National Institute for Health and Care Excellence

Final

Lyme disease: diagnosis and management

[L] Evidence review for the management of ongoing symptoms related to Lyme disease

NICE guideline 95

Evidence review

April 2018

Final

This evidence review was developed by the National Guideline Centre

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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1 Management (ongoing symptoms)

1.1 Review question: What is the most clinically and cost-effective treatment for people who have non-specific symptoms that may be related to Lyme disease?

1.2 Introduction

If Lyme disease is treated early, most people recover completely, but studies show that some people have ongoing symptoms following antibiotic treatment. It is not known whether these symptoms are due to persisting infection, tissue damage, autoimmune reaction or some other process. There is currently no test that helps determine this. It is important to assess whether repeat or longer courses of antibiotics might help.

A number of treated people have a slow recovery and may need support and access to additional services including social care. It is important that clinical practitioners consider these when managing people with long-term symptoms related to Lyme disease.

The term ‘ongoing symptoms’ was preferred for the guideline as it does not attribute cause of symptoms. Terms such as chronic Lyme disease imply possible chronic infection and may be misleading

The approach to evidence reviews in the guideline was that individual review protocols were set for the different clinical presentations of Lyme disease. People in whom a previous course of antibiotic treatment had failed were specified as a subgroup, meaning that the evidence would be analysed separately if there was heterogeneity and used to inform recommendations regarding ongoing symptoms. The non-specific symptoms review was the only review where people who had been previously treated with at least one course of antibiotics were clearly identified and these were the only studies in that review. The evidence report is therefore included in this section, as well as the committee discussion on antibiotic management of ongoing symptoms and the importance of provision of longer-term support and recommendations.

1.3 PICO table

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

Table 1: PICO characteristics of review question

Population	People with Lyme disease determined by a diagnostic tests or clinical diagnosis who have non-specific symptoms that may be related to Lyme disease. This includes symptoms such as: • disturbed cognitive function, for example, memory loss • dizziness • fatigue • fever and sweats • headache • lymphadenopathy • myalgia and muscle stiffness • neck pain or stiffness • paraesthesia • photophobia
Interventions	Antimicrobials, including but not limited to:

	• Penicillins
	  ○ Amoxicillin (oral, IV)
	  ○ Ampicillin (oral, IV)
	  ○ Benzylpenicillin sodium / Penicillin G (IV)
	  - Including Augmentin (Amoxicillin and clavulanic acid; oral, IV)
	  ○ Phenoxymethylpenicillin / Penicillin V (oral)
	• Tetracyclines
	  ○ Doxycycline (oral)
	  ○ Minocycline (oral)
	• Cephalosporins
	  ○ Cefotaxime (IV)
	  ○ Ceftriaxone (IV)
	  ○ Cefuroxime axetil (oral)
	• Macrolides
	  ○ Azithromycin (oral)
	  ○ Clarithromycin (oral, IV)
	• Fluoroquinolones
	  ○ Ciprofloxacin (oral, IV)
	  ○ Levofloxacin (oral, IV)
	  ○ Moxifloxacin (oral, IV)
	  ○ Nalidixic acid (oral)
	  ○ Norfloxacin (oral)
	  ○ Ofloxacin (oral, IV)
	• Rifampicin (oral, IV)

Comparisons	• Antimicrobial agents compared with each other
	  ○ If data are available, consider:
	  - Type of antimicrobial agent (within class or between class)
	  - Route of administration
	  - Duration of treatment: 1 month versus longer
	• Monotherapy versus polytherapy (any combination)
	• Antimicrobial agents compared to no treatment / placebo

Outcomes	**Critical:** 1. Quality of life (any validated measure) 2. Cure (resolution of symptoms) 3. Reduction of clinical symptoms 4. Symptom relapse **Important:** 5. Adverse events
Study design	• Randomised control studies (RCT) • Cohort studies (if no RCT evidence is found)

1.4 Clinical evidence

1.4.1 Included studies

The evidence reviews conducted for antibiotic management of Lyme disease did not pre-specify for how long a person with symptoms related to Lyme disease had those symptoms but was organised by symptom or symptom complex. The review question on the management of non-specific symptoms related to Lyme disease did not identify any studies in people with non-specific symptoms in the early stages of Lyme disease. The 5 studies (6 papers)[15, 29, 59, 74, 81, 86] identified were in adults in whom all or the majority had received

antibiotic treatment prior to enrolment. The committee agreed that these studies would inform recommendations about treating people with symptoms ongoing after treatment.

All participants in the PLEASE trial[15] received 2 grams intravenous ceftriaxone for 14 days prior to the study interventions. One treatment arm in this trial also used an indirect intervention as people received hydroxychloroquine in addition to clarithromycin.

The included studies are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

See also the study selection flow chart in appendix C, study evidence tables in appendix D, forest plots in appendix E and GRADE tables in appendix F.

1.4.2 Excluded studies

See the excluded studies list in appendix I.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Berende 2016 (PLEASE trial)[15]	Doxycycline (n=86): 100 mg oral twice daily. Duration 12 weeks. Concurrent medication/care: Placebo combined with study intervention. Clarithromycin (n=96): 500 mg clarithromycin orally twice daily plus 200 mg hydroxychloroquine orally twice daily. Duration 12 weeks. Concurrent medication/care: none Placebo (n=98): Two different placebo capsules orally twice daily. Duration 12 weeks. Concurrent medication/care: none	n=281 Diagnosis: ongoing symptoms attributed to Lyme disease temporarily related to an erythema migrans (EM) or an otherwise proven case of symptomatic Lyme disease or accompanied by *B. burgdorferi* IgM or IgG antibodies	Quality of life Adverse events	People in the clarithromycin group also received hydroxychloroquine All people received open-label intravenous ceftriaxone (2,000 mg daily) for 14 days prior to study intervention. Majority of people (87-91%) had received previous antibiotic treatment
Cameron 2008[29]	Amoxicillin (n=52): 3 g oral daily. Duration 3 months. Concurrent medication/care: not reported.	n=86 Presented with symptoms of arthralgia, cardiac or neurologic involvement with	Quality of life Adverse events	Patients had received mean 2.2 previous courses of antibiotics before entering the study Duration of

