

Lyme disease: diagnosis and management

[N] Evidence review for information needs

NICE guideline

Evidence review

September 2017

Draft for Consultation

*This evidence review was developed by
the National Guideline Centre*

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1 Information needs

1.1 Review question: What information do people with suspected, confirmed or treated Lyme disease need?

1.2 Introduction

Informative and clear communication for people with suspected Lyme disease is essential. Lyme disease is uncommon in the UK and many of the facts about diagnosis and treatment are contested. NICE has developed guidance on patient experience in adult NHS services that includes recommendations on information for patients (CG138). An evidence review was included in the guideline to understand what specific needs people with Lyme disease may have. This section includes report and discussion of the evidence review. Many of the recommendations on information are included and discussed in other sections of the guideline where they are presented with recommendations on diagnosis and management.

1.3 Characteristics table

For full details, see the review protocol in appendix A.

Table 1: Characteristics of review question

Objective	The aim of this review is to determine what information should be provided to people who have either received a diagnosis of Lyme disease, who are currently under investigation for Lyme disease or who were treated for Lyme disease previously.
Population and setting	<ul style="list-style-type: none"> • People with suspected Lyme disease • People with confirmed Lyme disease • People who were treated for Lyme disease previously
Context	<p>Any type of information described by studies</p> <ul style="list-style-type: none"> • Content of information required and how this information is delivered • Information for carers and family members as well as information for patients • Timing of information
Review strategy	<p>Study designs to be considered:</p> <ul style="list-style-type: none"> • Any type of qualitative study designs <p>Review strategy:</p> <ul style="list-style-type: none"> • Population size and directness: <ul style="list-style-type: none"> ○ No minimum sample size ○ Studies with indirect populations will not be considered (for example, people with other tick-borne illnesses) <p>Appraisal of methodological quality</p> <p>The methodological quality of each study will be assessed using NGC-modified NICE checklists and the quality of the body of evidence as a whole will be assessed by a GRADE CerQual approach for each review finding.</p> <p>Data synthesis</p> <p>Synthesis of qualitative research: thematic analysis – information will be synthesised into main review findings. Results presented in a detailed narrative and in table format with summary statements of main review findings.</p>

1 1.4 Qualitative evidence

2 1.4.1 Included studies

3 Two qualitative studies were included in the review;^{14,21} these are summarised in Table 2
4 below. Key findings from these studies are summarised in Section 1.4.5 below. See also the
5 study selection flow chart in appendix C, study evidence tables in appendix D, and excluded
6 studies lists in appendix G.

7 One study, which included people with chronic Lyme disease mainly recruited from self-help
8 groups, aimed to obtain greater insight into the dynamics of trust. The other study aimed to
9 gather information on people's experiences and ways of making sense of post-treatment
10 Lyme disease syndrome or chronic Lyme disease as a medically contested, chronic illness.

11 1.4.2 Excluded studies

12 See the excluded studies list in appendix G.

13 1.4.3 Summary of qualitative studies included in the evidence review

14 **Table 2: Summary of studies included in the review**

Study	Design	Population	Research aim	Comments
Mechanic 2000 ¹⁴	Qualitative study (semi-structured open-ended interview with thematic qualitative analysis)	N=30 Adults with physician-diagnosed Lyme disease who had a minimum of 2 visits with a physician who was treating them	To obtain greater insight into the dynamics of trust and to identify concepts that need development in surveys with more representative samples	90 people in total; (30 with chronic Lyme disease, 30 with breast cancer, 30 with mental illness) 25 people with Lyme disease were female 25 people with Lyme disease recruited from self-help groups, 3 by word-of-mouth, 2 through a Lyme disease clinic
Rebman 2015 ²¹	Qualitative study (semi-structured open-ended interview with thematic qualitative analysis)	N=29 Adults tentatively meeting a case definition for post-treatment Lyme disease syndrome (initial Lyme disease episode marked by either EM or positive blood serology and concurrent objective signs consistent with late Lyme disease or unexplained flu-like illness), all	To gather illness narratives to contribute to the small body of qualitative research that gives primacy to people's experiences and ways of making sense of PTLDS/CLD as a medically contested, chronic illness To examine how	Sample drawn from the clinical practice of 1 of the authors Substantial variation in the clinical histories and symptom severities

Study	Design	Population	Research aim	Comments
		had been ill for ≥ 6 months	people's experiences could inform an understanding of the personal and social cost of this illness and assist in setting future research priorities	

1 See appendix D for full evidence tables.

2 1.4.4 Qualitative evidence synthesis

3 **Table 3: Review findings**

Main findings	Statement of finding
Medical uncertainty	The absence of established treatment and disease prognosis guidance leads to uncertainty, frustration and fear among people with Lyme disease, as well as inter-physician subjectivity
Acknowledgement of medical uncertainty	The ability of the physician to admit a lack of technical knowledge or competency in a particular area is important to people with Lyme disease
Support from other people with Lyme disease	Interaction with other people through existing personal networks provides support and validation for people with Lyme disease, but not through support groups
Advocacy and information sharing	For people with Lyme disease who attend self-help groups, advocacy as well as getting and sharing information about physicians, insurance coverage and treatment approaches are important

4 1.4.4.1 Narrative summary of review findings

5 **Review finding 1: Medical uncertainty**

6 One study showed that for many people with Lyme disease, the absence of established
7 treatment and disease prognosis guidance leads to uncertainty, frustration and fear
8 regarding the nature and duration of expected future symptoms and an inability to gauge the
9 normality of their own experience. People often experience inter-physician differences, as
10 they receive a range of diagnoses and treatment plans by different physicians at different
11 stages of their disease.

12 Explanation of quality assessment: minor methodological limitations in the contributing
13 studies as the data are not sufficiently rich; minor concerns about the coherence of the
14 finding with nothing to lower our confidence; no concerns about relevance; minor concerns
15 about adequacy as the richness and quantity of the evidence supporting the finding is low.
16 There was a judgement of moderate confidence in this finding due to concerns regarding the
17 data richness and quantity.

18 **Review finding 2: Acknowledgement of medical uncertainty**

19 Evidence from 1 study, which recruited people with Lyme disease mainly from self-help
20 groups, showed that the ability of the physician to admit a lack of technical knowledge or
21 competency in a particular area is important to people with Lyme disease. This was reflected

1 in the greater frequency with which the Lyme disease group talked about competency
2 compared with the breast cancer and mental illness groups.

