people at Boston Children's Hospital.

What do I have to do if I am in this research study?

You will participate in this study for 6 months. Participation in the study will not require you to return to Boston Children's Hospital. During your time on the study, the following things will happen:

- Today, research staff will ask you for information about your background, medical history as well as current symptoms related to Lyme disease. We will review your medical record to determine what medications you are taking. The research team will also ask youa

few questions about your Lyme meningitis treatment preferences and your overall health using the Pediatric Quality of Life survey

- You will be asked to complete am electronic daily symptom report (called the Pediatric Lyme Meningitis Symptom Measurement Instrument) and a medication compliance survey until your symptoms resolve. Completion of the survey will only take a few minutes each day.
- We will contact you electronically today as well as 6 weeks and 6 months from enrollment to complete the Pediatric Quality of Life Survey
- 6 weeks after enrollment, the study team at Rhode Island Hospital may contact you by telephone to ask you a few questions about your Lyme meningitis treatment preferences. Children older than 8 years of age will be encouraged to participate in these interviews. At this time, a trained interviewer will ask you open-questions to help the research team better understand your experiences with Lyme meningitis treatment.

- If your doctor diagnoses facial palsy (i.e. facial droop) as part of your Lyme meningitis, we will measure time to resolution using the House-Brackmann Facial Paralysis scale. To apply this scale, we require weekly full-face photo documentation for the first 6 weeks and then monthly until your facial palsy resolves or the study ends at 6 months.

- Study schedule:

Study Visit Timeline	Visit 1 Enrollment	Day 1 - 30	6 weeks	6 months	Payment
Consent /Assent	**X**				
Medical history	**X**				
Baseline preferences	**X**				
Quality of Life Questionnaire	**X**		**X**	**X**	$10 x 3 surveys
Symptom survey	**X**	**X**			$1 per response
Qualitative interview (telephone call)			X		$25 x 1
Facial photo if you have facial palsy, weekly until resolution	**X**	**X**	**X**		$5 per photo set until resolution

What are the risks of this research study? What could go wrong?

Study participation will not impact the care you will receive for Lyme meningitis. The major risk of participation will be accidental disclosure of confidential medical information. All available measures will be taken to prevent this disclosure.

Another possible risk is if questions asked in the telephone interview cause emotional distress. This unlikely because most children with Lyme meningitis recover without problems, but it is possible that the interview may cause strong emotions based on your course.

What are the benefits of this research?

Being in this research may not help you right now. When we finish the research, we hope that we will know more about antibiotic treatment for Lyme meningitis. This may help other children and adults with Lyme meningitis in the future.

Will I receive my study results?

You will not receive your individual study results. If you would like, we can provide access to the published study results after completion.

Will my samples/information be used for research in the future?

Identifiable private information collected from you during this study may be used for future research studies or shared with other researchers for future research. The identifiable private information may be used for future research of many diseases or conditions. If the research investigator distributes your information to other researchers or institutions, your information will be labeled with a research code without identifiers so that you cannot be identified. No additional consent will be requested for the future use of your information.

Are there costs associated with this research? Will I receive any payments?

There will not be any costs associated with participating in this research. The costs of your clinical care will be covered by your health insurer.

You will be paid for completion of each study follow-up visit that you complete. This will add up to between $40 and $110 depending on the number of research activities that you complete. If you leave the research early, or if we have to take you out of the research, you will be paid only for the visits you have completed.

You will be issued a ClinCard, which is a specially designed debit card for clinical research onto which your funds will be loaded as appropriate. When a study visit is completed, funds will be loaded onto your card. The funds will be available within 3 days and can be used as you wish.

If I do not want to take part in this research, what are the other choices?

If you do not join this research your doctor will continue to treat you for Lyme meningitis.

Are there other things I should know about?

If we find out about new information from this research or other research that may affect your health, safety or willingness to stay in this research we will let you know as soon as possible.

Why would I be taken off the study early?

The research investigator or N.I.A.I.D. may take you out of this study at any time. This would happen if:

- The research is stopped.
- You are not able to attend the research visits required
- The treatment team feels that it is in your best interest to be taken out of this research. If this happens, the research investigator will tell you.

Other information that may help you:

Boston Children's Hospital is interested in hearing your comments, answering your questions, and responding to any concerns regarding clinical research. If you have questions or concerns, you may email IRB@childrens.harvard.edu or call (617) 355-7052 between the hours of 8:30 and 5:00, Monday through Friday.