Study	Intervention and comparison	Population	Outcomes	Comments
	Placebo (n=34): Duration 3 months. Concurrent medication/care: not reported.	or without fatigue; recurrence of Lyme disease symptoms after previous successful treatment Method of assessment /diagnosis not stated		symptoms (mean): amoxicillin group 6.3 months, placebo group 8.2 months
Fallon 2008[59]	Ceftriaxone (n=23): Ceftriaxone IV 2 g per day. Duration 10 weeks. Concurrent medication/care: not reported. Placebo (n=14) Placebo IV (0.9% normal saline). Duration 10 weeks. Concurrent medication/care: not reported.	n=37 History of physician documented EM or US Centers for Disease Control and Prevention (CDC) defined manifestations of Lyme disease and a positive or equivocal ELISA confirmed by positive Western blot serology; current positive IgG Western blot using CDC surveillance criteria, assessed using a single reference lab; treatment for Lyme disease with at least 3 weeks of IV ceftriaxone, completed at least 4 months before study entry; subjective memory impairment that, by participant report, started after the onset of Lyme disease; and objective evidence of memory impairment as documented by the Wechsler Memory Scale-III compared with age, sex and	Quality of life Reduction of symptoms Adverse events	Mean 2.3 months of prior IV antibiotics, Mean 7.2 months of prior oral antibiotics

Study	Intervention and comparison	Population	Outcomes	Comments
		education-adjusted population norms		
[74]Klempner 2001[81] Kaplan 2003[74]	Polytherapy (n=64): 2 g ceftriaxone per day intravenous for 30 days followed by 100 mg doxycycline orally twice per day for 60 days. Duration 90 days. Concurrent medication/care: Not reported Placebo (n=65): Dextrose solution intravenous for 30 days followed by oral capsules for 90 days. Duration 90 days. Concurrent medication/care: Not reported	n=129 Diagnosis: history of acute Lyme disease acquired in the US and at least 1 of the following: history of single or multiple EM, early neurologic or cardiac symptoms attributed to Lyme disease, radiculoneuropathy, or Lyme arthritis	Quality of life Adverse events Reduction of symptoms	33% had previously received intravenous antibiotic treatment for mean (±SD) 30 ± 12 days, all other previous treatment consisted of oral antibiotics (mean 3 ± 1.4 courses in the antibiotic group; 2.7 ± 1.3 in the placebo group) Seropositive n=77 (infected for mean 3.9 years) Seronegative n=48 (infected for 4.19 years)
Krupp 2003[86]	Ceftriaxone (n=28): 2 g per day, intravenous. Duration 28 days. Concurrent medication/care: Not reported Placebo (n=27): Placebo intravenous. Duration 28 days. Concurrent medication/care: Not reported	n=56 Diagnosis: history of physician-documented EM or CDC-defined late manifestation of Lyme disease confirmed by positive ELISA and WB serology, current severe fatigue defined by an elevated score (4 or more) on a modified version of the Fatigue Severity Scale	Reduction of symptoms	Eligibility criteria included completion (6 months before study entry) of standard antibiotic therapy for Lyme disease as defined by at least a 3 week course of oral antibiotic therapy or 3 weeks of IV ceftriaxone

See appendix D for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Ceftriaxone (IV) followed by doxycycline (PO) versus placebo

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Ceftriaxone (IV) + doxycycline (PO) versus placebo (95% CI)
Improvement in quality of life	115 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 1.11 (0.7 to 1.77)	362 per 1,000	40 more per 1,000 (from 109 fewer to 279 more)
Improvement in SF-36 (physical component) at 180 days; 0-100, higher values are beneficial	115 (1 study)	LOW[1,2] due to risk of bias, imprecision	RR 1.36 (0.77 to 2.38)	259 per 1,000	93 more per 1,000 (from 59 fewer to 357 more)
Improvement in SF-36 (mental component) at 180 days; 0-100, higher values are beneficial	115 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 0.88 (0.54 to 1.44)	379 per 1,000	46 fewer per 1,000 (from 174 fewer to 167 more)
Adverse events at 90 days	129 (1 study)	LOW[2] due to imprecision	RR 1.48 (0.74 to 2.93)	169 per 1,000	81 more per 1,000 (from 44 fewer to 327 more)
Reduction of symptoms Auditory Verbal Learning Test total score at 90 days; scale not reported; higher values are beneficial	129 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	Not applicable	The mean score in the control group was 44.1	The mean score in the intervention group was 4.2 higher (0.67 to 7.73 higher)
Reduction of symptoms Auditory Verbal Learning Test total score at 180 days; scale not reported; higher values are beneficial	129 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	Not applicable	The mean score in the control group was 47.6	The mean score in the intervention groups was 2 higher (1.7 lower to 5.7 higher)
Reduction of symptoms Symbol Digit Modalities Test written at 90 days; scale not reported; higher values are	129 (1 study)	LOW[1] due to risk of bias	Not applicable	The mean score in the control group was	The mean score in the intervention groups was 1.01 higher (2.27 lower to 4.29 higher)

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Ceftriaxone (IV) + doxycycline (PO) versus placebo (95% CI)
beneficial				51.5	
Reduction of symptoms Symbol Digit Modalities Test written at 180 days; scale not reported; higher values are beneficial	129 (1 study)	LOW[1] due to risk of bias	Not applicable	The mean score in the control group was 53.2	The mean score in the intervention groups was 0.7 lower (4.09 lower to 2.69 higher)
Reduction of symptoms Symbol Digit Modalities Test oral at 90 days; scale not reported; higher values are beneficial	129 (1 study)	LOW[1] due to risk of bias	Not applicable	The mean score in the control group was 59.2	The mean score in the intervention groups was 0.3 higher (4.1 lower to 4.7 higher)
Reduction of symptoms Symbol Digit Modalities Test oral at 180 days; scale not reported; higher values are beneficial	129 (1 study)	LOW[1] due to risk of bias	Not applicable	The mean score in the control group was 60.6	The mean score in the intervention groups was 0.5 lower (4.82 lower to 3.82 higher)
Reduction of symptoms Benton Visual Retention Test at 180 days; 0-10, higher values are beneficial	129 (1 study)	LOW[1] due to risk of bias	Not applicable	The mean score in the control group was 6.7	The mean score in the intervention groups was 0.1 higher (0.6 lower to 0.8 higher)
Reduction of symptoms Controlled Oral Word Association Test at 90 days; scale not reported, higher values are beneficial	129 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	Not applicable	The mean score in the control group was 44.5	The mean score in the intervention groups was 2.9 lower (7.55 lower to 1.75 higher)
Reduction of symptoms Controlled Oral Word Association Test at 180 days; scale not reported, higher values are beneficial	129 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	Not applicable	The mean score in the control group was 45.1	The mean score in the intervention groups was 3.2 lower (7.88 lower to 1.48 higher)
Reduction of symptoms	129	LOW[1]	Not	The mean	The mean score in the intervention groups was