3 Explanation of quality assessment: severe methodological limitations in the contributing
4 studies as the setting is not clearly described, the data are not sufficiently rich and the finding
5 is not convincing; minor concerns about the coherence of the finding with nothing to lower
6 our confidence; partial relevance due to the contributing studies mainly representing the
7 experience of female Lyme disease patients and those from self-help groups; substantial
8 concerns about adequacy as the richness and quantity of the evidence supporting the finding
9 is very low. There was a judgement of very low confidence in this finding due to concerns
10 regarding methodological limitations, partial applicability to the whole Lyme disease
11 population and the data richness and quantity.

12 **Review finding 3: Support from other people with Lyme disease**

13 People with Lyme disease in 1 study expressed feelings of validation and support from
14 interaction with other people from their own existing personal networks. By 'sharing our
15 experience' and 'being a sounding board for each other', they are able to cope better with
16 feelings of isolation and uncertainty. However, most people were not interested in attending
17 in-person or online support groups.

18 Explanation of quality assessment: minor methodological limitations in the contributing
19 studies as the data are not sufficiently rich; minor concerns about the coherence of the
20 finding with nothing to lower our confidence; no concerns about relevance; minor concerns
21 about adequacy as the richness and quantity of the evidence supporting the finding is low.
22 There was a judgement of moderate confidence in this finding due to concerns regarding the
23 data richness and quantity.

24 **Review finding 4: Advocacy and information sharing**

25 Lyme disease respondents, who were largely recruited from self-help groups, were more
26 focussed on issues of advocacy as well as getting and sharing information about physicians,
27 insurance coverage and treatment approaches than breast cancer or mentally ill
28 respondents.

29 Explanation of quality assessment: severe methodological limitations in the contributing
30 studies as the setting is not clearly described, the data are not sufficiently rich and the finding
31 is not convincing; minor concerns about the coherence of the finding with nothing to lower
32 our confidence; partial relevance due to the contributing studies mainly representing the
33 experience of females with Lyme disease and those from self-help groups; substantial
34 concerns about adequacy as the richness and quantity of the evidence supporting the finding
35 is very low. There was a judgement of very low confidence in this finding due to concerns
36 regarding methodological limitations, partial applicability to the whole Lyme disease
37 population and the data richness and quantity.

1.4.5 Qualitative evidence summary

Table 4: Summary of evidence

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
Medical uncertainty					
1	Semi-structured open-ended interviews	REVIEW FINDING: The absence of established treatment and disease prognosis guidance leads to uncertainty, frustration and fear among people with Lyme disease, as well as inter-physician subjectivity	Limitations	Minor concerns about methodological limitations	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy	
Acknowledgement of medical uncertainty					
1	Semi-structured open-ended interviews	REVIEW FINDING: The ability of the physician to admit a lack of technical knowledge or competency in a particular area is important to people with Lyme disease.	Limitations	Serious concerns about methodological limitations	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance	
			Adequacy	Serious concerns about adequacy	

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
Support from other people with Lyme disease					
1	Semi-structured open-ended interviews	REVIEW FINDING: Interaction with other people who have Lyme disease through existing personal networks provides support and validation for people with Lyme disease but not through support groups	Limitations	Minor concerns about methodological limitations	MODERATE
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Minor concerns about adequacy	
Advocacy and information sharing					
1	Semi-structured open-ended interviews	REVIEW FINDING: For people with Lyme disease who attend self-help groups, advocacy as well as getting and sharing information about physicians, insurance coverage and treatment approaches are important	Limitations	Serious concerns about methodological limitations	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Minor concerns about relevance	
			Adequacy	Serious concerns about adequacy	

1 1.5 Economic evidence

2 1.5.1 Included studies

3 No relevant health economic studies were identified.

4 1.5.2 Excluded studies

5 No health economic studies that were relevant to this question were excluded due to
6 assessment of limited applicability or methodological limitations.

7 1.6 Resource impact

8 We do not expect recommendations resulting from this review area to have a significant
9 impact on resources.

10 1.7 Evidence statements

11 1.7.1 Qualitative evidence statements

12 Two qualitative studies suggested the following about the information people with chronic
13 Lyme disease might need:

- 14 • Moderate quality evidence from 1 study suggested that people with Lyme disease need
15 established treatment and disease prognosis guidance to reduce experiences of
16 uncertainty, frustration and fear.
- 17 • Very Low quality evidence from 1 study suggested that the ability of the physician to admit
18 a lack of technical knowledge or competency in a particular area is important to people
19 with Lyme disease.
- 20 • Moderate quality evidence from 1 study suggested that interaction with other people who
21 have Lyme disease through existing personal networks provides support and validation for
22 people with Lyme disease but not through support groups.
- 23 • Very Low quality evidence from 1 study in people with Lyme disease who attend self-help
24 groups suggested that advocacy as well as getting and sharing information about
25 physicians, insurance coverage and treatment approaches are important.

26 1.7.2 Health economic evidence statements

27 No relevant economic evaluations were identified.

28 1.8 Recommendations

29 N1. Explain to people diagnosed with Lyme disease that:

- 30 • Lyme disease is a bacterial infection treated with antibiotics
- 31 • most people recover completely
- 32 • prompt antibiotic treatment reduces the risk of further symptoms developing and
33 increases the chance of complete recovery
- 34 • it may take time to get better, but their symptoms should continue to improve in the
35 months after antibiotic treatment
- 36 • they may need additional treatment for symptom relief.

- 1 N2. Explain to people who are starting antibiotic treatment for Lyme disease that some
2 people may experience a worsening of symptoms early in treatment. Tell them to contact
3 their doctor if this happens and not to stop their antibiotic treatment.
- 4 N3. Advise people to talk to their doctor if their symptoms have not improved or if symptoms
5 return after completing treatment.
- 6 N4. Explain to people with Lyme disease that infection does not give them lifelong immunity
7 and that it is possible for them to be re-infected and develop Lyme disease again.

8 **1.9 Rationale and impact**

9 **1.9.1 Why the committee made the recommendations**

10 There was a lack of evidence identified on the information needs of people with suspected or
11 confirmed Lyme disease, or specific Lyme disease presentations. However, some evidence
12 was identified that highlighted the need for information addressing medical uncertainty. The
13 guideline committee used this evidence, the evidence reviews on diagnosis and
14 management, and their experience to make recommendations to inform people being
15 investigated for and diagnosed with Lyme disease. The committee agreed that people would
16 benefit from a better understanding of the nature of Lyme disease, the accuracy and
17 limitations of testing, and issues with treatment and follow-up.