Who may see, use or share your health information?

A copy of this consent form will not be placed in your medical record. The results of the tests performed for research purposes will not be placed in your medical record. Because of this, it is unlikely that others within the hospital, an insurance company, or employer would ever learn of such results.

Identifiable study data and for some participants facial photography will be securely sent and stored by the study data coordinating center located at the University of Utah (Salt Lake, UT). Photos will be reviewed by a neurologist who is a consultant to the University of Utah. Study team members at Boston Children's Hospital (Boston, MA) will provide reminders when needed to complete electronic surveys. Qualitative interviews will be completed and analyzed by a team at Rhode Island Hospital (Providence, RI).

Contact for Future Studies:

Your participation in any research is completely voluntary and you should feel no pressure to participate if you are contacted about another research study.

Please check and initial one of the options below regarding future contact about other research done by us or other researchers we are working with (collaborators).

_____ ☐ Yes, I may be contacted about participating in other research projects studying Lyme disease or related conditions. I give permission for my contact information

(name and mailing address and/or phone number) to be given to other researchers working with the study investigator at Boston Children's Hospital.

_____ ☐ No, I do not want to be contacted about other research projects. **Do not** give my contact information to the staff of any other research studies.

What should you know about HIPAA and confidentiality?

Your health information is protected by a law called the Health Information Portability and Accountability act (HIPAA). In general, anyone who is involved in this research, including those funding and regulating the study, may see the data, including information about you. For example, the following people might see information about you:

- Research staff at Boston Children's Hospital involved in this study;
- Medical staff at Boston Children's Hospital directly involved in your care that is related to the research or arises from it;
- Other researchers and centers that are a part of this study, including people who oversee research at that hospital;
- People at Boston Children's Hospital who oversee, advise and evaluate research and care. This includes the ethics board and quality improvement program;
- People from agencies and organizations that provide accreditation and oversight of research;
- People that oversee the study information, such as data safety monitoring boards, clinical research organizations, data coordinating centers, and others;
- Sponsors or others who fund the research, including the government or private sponsors.
- Federal and state agencies that oversee or review research information, such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health, and public health and safety authorities;
- People or groups that are hired to provide services related to this research or research at Boston
  Children's Hospital, including services providers, such as laboratories and others;
- People or groups that are hired to conduct and analyze qualitative interviews at Rhode Island Hospital using video-conferencing and remote data collection.
- Your health insurer, for portions of the research and related care that are considered billable.

If some law or court requires us to share the information, we would have to follow that law or final ruling.

Some people or groups who get your health information might not have to follow the same privacy rules. Once your information is shared outside of Boston Children's Hospital, we cannot promise that it will remain private. If you decide to share private information with anyone not involved in the study, the federal law designed to protect privacy may no longer apply to this information. Other laws may or may not protect sharing of private health information. If you have a question

about this, you may contact the Boston Children's Hospital Privacy Officer at (857) 218-4680, which is set up to help you understand privacy and confidentiality.

Because research is ongoing, we cannot give you an exact time when we will destroy this information. Researchers continue to use data for many years, so it is not possible to know when they will be done. We will also create a code for the research information we collect about you so identifying information will not remain with the data and will be kept separately. The results of this research may be published in a medical book or journal or be used for teaching purposes.

Your privacy rights

If you want to participate in this research study, you must sign this form. If you do not sign this form, it will not affect your care at Boston Children's Hospital now or in the future and there will be no penalty or loss of benefits. You can withdraw from the study and end your permission for Boston Children's Hospital to use or share the protected information that was collected as part of the research; however, you cannot get back information that was already shared with others or included in research analysis. Once you remove your permission, no more private health information will be collected. If you wish to withdraw your health information, please contact the research team.

You may have the right to find out if information collected for this study was shared with others for research, treatment or payment. You may not be allowed to review the information, including information recorded in your medical record, until after the study is completed. When the study is over, you will have the right to access the information again. To request the information, please contact the Hospital's Privacy Officer at (857) 218-4680.