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Ceftriaxone (IV) + doxycycline (PO) versus placebo (95% CI)
Beck depression inventory at 90 days; 0-63, lower values are beneficial	(1 study)	due to risk of bias	applicable	score in the control group was 8.9	1.1 lower (3.37 lower to 1.17 higher)
Reduction of symptoms Beck depression inventory at 180 days; 0-63, lower values are beneficial	129 (1 study)	LOW[1] due to risk of bias	Not applicable	The mean score in the control group was 8.8	The mean score in the intervention groups was 0.6 lower (2.95 lower to 1.75 higher)

[1] Downgraded by 1 increment if the majority of evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 4: Clinical evidence summary: Ceftriaxone (IV) versus placebo

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Ceftriaxone (IV) versus placebo (95% CI)
Improvement in fatigue at 6 months	55 (1 study)	HIGH	RR 3.47 (1.5 to 8.02)	185 per 1,000	457 more per 1,000 (from 93 more to 1,000 more)
FSS-11 score (final values) at 3 months; 1-7, lower values are beneficial	32 (1 study) 12 weeks	LOW[1,2] due to risk of bias, imprecision	Not applicable	The mean score in the control group was 4.8	The mean FSS-11 score in the intervention groups was 0.6 lower (1.93 lower to 0.73 higher)
FSS-11 score (final values) at 6 months; 1-7, lower values are beneficial	80 (2 studies) 24 weeks	LOW[1,2] due to risk of bias, imprecision	Not applicable	Not applicable	The mean FSS-11 score in the intervention groups was 0.88 lower (1.55 to 0.21 lower)
Change in FSS-11 score from baseline at 6 months; 1-7, lower values are beneficial	48 (1 study)	LOW[1,2] due to risk of bias, imprecision	Not applicable	The mean change in score in the control group was -0.5	The mean change in FSS-11 score from baseline in the intervention groups was 0.8 lower (1.46 to 0.14 lower)
Improvement in cognitive measure at 6 months	48 (1 study)	LOW[2] due to imprecision	RR 0.85 (0.13 to 5.52)	91 per 1,000	14 fewer per 1,000 (from 79 fewer to 411 more)
A-A score (final values) at 6 months; cognitive processing speed measured in milliseconds, lower values are beneficial	48 (1 study)	MODERATE[2] due to imprecision	Not applicable	The mean score in the control group was 3.4	The mean A-A score in the intervention groups was 0.4 higher (0.38 lower to 1.18 higher)
Change in A-A score from baseline at 6 months; cognitive processing speed measured in milliseconds, lower values are beneficial	47 (1 study)	MODERATE[2] due to imprecision	Not applicable	The mean change in A-A score in the control group was -0.5	The mean change in A-A score from baseline in the intervention groups was 0.2 higher (0.32 lower to 0.72 higher)
Quality of life SF36 physical component at 12 weeks; 0-100, higher values are beneficial	32 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	Not applicable	The mean score in the control group was 36	The mean SF36 physical component score in the intervention groups was 4.4 higher (2.24 lower to 11.04 higher)
Quality of life SF36 physical component at 24	32 (1 study)	VERY LOW[1,2] due to risk of bias,	Not applicable	The mean score in the control	The mean SF36 physical component score in the intervention groups was

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Ceftriaxone (IV) versus placebo (95% CI)
weeks; 0-100, higher values are beneficial		imprecision		group was 36.8	5.2 higher (2.21 lower to 12.61 higher)
Quality of life SF36 mental component at 12 weeks; 0-100, higher values are beneficial	32 (1 study)	LOW[1,2] due to risk of bias, imprecision	Not applicable	The mean score in the control group was 51.6	The mean SF36 mental component score in the intervention groups was 8.6 lower (15.86 to 1.34 lower)
Quality of life SF36 mental component at 24 weeks; 0-100, higher values are beneficial	32 (1 study)	LOW[1,2] due to risk of bias, imprecision	Not applicable	The mean score in the control group was 50.7	The mean SF36 mental component score in the intervention groups was 8.6 lower (16.99 to 0.21 lower)
Reduction of symptoms McGill pain questionnaire at 12 weeks; scale not reported, higher values are beneficial	32 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	Not applicable	The mean score in the control group was 7.5	The mean McGill pain questionnaire score in the intervention groups was 0.9 higher (3.68 lower to 5.48 higher)
Reduction of symptoms McGill pain questionnaire at 24 weeks; scale not reported, higher values are beneficial	32 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	Not applicable	The mean score in the control group was 8.1	The mean McGill pain questionnaire score in the intervention groups was 1.7 lower (7.62 lower to 4.22 higher)
Reduction of symptoms McGill pain questionnaire visual analogue scale at 12 weeks; scale not reported, lower values are beneficial	32 (1 study)	LOW[1,2] due to risk of bias, imprecision	Not applicable	The mean score in the control group was 3	The mean McGill pain questionnaire visual analogue scale score in the intervention groups was 1 higher (0.99 lower to 2.99 higher)
Reduction of symptoms McGill pain questionnaire visual analogue scale at 24 weeks; scale not reported, lower values are beneficial	32 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	Not applicable	The mean score in the control group was 3.8	The mean McGill pain questionnaire visual analogue score in the intervention groups was 0 higher (2.4 lower to 2.4 higher)
Reduction of symptoms no. of joints with pain at 12 weeks	32 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	Not applicable	The mean no. of joints with pain in the control group was 4.4	The mean no. of joints with pain in the intervention groups was 1.1 lower (4.74 lower to 2.54 higher)