18 **1.9.2 Impact of the recommendations on practice**

19 The recommendations standardise and reinforce good practice, and many healthcare
20 professionals will not need to change their current practice.

21 **1.10 The committee's discussion of the evidence**

22 **1.10.1 Interpreting the evidence**

23 **1.10.1.1 The quality of the evidence**

24 The evidence quality ranged from Moderate to Very Low due to concerns regarding
25 methodological limitations, relevance and adequacy. In particular, issues concerning the
26 richness of the data, depth of analysis and the applicability of findings from the samples to
27 the whole Lyme disease population limited our confidence in the evidence. Both studies were
28 based on people with chronic Lyme disease and 1 study included mainly females attending
29 self-help groups.

30 **1.10.1.2 Findings identified in the evidence synthesis**

31 Evidence from 1 study suggested that people with Lyme disease need guidance on
32 established treatments and disease prognosis. Evidence from 1 study suggested that the
33 ability of the physician to admit a lack of technical knowledge or competency in a particular
34 area is important to people with Lyme disease. Evidence from 1 study suggested that
35 interaction with other people with Lyme disease through existing personal networks provides
36 support and validation for people with Lyme disease, but not through support groups.
37 Evidence from 1 study in people with Lyme disease who attend self-help groups suggested
38 that advocacy as well as getting and sharing information about physicians, insurance
39 coverage and treatment approaches are important.

40 No direct evidence on the information needs of people with suspected Lyme disease, acute
41 Lyme disease or specific Lyme disease presentations was identified. However, the guideline
42 committee agreed that the evidence highlighted the difficulties for people with Lyme disease

1 in their interactions with healthcare professionals; therefore, the committee made a series of
2 recommendations using other reviews in the guideline and consensus to inform people who
3 may have Lyme disease.

4 **1.10.2 Cost effectiveness and resource use**

5 No relevant economic evaluations were identified. The committee considered that although
6 these recommendations may have cost implications as a result of additional health care
7 professional time and additional resource requirements (for example, where information does
8 not already exist in a suitable format), this is an essential part of good patient care to ensure
9 people are adequately informed. The committee noted that good quality information was
10 accessible from sources such as NHS Choices, Public Health England and Lyme disease
11 charities.

12 **1.10.3 Other factors the committee took into account**

13 The guideline committee began by identifying 7 main areas for recommendations for
14 information that had been highlighted during discussion of the evidence in previous reviews.
15 These recommendations are included and discussed in sections of the guideline that cover
16 that area.

17 **Information for people with suspected or diagnosed Lyme disease.**

18 The guideline committee agreed the importance of giving advice to people about how to
19 prevent Lyme disease. Although there was no specific review of evidence for prevention of
20 Lyme disease, there are generally accepted methods in clinical practice. These include being
21 aware of common tick habitats, checking the skin for ticks, safe tick removal, wearing
22 clothing that does not expose the skin, and using insect repellents. Therefore, the guideline
23 committee decided to recommend that people are advised on Lyme disease prevention and
24 referred to further information from sources such as NHS Choices, Public Health England
25 and Lyme disease charities. These recommendations are included in the section of the
26 guideline on awareness of Lyme disease.

27 **Information about tests for Lyme disease**

28 Evidence from the review of diagnostic test accuracy suggested that diagnostic tests
29 correctly identify most people with Lyme disease but can produce false-negative results. The
30 guideline committee considered the impact of a negative test result on people with Lyme
31 disease. People with Lyme disease may feel anxious that they will not be helped or about the
32 possibility of receiving alternative diagnoses. It was therefore decided that people with Lyme
33 disease should be informed about how the tests work, factors that may reduce their accuracy
34 and the importance of using validated tests. People with Lyme disease should also be
35 reassured that they would continue to be assessed and reviewed. These recommendations
36 can be found in the diagnostic tests evidence report.

37 **Information for people diagnosed with Lyme disease.**

38 Evidence from 1 study showed that the absence of established treatment and disease
39 prognosis guidance leads to uncertainty, frustration and fear regarding the nature and
40 duration of expected future symptoms in people with Lyme disease and an inability to gauge
41 the normality of their own experience. Another study showed that the ability of the physician
42 to admit a lack of technical knowledge or competency in a particular area is important to
43 people with Lyme disease. The guideline committee considered how best to inform people
44 with Lyme disease on the likely prognosis, while acknowledging the uncertainty regarding
45 treatment success. The guideline committee considered evidence identified in the
46 management review and their clinical experience to form information recommendations for
47 people diagnosed with Lyme disease. It was agreed that people with Lyme disease should

1 be informed that most people recover completely, that prompt antibiotic treatment reduces
2 the risk of further symptoms developing, that it may take time to get better but symptoms
3 should continue to improve in the months after antibiotic treatment and that additional
4 treatment may be needed for their symptoms. People with Lyme disease should be advised
5 to consult their doctor if symptoms persist or return after completing treatment. It should also
6 be explained that a very small number of people with Lyme disease experience a worsening
7 of their symptoms usually in the first day of treatment although there are reports of this
8 occurring later in treatment, which may be a Jarisch-Herxheimer reaction; if this occurs, they
9 should continue their antibiotic treatment and inform their doctor. Finally, people with Lyme
10 disease should be informed that infection does not give lifelong immunity and that it is
11 possible to develop Lyme disease again. These recommendations are listed in section 1.8 of
12 this report.

13 **Information if symptoms persist after antibiotics.**

14 Evidence from the management review and the clinical experience of the guideline
15 committee showed that full recovery could sometimes take months after an initial course of
16 treatment. The guideline committee agreed that those with persistent symptoms after initial
17 antibiotics should be made aware of this possibility. They should also be informed that their
18 symptoms are likely to continue to improve so further tests and treatment may not be
19 needed. They should be told to return to their GP if symptoms worsen after the end of
20 treatment.

