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Lyme disease research in the HPRU EZI

The LYME-UK Study

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Research Fellow (non-clinical)

- Life scientist with an interest in molecular biology
- Disease models and personalized medicine
- Interest in clinical research through lab-based study
- Clinical research from protocol development to data analysis
- Alter Ego as a PT and fitness instructor

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Introduction

- HPRU EZI
- Lyme disease research study proposal from 2019
- LYME-UK Cohort study: Aims/Primary Care/Study Design
- Timescales and Further Proposals
- Problems
- Where we are now: Feasibility plans

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HPRU EZI

- National Institute for Health Research Health Protection Research Unit in Emerging Zoonotic Infections
  http://www.hpruezi.nihr.ac.uk
- One of 14 HPRU's: Conducting high quality research to support PHE
- Previous Lyme disease project by John Tulloch on healthcare data sets and Lyme disease surveillance with PHE

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Further Funding HPRU EZI 2020

Lyme disease one of three research projects:
Patient research for public health research theme

Plans for a prospective cohort study had been proposed in 2019

HPRU EZI Director: Tom Solomon
LYME-UK Study CI: Neil French
PHE study co-investigators

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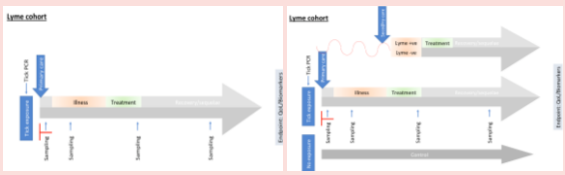
Original Prospective Study Proposal



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Study Aims

1. Describe the presenting symptoms and patient recollection of tick bite
2. Characterize the rash and generate a Photo 'library'.
3. To measure and describe the patient's health, quality of life and functional outcomes over 12 months
4. To describe the antibody evolution in patients with early Lyme disease over 6 months
5. To establish a panel of patient samples (serum/plasma/RNA/urine) that are well-characterized in terms of Lyme disease infection and including a smaller group of "Gold standard" samples

Further Aims

- Other tick-borne infections
- Identifying infecting genospecies (skin biopsy subgroup)
- Testing of the core outcome set

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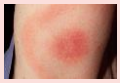
Why Early Lyme Disease in Primary Care?

- Serology is inaccurate in early Lyme disease
- Avoiding participant selection or stratification using serology
- Clinical diagnosis from Erythema Migrans (60% of cases)
- Gold standard group: directly confirmed infection in small subset of cases (skin biopsy PCR)
- Patient outcomes from early treated disease (observational)
- Seroconversion profile in treated early Lyme disease
- Diagnostic methodologies need to be effective at identifying active early disease



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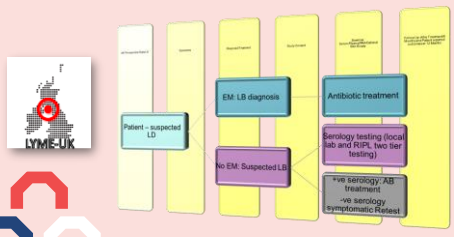
Current Protocol: Longitudinal Observational Study



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Primary and Secondary Care

Early Localised LD (days/weeks) LYME-UK Study: Feasibility phase proposed late summer 2021	Expanding EM at site of bite (60% +) +/- flu like symptoms (temperature/headaches/muscle pain/joint pain)
Early Disseminated LD (days/weeks) Joint Proposal (+ Paediatric cases): Applications for funding 2021/22 Proposed recruitment Spring/Summer 2022	EM/rash distant from bite, flu like symptoms, neurological, facial paralysis (Bell's palsy)/joint/cardiac/Paediatrics
Late disease (months/years) Further funding and collaborative work	Neurological/cardiac/joint/skin (ACA)/severe fatigue/memory loss

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The Pandemic and Other Issues!

