





BMJ Open Comparative effectiveness and complications of intravenous ceftriaxone compared with oral doxycycline in Lyme meningitis in children: a multicentre prospective cohort study

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ABSTRACT

Introduction Lyme disease is the most common vectorborne disease in the Northern hemisphere with more than 400 000 new cases in the USA 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 with intravenous 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 20 US paediatric centres located in diverse geographical 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 6 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 centre relying on the Boston Children's Hospital sIRB. Once the study is completed, we will publish our findings in a peer-reviewed medical journal.

INTRODUCTION

With more than 400 000 new cases of Lyme disease each year in the USA, children are disproportionately affected.^{1 2} Lyme meningitis, an uncommon but 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

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Inclusion of 20 centres located in Lyme disease-endemic areas in the Northeast, Mid-Atlantic and Upper Midwest regions of the USA will capture a clinically and geographically diverse group of children with Lyme meningitis.
- ⇒ The prospective pragmatic design allows for standardised 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.

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 healthcare 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 6-month post-treatment quality of life after treatment with either doxycycline



or ceftriaxone?; (3) What are patient and parent preferences regarding treatment decisions?

The updated Infectious Disease Society of America, American Academy of Neurology, and American College of Rheumatology Lyme disease guideline^{8–10} recommends 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 (eg, 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 intravenous 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 predominant *Borrelia* strains differ (ie, *B. garinii* and *B. afzelii*).^{5,6,12} A more recent retrospective study of 38 US 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 paediatric neuroborreliosis concluded that the current evidence is insufficient to recommend doxycycline instead of beta-lactam antibiotics.^{13–15} Factors limiting the rigour 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 paediatric 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 paediatric Lyme meningitis study, enrolling children at 20 US centres located in regions of the USA 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 6 months. We will enrol 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 hypothesise that oral doxycycline is non-inferior to intravenous ceftriaxone for time to resolution of Lyme meningitis symptoms.

Aim 2. Comparative effectiveness for 6-month post-treatment quality of life: to compare oral doxycycline with intravenous ceftriaxone on 6-month post-treatment quality of life in children with Lyme meningitis using the Pediatric Quality of Life Inventory. We hypothesise 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 (pretreatment and post-treatment surveys as well as exit interviews). We hypothesise 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 aims 1 and 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 20 centres located in Lyme disease-endemic areas of the Northeast, Mid-Atlantic and Upper Midwest (online supplemental figure

1) using Strengthening the Reporting of Observational Studies in Epidemiology standards.

Patient selection and inclusion/exclusion criteria

Study staff started screening for potentially eligible patients on 2 July 2022 (study start date varied by centre). 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

1. Age 1 year–≤21 years.
2. Definite or probable meningitis:
 - Definite: meningitis defined as cerebrospinal fluid white cell count ≥10 cells per mm³.
 - Probable: clinical diagnosis of meningitis.
3. Positive two-tiered Lyme disease serology obtained within 7 days of enrolment:
 - 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

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 enrolment.
3. Conditions that would preclude the assessment of the Pediatric Lyme Meningitis Symptom Survey (ie, pa-

tient/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 enrolment.

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 3 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 enrolment. The PedsQL Instrument, validated for many illnesses with neurological 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.

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		1 Yes	
5. Did you have any problems with their vision, such as double vision?			
0 No		1 Yes	

Figure 1 Pediatric Lyme Meningitis Symptom Measurement Instrument.

**Table 1** Lyme meningitis schedule of study activities

	Screening	Baseline	Follow-up							
	Day -7 up to Day 0	Consent (Day 0)	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) ± 2 w	Month 6 (Day180)±1 mo
Screening and eligibility	X									
Consent/Assent		X								
Demographics		X								
Medical history		X								
Medication history		X								
Laboratory results	X									
ECG	X									
Neuroimaging Report	X									
Treatment preference survey		X								
Clinician survey		X								
Facial palsy pictures		X	X	X	X	X		X	X	X
Qualitative interview									X	
Contact information		X								
History of present illness		X								
Paediatric Lyme Meningitis Symptoms Measurement		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 if <18 and self-report of >18 years)		X							X	X
Month 6 Treatment Chart Review										X
Month 6 Healthcare Utilisation Chart Review										X

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 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 (eg, corticosteroids) from the electronic health record at baseline and again 6 months from enrolment. 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 3 consecutive days up to 30 days from enrolment (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 6 weeks, biweekly then monthly after 2 months until resolution. Facial photographs will be taken at home and uploaded to a secure study database (online 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.