21 Information for people who have persisting symptoms after 2 courses of antibiotics

22 The guideline committee discussed the information and support needs of those with
23 symptoms that continue after antibiotic treatment. The management review identified no
24 evidence that further treatment with antibiotics after 2 courses has any benefit; however,
25 people with Lyme disease may be concerned that treatment has failed. Therefore, the
26 guideline committee recommended that it should be explained that continuing symptoms do
27 not always mean that they still have an active infection, that additional treatment with
28 antibiotics is not likely to improve their recovery in this case, and that continuing symptoms
29 are common after any infection. It should be explained to people that there is no test that can
30 distinguish active disease or any evidence on the appropriate treatment for persisting
31 symptoms. Those with persisting symptoms or with a slow recovery may require additional
32 services such as social and educational services to help manage their symptoms. People
33 with Lyme disease should be supported by encouraging and helping them to access
34 additional services, such as social services needs assessment if they would benefit from
35 these, communicating with social services, educational institutions, and employers about the
36 need for a gradual return to activities.

37 Recommendations about information when symptoms persist can be found in the
38 management of persistent symptoms evidence report.

39 **Information about Lyme disease affecting individual systems**

40 The guideline committee discussed the need to provide detailed information for people with
41 individual Lyme disease presentations such as joint symptoms and information about why
42 some courses of antibiotics are longer than other courses. It was agreed that such
43 information would be useful but that the inclusion of detailed recommendations of all these
44 aspects was outside the scope of the guideline.
45

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Appendices

Appendix A: Review protocols

Table 5: Review protocol for information needs

Question number: 6

Relevant section of Scope: information needs

Field	Content
Review question	What information do people with suspected, confirmed or treated Lyme disease, or their family members or carers need?
Type of review question	Qualitative A review of health economic evidence related to the same review question was conducted in parallel with this review. For details, see the health economic review protocol for this NICE guideline.
Objective of the review	The aim of this review is to determine what information should be provided to people who have either received a diagnosis of Lyme disease, who are currently under investigation or treated for Lyme disease, who were treated for Lyme disease previously, or to their family or carers.
Eligibility criteria – population / disease / condition / issue / domain	<ul style="list-style-type: none"> • People with suspected Lyme disease • People with confirmed Lyme disease • People who were previously treated or are currently being treated for Lyme disease <p>The review population also includes family members or carers of people with suspected or confirmed Lyme disease and people who were previously treated or are currently being treated for Lyme disease.</p>
Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	Not applicable
Eligibility criteria – comparator(s) / control or reference (gold) standard	Not applicable
Outcomes and prioritisation	Any type of information described by studies. For example: <ul style="list-style-type: none"> • What type of information is required and how can this information be best delivered? • Do family members and carers require specific information? • When should information be provided?
Eligibility criteria – study design	Any type of qualitative study designs
Other inclusion exclusion criteria	Any type of qualitative study designs
Proposed sensitivity / subgroup analysis, or meta-regression	Not applicable

Field	Content
Selection process – duplicate screening / selection / analysis	Studies will be sifted by title and abstract. Potentially significant publications obtained in full text will then be assessed against the inclusion criteria specified in this protocol.
Data management (software)	CERQual will be used to synthesise data from qualitative studies Bibliographies, citations, study sifting and reference management will be managed using EndNote
Information sources – databases and dates	Clinical searches Medline, Embase, The Cochrane Library, PsycINFO, CINAHL all years Health economic searches Medline, Embase, NHS Economic Evaluation Database (NHS EED), Health Technology Assessment (HTA) all years
Identify if an update	Not applicable
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10007
Highlight if amendment to previous protocol	For details, please see section 4.5 of Developing NICE guidelines: the manual.
Search strategy – for one database	For details, please see appendix B
Data collection process – forms / duplicate	A standardised evidence table format will be used and published as appendix D of the evidence report.
Data items – define all variables to be collected	For details, please see evidence tables in Appendix D (clinical evidence tables) or H (health economic evidence tables).
Methods for assessing bias at outcome / study level	Standard study checklists were used to appraise individual studies critically. For details, please see section 6.2 of Developing NICE guidelines: the manual The methodological quality of each study will be assessed using NGC modified NICE checklists.
Criteria for quantitative synthesis	Not applicable
Methods for quantitative analysis – combining studies and exploring (in)consistency	Synthesis of qualitative research: thematic analysis – information will be synthesised into the main findings of the review. Results will be presented in a detailed narrative and in table format with summary statements of the main review findings / themes. For details, please see the separate Methods report for this guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details, please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details, please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual. The quality of the body of evidence as a whole will be assessed by a GRADE CERQual approach for each review finding.
Rationale / context – what is known	For details, please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Saul Faust in line with section 3 of Developing NICE guidelines: the manual. Staff from the NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details, please see Developing NICE guidelines: the manual.

Field	Content
Sources of funding / support	The NGC is funded by NICE and hosted by the Royal College of Physicians.
Name of sponsor	The NGC is funded by NICE and hosted by the Royal College of Physicians.
Roles of sponsor	NICE funds the NGC to develop guidelines for those working in the NHS, public health and social care in England.
PROSPERO registration number	Not registered

1

Table 6: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	<ul style="list-style-type: none"> • Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	<p>Studies not meeting any of the search criteria above will be excluded. Studies published before 2001, abstract-only studies and studies from non-OECD countries or the US will also be excluded.</p> <p>Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).¹⁷</p> <p>Inclusion and exclusion criteria</p> <ul style="list-style-type: none"> • If a study is rated as both ‘Directly applicable’ and with ‘Minor limitations’, then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either ‘Not applicable’ or with ‘Very serious limitations’, then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as ‘Partially applicable’, with ‘Potentially serious limitations’ or both, then there is discretion over whether it should be included. <p>Where there is discretion</p> <p>The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to exclude the remaining studies selectively. All studies</p>

excluded based on applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the US will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2001 or later but that depend on unit costs and resource data entirely or predominantly before 2001 will be rated as ‘Not applicable’.
- Studies published before 2001 will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2017
<https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869>

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

The search for this review was constructed using population terms. An excluded studies filter was applied where appropriate.

Table 7: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 03 July 2017	Exclusions
Embase (OVID)	1974 – 03 July 2017	Exclusions
The Cochrane Library (Wiley)	Cochrane Reviews to 2017 Issue 7 of 12 CENTRAL to 2017 Issue 6 of 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 4 of 4	None
CINAHL, Current Nursing and Allied Health Literature (EBSCO)	Inception – 03 July 2007	Exclusions
PsycINFO (ProQuest)	Inception – 03 July 2007	Exclusions

Medline (Ovid) search terms

1.	exp Borrelia Infections/
2.	exp Lyme disease/
3.	Erythema Chronicum Migrans/
4.	(erythema adj3 migrans).ti,ab.
5.	lyme*.ti,ab.
6.	(tick* adj2 (bite* or bitten or biting or borne)).ti,ab.
7.	acrodermatitis chronica atrophicans.ti,ab.
8.	exp Ixodidae/
9.	(borreliosis or borrelia* or neuroborreliosis or ixodid or ixodidae or ixodes or b burgdorferi or b afzelii or b garinii or b bissettii or b valaisiana or b microti).ti,ab.
10.	(granulocytic anaplasmosis or babesia or babesiosis).ti,ab.
11.	or/1-10
12.	letter/
13.	editorial/
14.	news/
15.	exp historical article/
16.	Anecdotes as Topic/
17.	comment/
18.	(letter or comment*).ti.