- Difficulties with primary care and GP engagement due to capacity
- Virtual GP appointments
- Pandemic backlog and capacity with MIU's and Dermatology
- Priority to COVID research

- Small numbers of potential participants at each site
- Limited budget for prospective study costs
- Participant pathway for study participation and skin biopsy procedure (potential extra visits)
- Retaining participant engagement for follow-up

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Feasibility Phase

Initial pilot proposal at a single site is currently under development:

- Will focus on suspected Lyme disease with EM, but will NOT initially involve skin biopsy procedure
- Proposed to recruit (dependent on site capacity) August to October 2021
- Establish recruitment rates
- Screening log data analysis
- Participant retention for follow-up visits and patient reported data
- Recruitment will be paused November to March and feasibility assessed for the full study, with further sites identified for recruitment from April to October 2022

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ANY COMMENTS OR QUESTIONS?

Attendee	Question
Dorothy & Pete	How do you get on your patient cohort
Patient recruitment will be in primary care – patients who present at their GP or local MIU with suspected LD. Study sites will be selected in areas where LD is more commonly diagnosed.	
Janey Cringean	Why is the study over only 12 months when serious symptoms develop over years not months? Much longer study is required to see the full effect of symptom development, even for untreated patients.
Unfortunately the cost to fund a research study over years is substantial and the LYME-UK study has limited funding that restricts what we can do and how long we are able to follow patients. It can also be difficult in longitudinal studies to retain participants, even for a 12-month follow-up. Study consent will include an option for the participant to be contacted in the future to consider further participation or follow-up.	
ZH	The study assumes a level of awareness amongst primary and secondary care professionals of Lyme disease, and ability to recognise erythema migrans, and knowledge to treat it...
Recent experience suggests that participating study sites are likely to self-select with a bias towards those professionals with an interest in Lyme disease. Sites will be located in areas of high incidence and with professionals who are experienced in LD diagnosis.	
Anne Cruikshank	diagnosing/ recognising EM rashes even for experienced GPs is not necessarily straightforward
We are unlikely to be successful setting up sites where there is not a local interest in Lyme disease as we will need a local collaborator/Principle Investigator at each site. So far, these discussions have involved professionals who are interested in Lyme disease and recognise the issue locally. We also hope the study will contribute to understanding less characteristic rash presentation.	
Michael	The focus is on "suspected Lyme" with EM rash. However, EM rash is 100% diagnostic for Lyme. What was the source of the 60% EM rash with patients?
Agreed - "suspected" LD with EM IS a clinical diagnosis. For the study the "gold standard" samples will also have a positive PCR (i.e. confirmed infection). This is not disputing the clinical diagnosis, but to provide samples that link to confirmed active infection, for testing diagnostic methodologies. 60% relates to the number of patients infected with LD *who subsequently* develop the EM rash (Dryden et al 2014 – UK paper) – generally higher in US publications.	
ZH	Are there any plans for a retrospective arm, to look at patients with disseminated disease (months or years down the line from initial infection)?
Potentially there will be retrospective work, although the key aims are to develop a sample repository that is useful for diagnostics and representative of disease subgroups.	

ZH	Could you provide a link to the graphic of the map of borrelia prevalence?
This was meant to be a background for text (as shown in the pdf's_ - apologies for the glitch when transferring the slides over to LDA). It is not an official graphic, so there is not a link and represents tick species rather than borrelia.	
Julia Knight	It would be better if Gp's are informed about the behaviour of a developing EM rash rather that just straight photos. So many Drs don't seem to be aware of the significance of how it develops and don't take a history of the development of the rash
We may be able to get some patient reported data/photo's on this.	
Anne Cruikshank	Lyme disease isn't on most clinicians' radars - until that happens cases will continue to be missed
This is not really in the remit of the study and the study is likely to bias towards areas where there is more awareness (as already mentioned, sites are very unlikely to have the capacity or inclination to recruit if there is not an invested local collaborator/PI present). I think professional education on diagnosis is really linked in to surveillance and do not disagree that it is a whole other area of research that is needed.	
Geraldine	Study of developing rashes is a good idea
As above – this may be something that can be developed in the patient reported data.	