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Ceftriaxone (IV) versus placebo (95% CI)
Reduction of symptoms no. of joints with pain at 24 weeks	32 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	Not applicable	The mean no. of joints with pain in the control group was 2.6	The mean no. of joints with pain in the intervention groups was 0.8 higher (1.6 lower to 3.2 higher)
Reduction of symptoms Beck depression inventory at 12 weeks; 0-63, lower scores are beneficial	32 (1 study)	LOW[1,2] due to risk of bias, imprecision	Not applicable	The mean score in the control group was 7.4	The mean Beck Depression Inventory score in the intervention groups was 4.1 higher (1.57 lower to 9.77 higher)
Reduction of symptoms Beck depression inventory at 24 weeks; 0-63, lower scores are beneficial	32 (1 study)	LOW[1,2] due to risk of bias, imprecision	Not applicable	The mean score in the control group was 6.5	The mean Beck Depression Inventory score in the intervention groups was 5.4 higher (0.14 lower to 10.94 higher)
Reduction of symptoms Zung anxiety index at 12 weeks; 20-80, lower values are beneficial	32 (1 study)	LOW[1,2] due to risk of bias, imprecision	Not applicable	The mean score in the control group was 40.5	The mean Zung Anxiety Index score in the intervention groups was 6.2 higher (0.72 lower to 13.12 higher)
Reduction of symptoms Zung anxiety index at 24 weeks; 20-80, lower values are beneficial	32 (1 study)	LOW[1,2] due to risk of bias, imprecision	Not applicable	The mean score in the control group was 38.4	The mean Zung Anxiety Index score in the intervention groups was 7.9 higher (1.21 to 14.59 higher)
Reduction in symptoms SCL-90 Global Symptom Index at 12 weeks; scale not reported, lower values are beneficial	32 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	Not applicable	The mean score in the control group was 54.8	The mean SCL-90 score in the intervention groups was 2.7 higher (6.23 lower to 11.63 higher)
Reduction of symptoms SCL-90 Global Symptom Index at 24 weeks; scale not reported, lower values are beneficial	32 (1 study) 24 weeks	LOW[1,2] due to risk of bias, imprecision	Not applicable	The mean score in the control group was 53.1	The mean SCL-90 score in the intervention groups was 4.4 higher (4.57 lower to 13.37 higher)
Adverse events	37 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	RR 3.65 (0.49 to 27.26)	71 per 1,000	189 more per 1,000 (from 36 fewer to 1,000 more)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Ceftriaxone (IV) versus placebo (95% CI)
at very high risk of bias [2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs					

Table 5: Clinical evidence summary: Ceftriaxone (IV) followed by doxycycline (PO) versus ceftriaxone (IV) followed by clarithromycin (PO) plus hydroxychloroquine

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ceftriaxone plus clarithromycin plus hydroxychloroquine	Risk difference with ceftriaxone plus doxycycline (95% CI)
SF-36 (physical component – final values) at 14 weeks; 15-61 (norm-based T-score), general population score 50 (SD 10), higher values are beneficial	182 (1 study)	LOW[1,2] due to indirectness, imprecision	Not applicable	The mean SF-36 (physical component) in the control group was 35.6	The mean SF-36 (physical component) in the intervention group was 0.6 lower (2.62 lower to 1.42 higher)
Adverse events at 14 weeks	182 (1 study)	LOW[1,2] due to indirectness, imprecision	RR 1.12 (0.82 to 1.53)	438 per 1,000	53 more per 1,000 (from 79 fewer to 232 more)
Discontinued treatment due to adverse events at 14 weeks	182 (1 study)	VERY LOW[1,2] due to indirectness, imprecision	RR 0.48 (0.13 to 1.79)	73 per 1,000	38 fewer per 1,000 (from 63 fewer to 58 more)
[1] People in the clarithromycin group also received hydroxychloroquine [2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs					

Table 6: Clinical evidence summary: Ceftriaxone (IV) followed by doxycycline (PO) versus ceftriaxone (IV)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ceftriaxone	Risk difference with ceftriaxone plus doxycycline (95% CI)
SF-36 (physical component – final values) at 14 weeks; 15-61 (norm-based T-score), general population score 50 (SD 10), higher values are beneficial	184 (1 study)	MODERATE[1] due to imprecision	Not applicable	The mean SF-36 (physical component) in the control group was 34.8	The mean SF-36 (physical component) in the intervention group was 0.2 higher (1.82 lower to 2.22 higher)
Adverse events at 14 weeks	184 (1 study)	MODERATE[1] due to imprecision	RR 1.41 (0.99 to 1.99)	347 per 1,000	142 more per 1,000 (from 3 fewer to 343 more)
Discontinued treatment due to adverse events at 14 weeks	184 (1 study)	LOW[1] due to imprecision	RR 0.85 (0.2 to 3.71)	41 per 1,000	6 fewer per 1,000 (from 33 fewer to 111 more)

[1] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 7: Clinical evidence summary: Ceftriaxone (IV) followed by clarithromycin (PO) plus hydroxychloroquine versus ceftriaxone (IV)

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ceftriaxone	Risk difference with ceftriaxone plus clarithromycin plus hydroxychloroquine (95% CI)
SF-36 (physical component – final values) at 14 weeks; 15-61 (norm-based T-score), general population score 50 (SD 10), higher values are beneficial	194 (1 study)	LOW[1,2] due to indirectness, imprecision	Not applicable	The mean SF-36 (physical component) in the control group was 34.8	The mean SF-36 (physical component) in the intervention group was 0.8 higher (1.15 lower to 2.75 higher)
Adverse events at 14 weeks	194 (1 study)	LOW[1,2] due to indirectness, imprecision	RR 1.26 (0.89 to 1.8)	347 per 1,000	90 more per 1,000 (from 38 fewer to 278 more)
Discontinued treatment due to adverse events at 14	194	VERY LOW[1,2] due to indirectness,	RR 1.79	41 per 1,000	32 more per 1,000

Outcomes	Number of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with ceftriaxone	Risk difference with ceftriaxone plus clarithromycin plus hydroxychloroquine (95% CI)
weeks	(1 study)	imprecision	(0.54 to 5.91)		(from 19 fewer to 200 more)

[1] People in the clarithromycin group also received hydroxychloroquine
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 8: Clinical evidence summary: Amoxicillin (po) versus placebo

Outcomes	No of Participants (studies)	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Amoxicillin (po) versus placebo (95% CI)
Quality of life SF36 physical component (change score) at 6 months; higher values are beneficial	45 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	Not applicable	The mean change in score in the control group was 7	The mean change in SF36 physical component score in the intervention groups was 1.5 higher (3.83 lower to 6.83 higher)
Quality of life SF36 mental component (change score) at 6 months; higher values are beneficial	45 (1 study)	VERY LOW[1,2] due to risk of bias, imprecision	Not applicable	The mean change in score in the control group was 6.2	The mean change in SF36 mental component score in the intervention groups was 8.2 higher (2.04 to 14.36 higher)
Adverse events	86 (1 study)	LOW[2] due to imprecision	RR 1.09 (0.62 to 1.93)	353 per 1,000	32 more per 1,000 (from 134 fewer to 328 more)

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

See appendix F for full GRADE tables.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified.