19.	or/12-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20
22.	animals/ not humans/
23.	exp Animals, Laboratory/
24.	exp Animal Experimentation/
25.	exp Models, Animal/
26.	exp Rodentia/
27.	(rat or rats or mouse or mice).ti.
28.	or/21-27
29.	11 not 28
30.	limit 29 to English language

1

Embase (Ovid) search terms

1.	exp Borrelia Infection/
2.	exp Lyme disease/
3.	Erythema Chronicum Migrans/
4.	(erythema adj3 migrans).ti,ab.
5.	lyme*.ti,ab.
6.	(tick* adj2 (bite* or bitten or biting or borne)).ti,ab.
7.	acrodermatitis chronica atrophicans.ti,ab.
8.	exp Ixodidae/
9.	(borreliosis or borrelia* or neuroborreliosis or ixodidae or ixodes or b burgdorferi or b afzelii or b garinii or b bissettii or b valaisiana or b microti).ti,ab.
10.	(granulocytic anaplasmosis or babesia or babesiosis).ti,ab.
11.	or/1-10
12.	letter.pt. or letter/
13.	note.pt.
14.	editorial.pt.
15.	(letter or comment*).ti.
16.	or/12-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animal/ not human/
20.	Nonhuman/
21.	exp Animal Experiment/
22.	exp Experimental animal/
23.	Animal model/
24.	exp Rodent/
25.	(rat or rats or mouse or mice).ti.
26.	or/18-25
27.	11 not 26
28.	limit 27 to English language

2

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Borrelia Infections] explode all trees
#2.	MeSH descriptor: [Lyme Disease] explode all trees
#3.	MeSH descriptor: [Erythema Chronicum Migrans] explode all trees

#4.	(erythema near/3 migrans):ti,ab
#5.	lyme*:ti,ab
#6.	(tick* near/2 (bite* or bitten or biting or borne)):ti,ab
#7.	acrodermatitis chronica atrophicans:ti,ab
#8.	MeSH descriptor: [Ixodidae] explode all trees
#9.	(borreliosis or borrelia* or neuroborreliosis or ixodidae or ixodes or ixodid or b burgdorferi or b afzelii or b garinii or b bissettii or b valaisiana or b microti):ti,ab
#10.	(granulocytic anaplasmosis or babesia or babesiosis):ti,ab
#11.	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10

1

CINAHL (EBSCO) search terms

S1.	(MH "Borrelia Infections+")
S2.	(MH "Lyme Neuroborreliosis") OR (MH "Lyme Disease+")
S3.	erythema n3 migrans
S4.	lyme*
S5.	tick* n2 bite* OR tick* n2 bitten OR tick* n2 biting OR tick* n2 borne
S6.	acrodermatitis chronica atrophicans
S7.	borreliosis or borrelia* or neuroborreliosis or ixodid or ixodidae or ixodes or b burgdorferi or b afzelii or b garinii or b bissettii or b valaisiana or b microti
S8.	granulocytic anaplasmosis or babesia or babesiosis
S9.	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
S10.	PT anecdote or PT audiovisual or PT bibliography or PT biography or PT book or PT book review or PT brief item or PT cartoon or PT commentary or PT computer program or PT editorial or PT games or PT glossary or PT historical material or PT interview or PT letter or PT listservs or PT masters thesis or PT obituary or PT pamphlet or PT pamphlet chapter or PT pictorial or PT poetry or PT proceedings or PT "questions and answers" or PT response or PT software or PT teaching materials or PT website
S11.	S9 NOT S10

2

PsycINFO (ProQuest) search terms

1.	SU.EXACT("Borrelia Infections") OR SU.EXACT("Lyme neuroborreliosis") OR SU.EXACT("Lyme disease") OR TI,AB(erythema N/3 migrans) OR TI,AB(tick* N/2 (bite* or bitten or biting or borne)) OR TI,AB("acrodermatitis chronica atrophicans") OR TI,AB(borreliosis or borrelia* or neuroborreliosis or ixodid or ixodidae or ixodes or b burgdorferi or b afzelii or b garinii or b bissettii or b valaisiana or b microti) OR TI,AB(granulocytic anaplasmosis or babesia or babesiosis)
2.	(su.exact.explode("rodents") or su.exact.explode("mice") or (su.exact("animals") not (su.exact("human males") or su.exact("human females")))) or ti(rat or rats or mouse or mice))
3.	S1 NOT S2 Limited to English

3 B.2 Health Economics literature search strategy

4 Health economic evidence was identified by conducting a broad search relating to Lyme
5 disease population in NHS Economic Evaluation Database (NHS EED – this ceased to be
6 updated after March 2015) and the Health Technology Assessment database (HTA) with no
7 date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and
8 Dissemination (CRD). Additional searches were run on Medline and Embase for health
9 economics, economic modelling and quality of life studies.

10

Table 8: Database date parameters and filters used

Database	Dates searched	Search filter used
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Database	Dates searched	Search filter used
Medline	1946 – 03 July 2017	Exclusions Health economics studies Health economics modelling studies Quality of life studies
Embase	1974 – 03 July 2017	Exclusions Health economics studies Health economics modelling studies Quality of life studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 03 July 2017 NHSEED - Inception to March 2015	None

1

Medline (Ovid) search terms

1.	exp Borrelia Infections/
2.	exp Lyme disease/
3.	Erythema Chronicum Migrans/
4.	(erythema adj3 migrans).ti,ab.
5.	lyme*.ti,ab.
6.	(tick* adj2 (bite* or bitten or biting or borne)).ti,ab.
7.	acrodermatitis chronica atrophicans.ti,ab.
8.	exp Ixodidae/
9.	(borreliosis or borrelia* or neuroborreliosis or ixodid or ixodidae or ixodes or b burgdorferi or b afzelii or b garinii or b bissettii or b valaisiana or b microti).ti,ab.
10.	(granulocytic anaplasmosis or babesia or babesiosis).ti,ab.
11.	or/1-10
12.	letter/
13.	editorial/
14.	news/
15.	exp historical article/
16.	Anecdotes as Topic/
17.	comment/
18.	(letter or comment*).ti.
19.	or/12-18
20.	randomized controlled trial/ or random*.ti,ab.
21.	19 not 20
22.	animals/ not humans/
23.	exp Animals, Laboratory/
24.	exp Animal Experimentation/
25.	exp Models, Animal/
26.	exp Rodentia/
27.	(rat or rats or mouse or mice).ti.