Stopping Rules
 1) If parent/patient has 3 missing days in a row, then stop. Parent/patient is considered censored.
 2) If parent/patient has 3 days with a score = 0, without any days with a score > 0 inbetween, then stop. Parent/patient is considered resolved.
 3) If parent/patient hits Day 30 without resolution, then stop. Parent/patient 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

Figure 2 Stopping rules for the daily Lyme Meningitis Symptom Score Survey.

To assess treatment preferences, we will survey patient/parents as well as the treating clinician about baseline treatment preferences. At the 6-week 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 semistructured interview format and last approximately 30 min. 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 ClinCards¹⁸ for each study activity completed.

Withdrawal from study

Anytime 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 centre

The data coordinating centre (DCC) at the University of Utah provides data coordination and management

including a state-of-the-art, energy-efficient data centre 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 computer 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. Standardised 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 enrolment, follow-up rates and data quality. Study monitoring will be used to ensure data quality. The DCC uses risk-based methodology to identify and correct problems that may arise at sites. The risk-based approach to monitoring focuses on oversight activities and prevents or mitigates key risks to data quality, as well as to processes critical to human subject protection and integrity of the trial or study.

Table 2 House-Brackmann score for assessment of peripheral facial palsy

Score	Overall severity	Appearance at rest	With motion			Abnormal involuntary contraction*
			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	Moderately 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

*Facial muscle spasm, synkinesis or contracture.



Site monitoring

Site monitoring visits will be performed by a trained site monitor either in person or remotely to ensure regulatory compliance and 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 enrolment), 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 programme for investigators and research staff prior to the start of enrolment 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 utilisation rates of doxycycline and ceftriaxone in Lyme meningitis, volume, quality measures and case mix. Categorical data will be analysed using either a χ^2 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 vs intravenous ceftriaxone) as the primary predictor.

For aim 1, if the upper bound on the 95% CI for the increase in propensity score adjusted mean time to resolution of symptoms for patients treated with oral doxycycline compared with intravenous ceftriaxone is 3 days or less, then we will consider doxycycline non-inferior to ceftriaxone. We identified the 3-day threshold as a meaningful cut-off in our previous study of parental preferences.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 with 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 analysis²⁰ will be used to analyse exit interview data. Passages of the transcript that represent areas of particular interest are identified with codes (eg, 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 intercoder concordance is $\geq 85\%$. 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 summarised. 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 enrolment. Based on our Delphi survey, we estimate that children with Lyme meningitis average 5 days to resolution of symptoms with an SD 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 with intravenous ceftriaxone, a sample size of 250 patients ($n=200$ in oral doxycycline group and $n=50$ in intravenous ceftriaxone group) will obtain 93% power assuming a 5% type I error rate (table 3).

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

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%

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 an SD 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 approval

Boston Children's Hospital will be the single Institutional Review Board (sIRB) of record for this multicentre study, responsible for maintaining records related to the reliance agreements and the communication plan. The Boston Children's study principal investigator 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 centres and will not permit subject enrolment 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 authorisation

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

Parental permission/subject consent

We will obtain informed consent from parents or legal guardians of eligible children under 18 years of age (online supplemental figure 3). Patients 18 years and older will consent for themselves. If a child turns 18 years in the follow-up period, the participant will be reconsented. 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 (online supplemental figure 4). If positive Lyme disease serology results return 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 and 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 (online 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 as minimal risk. Loss of subject confidentiality is a potential study risk; 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 interviewer will proceed carefully in the case structured discussion causes 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 minimise 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

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 organise and disseminate those experiences with clinicians, other scientists and the public to inform future practice for children with Lyme meningitis.

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Contributors 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. SV designed qualitative methods and contributed to study design. JH 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. BJB 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.

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