See also the health economic study selection flow chart in appendix G.

1.5.2 Excluded studies

No relevant health economic studies were identified and excluded.

1.5.3 Unit costs

The following unit costs were presented to the committee to aid consideration of cost-effectiveness.

Table 9: UK costs of antimicrobials

Class	Drug	Age	Preparation	Mg/unit	Cost/unit (£)	Units/day	Course duration (days)	Cost per course (£)
Penicillins	Amoxicillin	7 days-11 months	125 mg/1.25 ml oral suspension paediatric	125	0.20	3	14–28	8.35–16.70
		1-4 years	250 mg/5 ml oral suspension	250	0.06	3	14–28	2.37–4.75
		>5 years	capsules	500	0.06	3	14–28 (g)	2.54–5.08
Penicillins	Phenoxymethylpenicillin	Adults (a)	tablets	250	0.04	4	10	1.49
Tetracyclines	Doxycycline	>12 years	capsules	100	0.11	2	10–28 (h)	2.18–6.09
Cephalosporins	Cefuroxime axetil	>3 months	tablets	250	1.27	4	14–28 (g)	70.88–141.76
Macrolide	Clarithromycin	>1 month	tablets	500	0.16	2	14–21	4.42–6.63
Macrolide	Azithromycin	<12 years	40 mg/1 ml oral suspension	40	0.27	10 mg/kg	9 (i)	Weight dependent
		Adults	tablets	500	0.42	1	9 (i)	3.75
Cephalosporins	Cefotaxime	Adults (b)	2 g powder for solution for injection vials (IV)	2,000	3.75	3	10	112.50
Cephalosporins	Ceftriaxone	>9 years (c) (d)	2 g powder for solution for injection vials (IV) (e)	2,000	1.03	1	14–21	14.42–21.63
Penicillins	Benzylpenicillin sodium	Adults (f)	600 mg powder for solution for injection vials (IM)	600	2.73	2	3	16.38

Abbreviations: IM: intramuscular; IV: intravenously.

Sources: Unit costs from NHS Electronic Drug Tariff January 2017,[121] except cefotaxime from BNF, January 2017[21] and ceftriaxone from EMIT March 2017;[39] dosage from BNF and BNF for Children January 2017,[21, 22] exceptions below:

(a) Source of dosage from RCT in adults with EM: Steere 1983,[168] dosage for Lyme disease not available from BNF or BNF for children.

(b) Source of dosage from RCT in adults with neuroborreliosis: Pfister 1989[133] and Pfister 1991,[134] dosage for Lyme disease not available from BNF or BNF for children.[21, 22]

(c) For disseminated Lyme borreliosis.

(d) Dose for neonate and child up to 11 years (body weight <50 kg) 50-80 mg/kg once daily for 14-21 days. BNF for children January 2017.[22]

(e) Administration can vary in adults and children >1 month: IV infusion over 30 mins or IV injection over 5 mins or deep muscular injection (doses over 1 g divided between more than 1 site): 2 g per day for 14-21 days BNF January 2017[21].

(f) Source of dosage from RCT in adults with Lyme arthritis: Steere 1985:[167] 1.2 million U injected in each buttock weekly intramuscularly. Duration 3 weeks. Dosage for Lyme disease not available from BNF or BNF for children. [21, 22]

(g) Course duration for early Lyme 14-21 days; 28 days for Lyme arthritis. BNF January 2017.[21]

(h) Course duration for early Lyme 10-14 days; 28 days for Lyme arthritis. BNF January 2017.[21]

(i) Course dose and duration for adults: 500 mg once daily for 3 days, for 3 weeks. For children under 12 years: 10 mg/kg once daily for 3 days for 3 weeks. Committee expert opinion.

The cost of intravenous antibiotics will vary depending on where these are administered and by whom. These costs will include some of the following cost components:

- antibiotic
- nursing time (for example, Band 6 nurse, £44 per hour, PSSRU 2016[42])
- clinic space and clerical time (for outpatient administration)
- travel time (for home administration)
- hospital bed (for inpatient administration)
- consumables (for example, cannula, needles, syringes, dressing, IV giving set and glucose or sodium chloride solution).

A large proportion of the total cost of intravenous antibiotics is likely to be the cost of administration rather than the drug itself. As a result, intravenous drugs that have multiple doses administered per day will be more costly than those administered once daily. This was explored in a detailed costing analysis conducted for the NICE CG102 (Meningitis [bacterial] and meningococcal septicaemia in under 16s).[118] In this analysis, they found that ceftriaxone was the cheapest antibiotic when compared to cefotaxime and benzylpenicillin. This was due to savings in staff time associated with once daily dosing, which offset the higher cost of the drug itself.

Inpatient administration

Intravenous antibiotics administered in an inpatient setting will incur the cost of an inpatient stay, which is assumed to include intravenous antibiotics treatment as part of the unit cost. The weighted average unit cost of non-elective inpatient stays and day cases for infectious disease in adults and children are summarised estimated in the table below using the NHS reference costs 2015/2016.[47]