28.	or/21-27
29.	11 not 28
30.	limit 29 to English language
31.	Economics/
32.	Value of life/
33.	exp "Costs and Cost Analysis"/
34.	exp Economics, Hospital/
35.	exp Economics, Medical/
36.	Economics, Nursing/
37.	Economics, Pharmaceutical/
38.	exp "Fees and Charges"/
39.	exp Budgets/
40.	budget*.ti,ab.
41.	cost*.ti.
42.	(economic* or pharmaco?economic*).ti.
43.	(price* or pricing*).ti,ab.
44.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
45.	(financ* or fee or fees).ti,ab.
46.	(value adj2 (money or monetary)).ti,ab.
47.	or/31-46
48.	exp models, economic/
49.	*Models, Theoretical/
50.	*Models, Organizational/
51.	markov chains/
52.	monte carlo method/
53.	exp Decision Theory/
54.	(markov* or monte carlo).ti,ab.
55.	econom* model*.ti,ab.
56.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
57.	or/48-56
58.	quality-adjusted life years/
59.	sickness impact profile/
60.	(quality adj2 (wellbeing or well being)).ti,ab.
61.	sickness impact profile.ti,ab.
62.	disability adjusted life.ti,ab.
63.	(qal* or qtime* or qwb* or daly*).ti,ab.
64.	(euroqol* or eq5d* or eq 5*).ti,ab.
65.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
66.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
67.	(hui or hui1 or hui2 or hui3).ti,ab.

68.	(health* year* equivalent* or hye or hyes).ti,ab.
69.	discrete choice*.ti,ab.
70.	rosser.ti,ab.
71.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
72.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
73.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
74.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
75.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
76.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
77.	or/58-76
78.	30 and 47
79.	30 and 57
80.	30 and 77

1

Embase (Ovid) search terms

1.	exp Borrelia Infection/
2.	exp Lyme disease/
3.	Erythema Chronicum Migrans/
4.	(erythema adj3 migrans).ti,ab.
5.	lyme*.ti,ab.
6.	(tick* adj2 (bite* or bitten or biting or borne)).ti,ab.
7.	acrodermatitis chronica atrophicans.ti,ab.
8.	exp Ixodidae/
9.	(borreliosis or borrelia* or neuroborreliosis or ixodidae or ixodes or b burgdorferi or b afzelii or b garinii or b bissetii or b valaisiana or b microti).ti,ab.
10.	(granulocytic anaplasmosis or babesia or babesiosis).ti,ab.
11.	or/1-10
12.	letter.pt. or letter/
13.	note.pt.
14.	editorial.pt.
15.	Case report/ or Case study/
16.	(letter or comment*).ti.
17.	or/12-16
18.	randomized controlled trial/ or random*.ti,ab.
19.	17 not 18
20.	animal/ not human/
21.	Nonhuman/
22.	exp Animal Experiment/
23.	exp Experimental animal/
24.	Animal model/
25.	exp Rodent/

26.	(rat or rats or mouse or mice).ti.
27.	or/19-26
28.	11 not 27
29.	limit 28 to English language
30.	health economics/
31.	exp economic evaluation/
32.	exp health care cost/
33.	exp fee/
34.	budget/
35.	funding/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/30-42
44.	statistical model/
45.	exp economic aspect/
46.	44 and 45
47.	*theoretical model/
48.	*nonbiological model/
49.	stochastic model/
50.	decision theory/
51.	decision tree/
52.	monte carlo method/
53.	(markov* or monte carlo).ti,ab.
54.	econom* model*.ti,ab.
55.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
56.	or/46-55
57.	quality adjusted life year/
58.	"quality of life index"/
59.	short form 12/ or short form 20/ or short form 36/ or short form 8/
60.	sickness impact profile/
61.	(quality adj2 (wellbeing or well being)).ti,ab.
62.	sickness impact profile.ti,ab.
63.	disability adjusted life.ti,ab.
64.	(qal* or qtime* or qwb* or daly*).ti,ab.
65.	(euroqol* or eq5d* or eq 5*).ti,ab.
66.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.

67.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
68.	(hui or hui1 or hui2 or hui3).ti,ab.
69.	(health* year* equivalent* or hye or hyes).ti,ab.
70.	discrete choice*.ti,ab.
71.	rosser.ti,ab.
72.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
73.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
74.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
75.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
76.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
77.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
78.	or/57-77
79.	29 and 43
80.	29 and 56
81.	29 and 78