Certificate of Confidentiality

The National Institutes of Health has issued a Certificate of Confidentiality for this research. This adds special protection for the research information and specimens that may identify you. The researchers may not disclose information that may identify you, even under a court order or subpoena unless you give permission. However, a Certificate of Confidentiality does not prevent researchers from disclosing information about you if required by law (such as to report child abuse, communicable diseases or harm to self or others); if you have consented to the disclosure (such as for your medical treatment); or if it is used for other research as allowed by law. In addition the Certificate cannot be used to refuse a request if a governmental agency sponsoring the project wants to audit the research. Any research information that is placed in your medical record would not be covered under this Certificate. The Certificate will not be used to prevent disclosure for any purpose you have consented to in this informed consent document. The Certificate does not stop you from voluntarily releasing information about yourself or your involvement in this research. If others obtain your written consent to receive research information, then the researchers may not use the Certificate to withhold that information

Boston Children's Hospital

RESEARCH CONSENT FORM

Contact Information

I understand that I may use the following contact information to reach the appropriate person/office to address any questions or concerns I may have about this study. I know:

I can call…	At	If I have questions or concerns about
Investigator: **Lise Nigrovic, MD MPH**	Phone: **617-355-5862** Pager: 617-355-7243 **[2745]**	▪ General questions about the study ▪ Research-related injuries or emergencies ▪ Any research-related concerns or complaints
Research Contact	Phone: **617-355-4897** Pager: 617-355-7243	▪ Rights of a research participant▪ Use of protected health information. ▪ Compensation in event of research-related injury ▪ Any research-related concerns or complaints. ▪ If investigator/research contact cannot be reached. ▪ If I want to speak with someone other than the Investigator, Research Contact or research staff.
Institutional Review Board	Phone: **617-355-7052**	▪ General questions about the research ▪ Research-related injuries or emergencies ▪ Any research-related concerns or complaints

Documentation of Informed Consent and Authorization

☐ I have read this consent form and was given enough time to consider the decision to participate in this research.

☐ This research has been satisfactorily explained to me, including possible risks and benefits.

☐ All my questions were satisfactorily answered.

☐ I understand that participation in this research is voluntary and that I can withdraw at any time.

☐ I am signing this consent form prior to participation in any research activities.

I give permission for participation in this research and for the use of associated protected health information as described above (HIPAA).

Boston Children's Hospital

RESEARCH CONSENT FORM

Parent/Legal Guardian Permission (if applicable)

If the child to be involved in this research is a foster child or a ward of the state please notify the researcher or their staff who is obtaining your consent.

■ ___ _____ _____
Date (MM/DD/YEAR) Signature of **Parent #1** or **Legal Guardian** Relationship to child

Child Assent

■ _____ _____
Date (MM/DD/YEAR) Signature of **Child/Adolescent Participant**

■ If child/adolescent's assent is **not** documented above, please indicate reason below (check one):
- ☐ Assent is documented on a separate IRB-approved assent form
- ☐ Child is too young
- ☐ Other reason (e.g., sedated), please specify:_____

Adult Participant (if applicable)

■ _____ _____
Date (MM/DD/YEAR) Signature of **Adult Participant (***18+ years)*

Research Investigator /or Associate's Statement & Signature

☐ I have fully explained the research described above, including the possible risks and benefits, to all involved parties (participant /parents/legal guardian as applicable).

☐ I have answered and will answer all questions to the best of my ability.

☐ I will inform all involved parties of any changes (if applicable) to the research procedures or the risks and bene☐ I have provided a copy of the consent form signed by the participant / parent / guardian and a copy of the hospital's privacy notification (if requested).

■ _____ _____ Date (MM/DD/YEAR)
Signature of **Research Investigator or Associate**

Boston Children's Hospital

RESEARCH CONSENT FORM

Witness Statement & Signature

A witness must be present for the entire consent process in the following situations (please check the appropriate box)

☐ The individual cannot read and this consent document was read to the participant or legal representative,

or

☐ The individual has certain communication impairments that limit the participant's ability to clearly express consent

I confirm that the information in this consent form was accurately explained to the participant, parent or legally authorized representative, the individual appeared to understand the information and had the opportunity to ask questions, and that informed consent was given freely.

☐ _____ _____

Date (MM/DD/YEAR) Signature of Witness

Or

☐ The individual is not English speaking and, through an interpreter, a short form consent document was presented orally to the participant or legal representative and this consent document serves as the summary for such consent.

I confirm that the information in this consent form was presented orally to the participant, parent or legally authorized representative, in a language they could understand and the individual had the opportunity to ask questions.