Table 10: Unit costs of inpatient administration

Schedule	Currency description	Currency codes	Weighted average unit costs (per day)
Day-case adults	Standard/major/complex infectious diseases with/without single/multiple interventions, with/without CC	WJ01B, WJ01D, WJ01E, WJ02B, WJ02C,WJ02D, WJ02E, WJ03A, WJ03B, WJ03C, WJ03D, WJ03E, WJ03F, WJ03G	£352
Day-case paediatrics	Paediatric minor/major/intermediate infections with/without CC	PW01A, PW01B, PW01C, PW16A, PW16B, PW16C, PW16D, PW16E, PW17D, PW17E, PW17F, PW17G	£448
Non-elective inpatient short-stay adults	Standard/major/complex infectious diseases with/without single/multiple interventions, with/without CC	WJ01A, WJ01B, WJ01C, WJ01D, WJ01E, WJ02A, WJ02B, WJ02C,WJ02D, WJ02E, WJ03A, WJ03B, WJ03C, WJ03D, WJ03E, WJ03F, WJ03G	£432
Non-elective inpatient short-stay paediatrics	Paediatric minor/major/intermediate infections with/without CC	PW01A, PW01B, PW01C, PW16A, PW16B, PW16C, PW16D, PW16E, PW17D, PW17E, PW17F, PW17G	£521
Non-elective inpatient long-stay adults	Standard/major/complex infectious diseases with/without single/multiple interventions, with/without CC	WJ01A, WJ01B, WJ01C, WJ01D, WJ01E, WJ02A, WJ02B, WJ02C,WJ02D, WJ02E, WJ03A, WJ03B, WJ03C, WJ03D, WJ03E, WJ03F, WJ03G	£473
Non-elective inpatient long-stay paediatrics	Paediatric minor/major/intermediate infections with/without CC	PW01A, PW01B, PW01C, PW16A, PW16B, PW16C, PW16D, PW16E, PW17D, PW17E, PW17F, PW17G	£699

Source: NHS reference costs 2015/2016[47]

Outpatient administration

Intravenous antibiotics may also be administered as part of an outpatient parenteral antibiotic therapy (OPAT) service, which is available in some hospitals. This allows for administration in an outpatient clinic or in a home setting by a district nurse and is for people who require parenteral treatment but are otherwise stable and well enough not to be in hospital. There is currently no NHS reference cost for this service.

A UK study by Chapman 2009[31] reports that this type of service costs between 41% and 61% of the equivalent inpatient costs. Based on these estimates from Chapman 2009 and the unit cost for an adult day case in Table 10, the cost of OPAT would be approximately £144 to £215 per day. These costs would include the cost of the drug as well as the administration.

1.6 Resource impact

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

1.7 Evidence statements

1.7.1 Clinical evidence statements

Adults and young people:

- Low to Very Low quality evidence from 1 RCT did not find any clinical difference between intravenous ceftriaxone followed by oral doxycycline versus placebo.
- High to Low quality evidence from 2 RCTs found a clinical benefit of intravenous ceftriaxone over placebo regarding improvement in fatigue. Moderate to Low quality evidence from 1 RCT showed no difference between intravenous ceftriaxone and placebo regarding cognitive function. Very Low quality evidence from 1 RCT showed a benefit of ceftriaxone for improvement in physical aspects of quality of life, but Low quality evidence from 1 RCT showed harm of ceftriaxone for mental aspects of quality of life, depression and anxiety. Very Low quality evidence from 1 RCT showed no difference between ceftriaxone and placebo for pain reduction or reduction of symptoms measured by Global Symptom Index. Very Low quality evidence from 1 RCT showed a higher rate of adverse events for ceftriaxone.
- Low to Very Low quality evidence from 1 RCT did not find any difference between intravenous ceftriaxone followed by oral doxycycline and intravenous ceftriaxone followed by oral clarithromycin and hydroxychloroquine.
- Moderate quality evidence from 1 RCT did not find any difference in quality of life between intravenous ceftriaxone followed by oral doxycycline and intravenous ceftriaxone alone. Moderate quality evidence from 1 RCT showed a higher rate of adverse events for intravenous ceftriaxone followed by oral doxycycline. Low quality evidence from 1 RCT did not find any difference in the number of people discontinuing treatment due to adverse events between the treatment arms.
- Low to Very Low quality evidence did not find any difference between intravenous ceftriaxone followed by oral clarithromycin plus hydroxychloroquine and intravenous ceftriaxone alone.
- Very Low quality evidence from 1 RCT showed a benefit of amoxicillin for improving mental aspects of quality of life but no difference in physical aspects of quality of life. Low quality evidence from 1 RCT showed no difference between amoxicillin and placebo in adverse events.

Children:

- No evidence was found.

1.7.2 Health economic evidence statements

No relevant economic evaluations were identified.

1.8 The committee's discussion of the evidence

1.8.1 Interpreting the evidence

1.8.1.1 The outcomes that matter most

The evidence included in this chapter was identified through the review on the management of non-specific symptoms associated with Lyme disease. The identified evidence was in people with Lyme disease who had ongoing, non-specific symptoms despite having previous antibiotic treatment. The committee acknowledged that the included studies provided some limited evidence on the effectiveness of long-term antibiotic treatment for Lyme disease.

The guideline committee considered quality of life, cure or the resolution of Lyme disease symptoms, the reduction of Lyme disease symptoms, and the relapse of Lyme disease symptoms to be critical outcomes. Adverse events as a result of treatment were considered to be an important outcome.

This review only found evidence for the outcomes quality of life, reduction of clinical symptoms and adverse events. No evidence was found for the outcomes cure or resolution of symptoms and symptom relapse.

1.8.1.2 The quality of the evidence

The evidence was generally of Moderate to Very Low quality due to risk of bias, indirectness and imprecision. There were particular concerns around a lack of outcome assessor blinding for subjective outcomes, such as quality of life, high participant dropout rates and differences between treatment groups in outcomes at baseline. One treatment arm in the PLEASE trial also used an indirect intervention as people received hydroxychloroquine in addition to clarithromycin.

One outcome, improvement in fatigue for the comparison of intravenous ceftriaxone versus placebo, was of High quality.

There were no concerns regarding the risk of bias for any of the outcomes reported by the PLEASE trial. However, all participants in the trial received a 2-week course of open-label intravenous ceftriaxone before their assigned study drug. This antibiotic treatment might have resulted in people experiencing a quality of life improvement.

There was a general lack of evidence with only single, small studies identified for most comparisons. The committee agreed that while the evidence had to be interpreted with caution, there was a trend suggesting that continuous long-term treatment did not provide an additional benefit.

1.8.1.3 Benefits and harms

The evidence identified was in people with Lyme disease who had ongoing non-specific symptoms despite having undergone antibiotic treatment. The majority of the people included in the studies received oral or intravenous antibiotic treatment for their Lyme disease symptoms prior to enrolment in the study.

Four included studies assessed the effectiveness of intravenous ceftriaxone, alone or in combination with oral doxycycline or oral clarithromycin and 1 study assessed the effectiveness of oral amoxicillin.