1

NHS EED and HTA (CRD) search terms

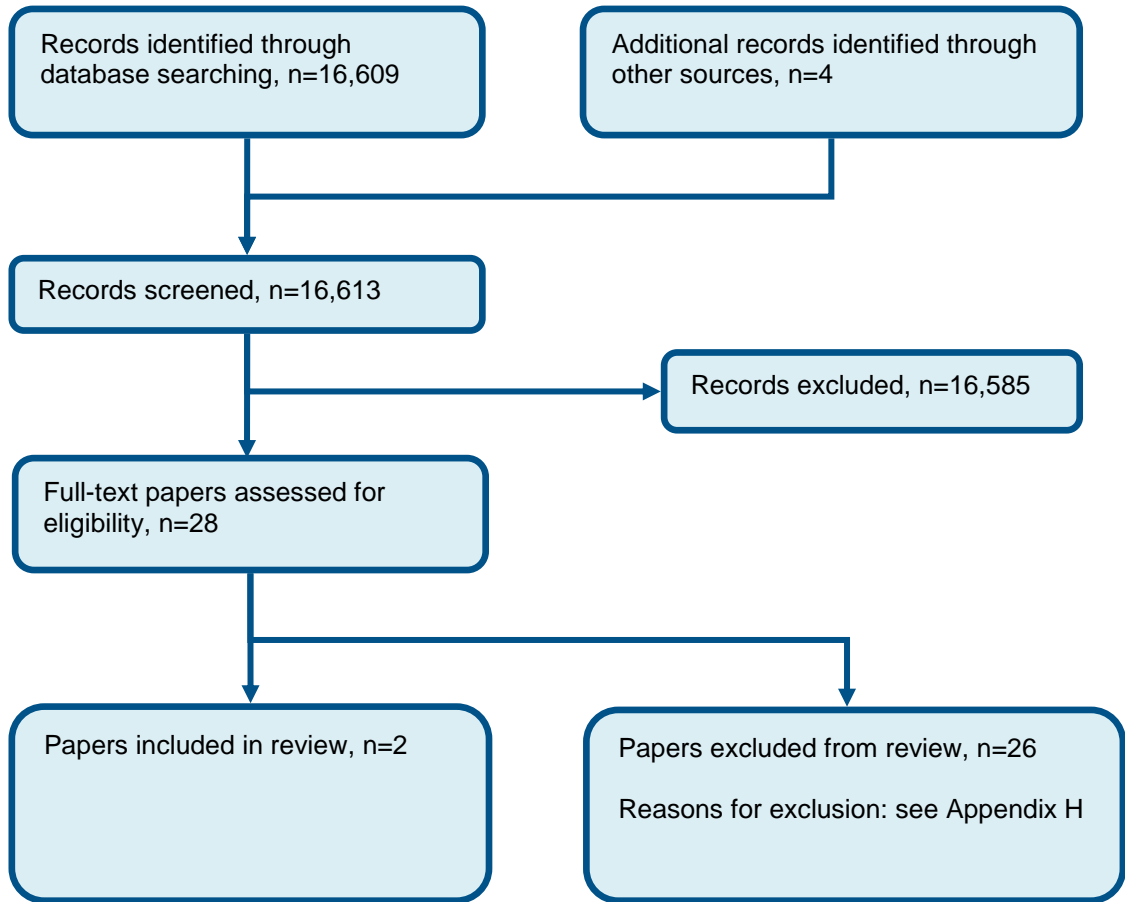
#1.	MeSH DESCRIPTOR Borrelia Infections EXPLODE ALL TREES IN NHSEED,HTA
#2.	MeSH DESCRIPTOR Erythema Chronicum Migrans EXPLODE ALL TREES IN NHSEED,HTA
#3.	((erythema adj3 migrans)) IN NHSEED, HTA
#4.	(lyme*) IN NHSEED, HTA
#5.	((tick* adj2 (bite* or bitten or biting or borne))) IN NHSEED, HTA
#6.	(acrodermatitis chronica atrophicans) IN NHSEED, HTA
#7.	MeSH DESCRIPTOR Ixodidae EXPLODE ALL TREES IN NHSEED,HTA
#8.	((borreliosis or borrelia* or neuroborreliosis or ixodidae or ixodes or b burgdorferi or b afzelii or b garinii or b bissettii or b valaisiana or b microti)) IN NHSEED, HTA
#9.	((granulocytic anaplasmosis or babesia or babesiosis)) IN NHSEED, HTA
#10.	MeSH DESCRIPTOR Lyme Disease EXPLODE ALL TREES IN NHSEED,HTA
#11.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10

2

1

Appendix C: Qualitative study selection

Figure 1: Flow chart of qualitative study selection for the review of information needs



2

Appendix D: Qualitative evidence tables

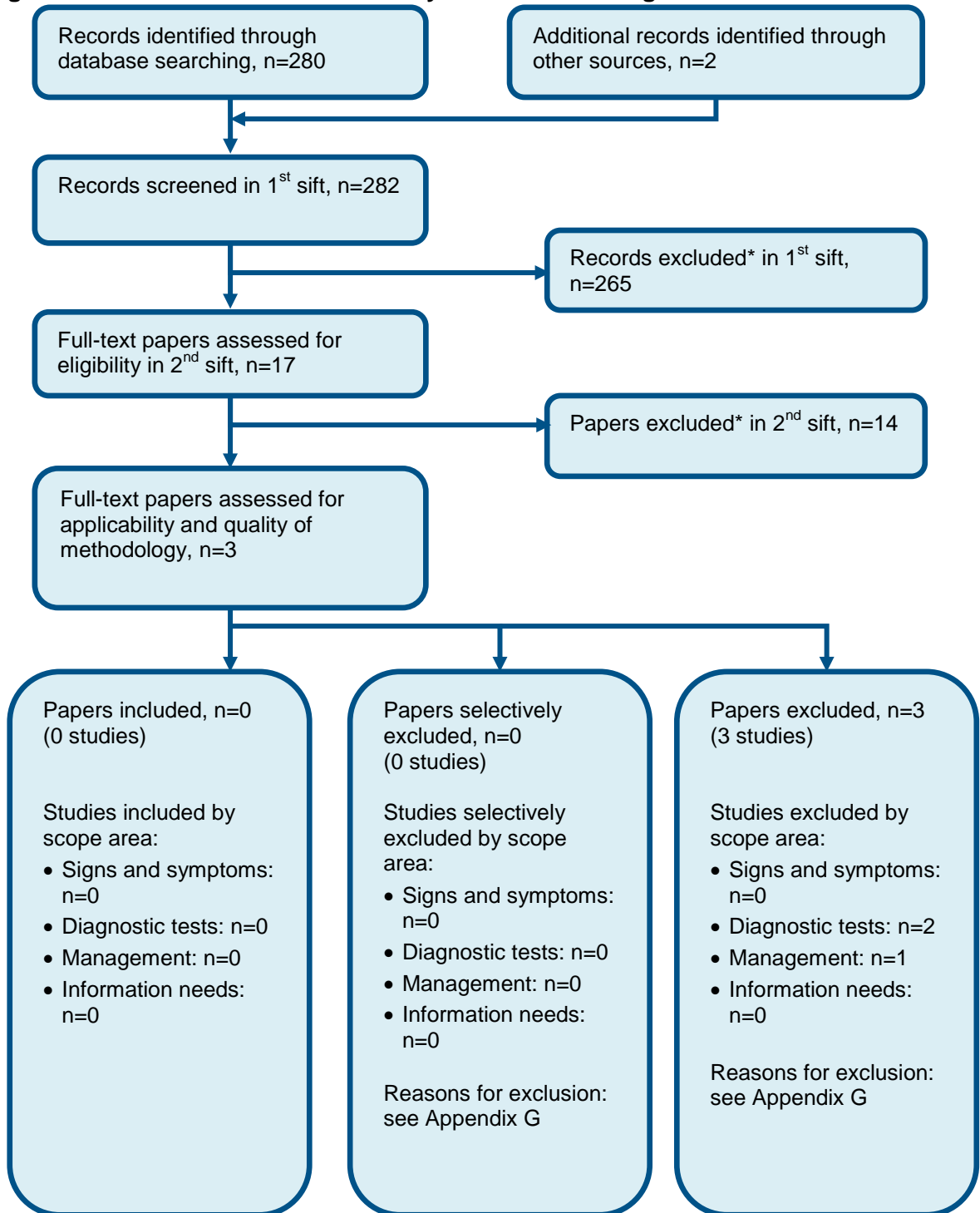
Study	Mechanic 2000 ¹⁴
Aim	To obtain greater insight into the dynamics of trust and to identify concepts that need development in surveys with more representative samples
Population	n=30 Adults with physician-diagnosed Lyme disease who had a minimum of 2 visits with a physician who was treated them. Majority of respondents were recruited from self-help groups. The study was described during a meeting and information provided on the group's website. Additional people were recruited by word-of-mouth (n=3) and through a Lyme disease clinic (n=2) Exclusions: evidence of physical, mental or emotional inability to complete the interview Male/female ratio 5/25; 2 age ≤40 years, 20 age 41-60 years, 8 age 61+ years; family origin: 25 white, 5 other
Setting	Not stated
Study design	Qualitative interview study
Methods and analysis	Semi-structured open-ended interview with thematic qualitative analysis. The open-ended interview questions were derived from a literature review and queried people about various aspects of their interactions with physicians, medical institutions and healthcare plans. Interviews conducted by a single interviewer (clinical psychologist with experience in qualitative interviews). Transcripts were organised using NUDIST© software package, responses broken down in to phrases that expressed a single idea or theme, each phrase was then coded (by multiple coders). Codes were initially created based on the literature review but additional codes were added as the analysis proceeded.
Findings	The ability of the physician to admit a lack of technical knowledge or competency in a particular area is important to people with Lyme disease For people with Lyme disease who attend self-help groups, advocacy as well as getting and sharing information about physicians, insurance coverage and treatment approaches are important
Limitations and applicability of evidence	The interview setting was not clearly described. The researchers reached conclusions with no detailed discussion of the evidence supporting them. The study only included mainly females and mainly people recruited from self-help groups, limiting the applicability to the entire Lyme disease population. The main theme of the study was trust, which did not directly relate to our review and most of the analysis was on the whole study cohort that included people with breast cancer and people with mental illness.