☐ _____ _____

Date (MM/DD/YEAR) Signature of Witness

Boston Children's Hospital

RESEARCH ASSENT FORM

Protocol Title: Comparative effectiveness and complications of intravenous ceftriaxone compared with oral doxycycline in Lyme meningitis

Principal Investigator: Lise Nigrovic, MD MPH

We want to tell you about a research study we are doing. A research study is a way to learn more about something. We would like to find out more about the treatment for Lyme meningitis. You are being asked to join the study because you have been diagnosed with Lyme meningitis.

If you agree to join this study, your treatment will be the exact same as if you were not in the study. Your doctors will still work with your family to choose the treatment they believe is best for you. We seek to find out how well this treatment works by asking you to report how you are feeling every day (up to 30 days) until you get better. If your face is not moving normally due to the Lyme disease, we will ask you to provide weekly pictures showing how your face moves. At 6 weeks, we may ask you and your parent questions about how you are feeling and your thoughts about the treatment you received.

The risk of study participation is possible disclosure of your confidential medical information. We will do everything possible to prevent that from happening

Being in this study will not help you, but we hope that what we learn will help other people with Lyme meningitis someday.

You do not have to join this study. It is up to you. You can say okay now and change your mind later. All you have to do is tell us you want to stop. No one will be mad at you if you don't want to be in the study or if you join the study now and change your mind later.

Before you say **yes or no** to being in this study, we will answer any questions you have. If you join the study, you can ask questions at any time. Just tell the researcher that you have a question.

If you have any questions about this study please feel free to contact the Pedi Lyme Net study coordinator [Rachael Aresco, BA at 617-355-4897 or by page at 617-355-7243].

If you sign your name below, it means that you agree to take part in this research study.

Child/Adolescent Assent

■ _____ _____

Date (MM/DD/YEAR) Signature of **Child/Adolescent Subject**

Boston Children's Hospital

Lyme Meningitis Study

With more than 300,000 new cases of Lyme disease each year in the U.S., approximately half of new cases occur in children. Children with Lyme meningitis usually have a headache, fever and fatigue. Children diagnosed with Lyme meningitis are treated with either oral or intravenous antibiotics.

We are conducting a study to evaluate 2 things:

1. Compare the two medications usually used to treat Lyme Meningitis to determine if one has better outcomes or is more manageable for families.
2. Determine patient, parent and clinician preferences for the treatment of Lyme meningitis to inform future decision-making

To do this, we will be enrolling 250 children at 20 U.S. medical centers where Lyme disease is endemic. Treatment decisions will be made by you and your child's medical team. **This study will not affect in any way how you/your child are treated for Lyme meningitis. We seek simply to learn how quickly your treatment works for you.** You may be in this study if you:

- ✓ Are between 1 and 21 years old
- ✓ Have been recently diagnosed with Lyme Meningitis
- ✓ Treatment plan includes oral doxycycline or IV ceftriaxone/cefotaxime

If you decide to join this research study, we will collect the following information:

- Current symptoms and treatment preferences
- Daily symptoms until improved (30 days maximum)
- Phone interview at 6 weeks
- If your child has peripheral facial palsy, weekly facial photos until resolution

If you are discharged today, without knowing all of your test results, you may be called within the next week to provide verbal consent for the study and to begin the above study procedures. Participation in this study will not benefit you directly. Participation will inform the best treatment for children with Lyme meningitis in the future. It will take you about 6 months to complete this study. The most likely risk is accidental disclosure of confidential medical information. Many measures have been taken to prevent this risk.

Your clinical care will be covered by your health insurer as your treatment will not change by taking part in this research. **You will receive between $50 and $110 in gift cards for the completion of study activities.**

If you have any questions about this study, please contact the Principal Investigator at Boston Children's Hospital by calling:617-355-5862 or Email: **LymeMeningitis@childrens.harvard.edu.**

PEDILYMENET MENINGITIS STUDY

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5 Supplemental Table 1
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6 Table 1
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	*
		(*d*) If applicable, explain how loss to follow-up was addressed	*
		(*e*) Describe any sensitivity analyses	n/a
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	n/a Study protocol only
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	n/a
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) Summarise follow-up time (e.g., average and total amount)	n/a
Outcome data	15*	Report numbers of outcome events or summary measures over time	n/a
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	n/a
		(*b*) Report category boundaries when continuous variables were categorized	n/a
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	n/a
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	n/a
Generalisability	21	Discuss the generalisability (external validity) of the study results	n/a
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1-2

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.