Evidence from 2 RCTs showed a clear benefit of intravenous ceftriaxone compared to placebo in the improvement of fatigue and quality of life as measured by the FSS-11 score. There was no difference between intravenous ceftriaxone and placebo regarding changes in cognitive function. Evidence from 1 RCT showed a benefit of ceftriaxone for improvement in

physical aspects of quality of life, a harm of ceftriaxone for mental aspects of quality of life, depression and anxiety, and no difference between ceftriaxone and placebo for pain reduction or reduction of symptoms measured by Global Symptom Index. However, the committee was unable to interpret the effect of the intervention with high confidence due to differences in outcome scores at baseline. Evidence showed a higher rate of adverse events for ceftriaxone.

Two RCTs assessed the effectiveness of intravenous ceftriaxone followed by long-term oral doxycycline or clarithromycin in people with ongoing symptoms associated with Lyme disease. In the PLEASE trial, all participants received 2 grams of open-label intravenous ceftriaxone once daily for 14 days before their assigned masked study intervention; either 12 weeks of oral doxycycline (100 milligrams twice daily) or 12 weeks of oral clarithromycin (500 milligrams clarithromycin plus 200 milligrams hydroxychloroquine twice daily). In the other study, people were randomly assigned 2 grams of intravenous ceftriaxone once daily for 30 days followed by 100 milligrams oral doxycycline twice daily for 60 days or a 90-day course of placebo. People with a presumed diagnosis of neuroborreliosis as indicated by a positive PCR in plasma or CSF were excluded from this study.

Evidence from these 2 RCTs found that the addition of long-term oral doxycycline or oral clarithromycin increased the number of adverse events and led to a significantly higher treatment discontinuation rate due to adverse events. There was, however, no additional benefit of taking long-term oral dosages of doxycycline or clarithromycin after intravenous ceftriaxone on quality of life.

Evidence from 1 RCT showed no difference in quality of life measured by SF36 physical component or adverse events. There was a benefit of amoxicillin for the SF36 mental component; however, the guideline committee considered that the evidence for this outcome might have been biased by the high participant dropout rate and the difference in SF36 mental component scores at baseline.

1.8.2 Cost effectiveness and resource use

No relevant health economic evidence was identified. The unit costs of different oral and intravenous antimicrobials were presented to the committee. The committee agreed it was important to establish if ongoing symptoms are related to Lyme disease. This may require additional healthcare practitioner time to allow for a review of history and examination. The committee noted that establishing if a re-infection has occurred would be done clinically not through further testing. Although no cost-effectiveness evidence was identified, it is considered good clinical practice to assess a person with ongoing symptoms. Treating people who have been re-infected is considered standard practice for all infections. A recommendation to offer a second course of antibiotics to people with ongoing symptoms, who may have treatment failure, was based on the clinical evidence identified and committee discussion as described below. This additional treatment cost is unlikely to apply to a large population and therefore not expected to have a significant resource impact.

1.8.3 Other factors the committee took into account

The committee considered it important to acknowledge that recovery from infection can take time and this occurs in many infections including Lyme disease.

The committee considered evidence from the PLEASE trial to be particularly relevant when developing clinical recommendations for people with ongoing symptoms related to Lyme disease. In the study, all participants received open-label intravenous ceftriaxone for 2 weeks followed by their randomly assigned study drug; 12 weeks of oral doxycycline, 12 weeks of oral clarithromycin, or 12 weeks of oral placebo. Although the PLEASE trial showed a quality of life improvement in all treatment arms, there was no difference between treatment arms. The committee considered that any quality of life improvements could be due to the initial 2-

week treatment of intravenous ceftriaxone with no clear additional benefit from long-term treatment with oral doxycycline or clarithromycin. To determine the effectiveness of long-term antibiotic treatment, study participants should have also been blinded to the intravenous ceftriaxone treatment, and a fourth treatment arm consisting of only placebo should have been introduced. The committee considered that the evidence did not provide support for long-term antibiotic treatment.

The committee also discussed the possibility of treatment failure. Evidence for management of different presentations of Lyme disease all indicated some treatment failures. People respond to treatments differently for various reasons and this is not specific to Lyme disease. The committee agreed that the emphasis on higher doses and 3- or 4-week treatment courses in this guideline should reduce treatment failure but recognised that this can still occur.

The committee therefore recommended the consideration of a second course of antibiotic treatment using an alternative antibiotic to the antibiotic initially prescribed if a person has ongoing symptoms and treatment failure is suspected.

The committee agreed that there was no evidence for further or prolonged antibiotic treatment beyond this. People with ongoing symptoms attributed to Lyme disease despite 2 adequate courses of antibiotics should have their care discussed with a specialist appropriate to their symptoms, for example a rheumatologist if they have joint problems. The committee was concerned about both missing alternate diagnoses and problems caused by inappropriate treatment with antibiotics. Discussion with the reference laboratory may also be appropriate in case assessment for other tick borne disease is required.

The committee also acknowledged that the antibiotic treatment might result in an eradication of the bacteria but may not have any immediate effect on the organ damage. Symptoms associated with organ damage may take a long time to heal or even remain permanent. These symptoms are therefore not necessarily indicative of treatment failure. There are various terms used to describe symptoms and syndromes associated with ongoing symptoms such as post Lyme symptoms or post treatment Lyme syndrome. The symptoms and presentation are similar to other infections where symptoms continue for some time without evidence of active infection.

The committee made a number of high priority research recommendations, which include the clinical epidemiology of Lyme disease, the development of a core outcome set for studies of management of Lyme disease and the evaluation of antibiotic regimens for management of Lyme disease. Research in these areas would ensure improved understanding of presentations and treatments for people with ongoing symptoms. These research recommendations are outlined in more detail in appendix J of evidence report A and appendix J of evidence report D.

1.9 Recommendations

L6. Offer regular clinical review and re-assessment to people with ongoing symptoms, including people who have no confirmed diagnosis.

L7. Explore any ongoing symptoms with the person and offer additional treatment if needed following usual clinical practice.

L8. Be alert to the possibility of symptoms related to Lyme disease that may need assessment and management including:

- chronic pain
- depression and anxiety (see NICE's guideline on common mental health disorders)
- fatigue
- sleep disturbance.

L9. Support people who have ongoing symptoms after treatment for Lyme disease by:

- encouraging and helping them to access additional services, including referring to adult social care for a care and support needs assessment, if they would benefit from these
- communicating with children and families social care, schools and higher education, and employers about the person's need for a gradual return to activities, if relevant.