Study	Rebman 2015 ²¹
Aim	<p>To gather illness narratives to contribute to the small body of qualitative research that gives primacy to people's experiences and ways of making sense of PTLDS/CLD as a medically contested, chronic illness</p> <p>To examine how people's experiences could inform an understanding of the personal and social cost of this illness and assist in setting future research priorities</p>
Population	<p>n=29 Adults tentatively meeting a case definition for post-treatment Lyme disease syndrome (initial Lyme disease episode marked by either EM or positive blood serology and concurrent objective signs consistent with late Lyme disease or unexplained flu-like illness), all had been ill for ≥6 months. Substantial variation in the clinical histories and symptom severities</p> <p>52% female; mean age 54 years; family origin not reported</p>
Setting	<p>45-60 minute interview either in a private room in a clinical setting or at the participant's home. Roughly half were interviewed again for 30 minutes when follow-up questions arose or participants indicated that they had more to discuss</p>
Study design	<p>Qualitative interview study</p>
Methods and analysis	<p>Initially 3 people were interviewed in order to refine key themes and develop the interview guide for the other 26 people. Broad similarities were found in the issues raised. Two independent coders performed open coding on transcriptions with ATLAS.ti software, the list of open codes were synthesised into higher codes through discussion with the study team. Two individuals with PTLDS provided feedback on the manuscript.</p>
Findings	<p>The absence of established treatment and disease prognosis guidance leads to uncertainty, frustration and fear among people with Lyme disease, as well as inter-physician subjectivity</p> <p>Interaction with other people through existing personal networks provides support and validation for people with Lyme disease but not through support groups</p>
Limitations and applicability of evidence	<p>The researchers adequately described the study design and data analysis methods. There was some discussion of the evidence supporting the author's conclusions; however, there were some concerns over the richness and quantity of the data. There were no serious concerns about applicability.</p>

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2

Appendix E: Health economic evidence study selection

Figure 2: Flow chart of economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language

3

Appendix F: Health economic evidence tables

None.

Appendix G: Excluded studies

G.1 Excluded qualitative studies

Table 9: Studies excluded from the qualitative review

Reference	Reason for exclusion
Ali 2012 ¹	Poster presentation
Ali 2014 ²	Excluded due to an incorrect theme
Beaujean 2013 ³	Excluded due to an incorrect theme
Beaujean 2016 ⁴	Excluded due to an incorrect theme
Dyer 2015 ⁵	Editorial
Edwards 2012 ⁶	Excluded due to an incorrect population
Eppes 1994 ⁷	Excluded due to an incorrect population
Gould 2008 ⁸	Excluded due to an incorrect theme
Heller 2010 ⁹	Excluded due to an incorrect population
Johnson 2011 ¹⁰	Excluded due to an incorrect theme
Marcu 2013 ¹¹	Excluded due to an incorrect theme
Marcu 2011 ¹²	Excluded due to an incorrect theme
Marzano 2013 ¹³	Excluded due to an incorrect population
Moloney 2016 ¹⁵	Personal paper
Nathan 2007 ¹⁶	Excluded due to an incorrect study design
Pearson 2014 ¹⁸	Excluded due to an incorrect study design
Quine 2011 ¹⁹	Excluded due to an incorrect study design
Ramsey 2004 ²⁰	Excluded due to an incorrect population
Reece 1999 ²²	Excluded due to an incorrect study design
Sood 2002 ²³	Excluded due to an incorrect study design
Swigar 1990 ²⁴	Excluded due to an incorrect study design
van Velsen 2015 ²⁵	Excluded due to an incorrect population
Vartiovaara 1995 ²⁶	Personal paper
Wilson 1999 ²⁷	Personal paper
Woodcock 2005 ²⁸	Comment
Zeller 2007 ²⁹	Patient information sheet

G.2 Excluded health economic studies

Table 10: Studies excluded from the health economic review

Reference	Reason for exclusion
None	