1.10 The committee's discussion of the evidence

1.10.1 Interpreting the evidence

1.10.1.1 The outcomes that matter most

No specific evidence review was undertaken for the assessment and management of ongoing symptoms related to Lyme disease and support of people who have a slow recovery from Lyme disease. The recommendations are based on consensus with regard for the long-term difficulties people with Lyme disease often face.

1.10.1.2 The quality of the evidence

No specific evidence review was undertaken.

1.10.1.3 Benefits and harms

No specific evidence review was undertaken.

1.10.2 Cost effectiveness and resource use

No health economic review was undertaken. Providing information and support towards access to further services such as social care is considered good patient care, particularly in people who experience a slow recovery from illness. In addition, it is considered current practice to assess and manage people for all their presenting symptoms.

These recommendations are not expected to apply to all people with Lyme disease and so are not anticipated to have a significant resource impact.

1.10.3 Other factors the committee took into account

The committee discussed the difficulties people with Lyme disease often face, particularly in the absence of a speedy recovery. The committee considered it important to include a recommendation to provide regular review to people with ongoing symptoms for support and to monitor symptoms. The committee emphasized that some people may require a gradual return to education and work, and healthcare professionals can help by ensuring these needs are understood by schools and employers. This is similar to other conditions where recovery is slow, but the committee considered it appropriate to emphasise the need for this in people with Lyme disease.

People who have a slow recovery or who experience a significant impact on their personal and professional life may benefit from access to addition services, such as a social services needs assessment.

The committee also wished to emphasise the needs of people with Lyme disease for management of symptoms that may need further assessment and management. These symptoms include depression and anxiety, chronic pain, sleep disturbance and fatigue. The committee agreed that these symptoms were not specific to Lyme disease and that guidance on the assessment and management for these already exist. It was therefore decided to highlight the need to consider these symptoms and refer to relevant existing guidance.

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Appendices

Appendix A: Review protocols

No separate review was undertaken to assess the effectiveness of treatment in people with ongoing symptoms. People with ongoing symptoms were included in the review population for the review question on the management of non-specific symptoms related to Lyme disease.

Table 11: Review protocol for the management of non-specific symptoms

Question number: 4.1

Relevant section of Scope: management

Field	Content
Review question	What is the most clinically and cost-effective treatment for seropositive people, who have non-specific symptoms that may be related to Lyme disease?
Type of review question	Intervention 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 review questions on the condition-specific management of Lyme disease aim to identify the most effective treatment in different clinical scenarios. The questions have been developed in a way to identify the evidence for all potential populations and scenarios, even if clinical presentations are more diverse. The population for this review consists of people with a seropositive test result for Lyme disease, who have non-specific symptoms that may be related to Lyme disease.
Eligibility criteria – population / disease / condition / issue / domain	People with Lyme disease determined by a diagnostic tests or clinical diagnosis who have non-specific symptoms that may be related to Lyme disease. This includes symptoms such as: • disturbed cognitive function, for example, memory loss • dizziness • fatigue • fever and sweats • headache • lymphadenopathy • myalgia and muscle stiffness • neck pain or stiffness • paraesthesia • photophobia

Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	Antimicrobials, including but not limited to:
	• Penicillins
	  ○ Amoxicillin (oral, IV)
	  ○ Ampicillin (oral, IV)
	  ○ Benzylpenicillin sodium / Penicillin G (IV)
	  - Including Augmentin (Amoxicillin and clavulanic acid; oral, IV)
	  ○ Phenoxymethylpenicillin / Penicillin V (oral)
	• Tetracyclines

Field	Content
	○ Doxycycline (oral) ○ Minocycline (oral) • Cephalosporins ○ Cefotaxime (IV) ○ Ceftriaxone (IV) ○ Cefuroxime axetil (oral) • Macrolides ○ Azithromycin (oral) ○ Clarithromycin (oral, IV) • Fluoroquinolones ○ Ciprofloxacin (oral, IV) ○ Levofloxacin (oral, IV) ○ Moxifloxacin (oral, IV) ○ Nalidixic acid (oral) ○ Norfloxacin (oral) ○ Ofloxacin (oral, IV) • Rifampicin (oral, IV)
Eligibility criteria – comparator(s) / control or reference (gold) standard	• Antimicrobial agents compared with each other ○ If data are available, consider: - Type of antimicrobial agent (within class or between class) - Route of administration - Duration of treatment: 1 month versus longer • Monotherapy versus polytherapy (any combination) • Antimicrobial agents compared to no treatment / placebo
Outcomes and prioritisation	**Critical:** 1. Quality of life (any validated measure) 2. Cure (resolution of symptoms) 3. Reduction of clinical symptoms 4. Symptom relapse **Important:** 5. Adverse events
Eligibility criteria – study design	• RCTs • Cohort studies (if no RCT evidence is found)
Other inclusion exclusion criteria	Date limits for search: none Language: English only Setting: all settings in which NHS care is provided or commissioned The following interventions will not be considered for inclusion: • Metronidazole • Trimethoprim
Proposed sensitivity / subgroup analysis, or meta-regression	The following groups will be considered separately if data are available (strata): • Children (under 12 years); young people and adults (12 years and over) • Onset of specific symptoms less than 6 weeks; 6 weeks to 6 months; over 6 months Subgroups (to be investigated if heterogeneity is identified): • Pregnant women • People who are immunocompromised • People in whom a previous course of antimicrobial treatment has

Field	Content
	failed
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)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). GRADEpro will be used to assess the quality of evidence for each outcome Bibliographies, citations, study sifting and reference management will be managed using EndNote. Data extractions will be performed using EviBase, a platform designed and maintained by the National Guideline Centre (NGC)
Information sources – databases and dates	Clinical searches Medline, Embase, The Cochrane Library 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 risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details, please see section 6.4 of Developing NICE guidelines: the manual. Meta-analysis will be conducted wherever possible (that is, where similar studies can be combined) In the absence of clinically established MIDs, standard MIDs for dichotomous (25% risk reduction or risk increase) and continuous outcomes (+/-0.5 standard deviation) will be used If heterogeneity is found, the influence of subgroups will be examined
Methods for quantitative analysis – combining studies and exploring (in)consistency	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	For details, please see sections 6.4 and 9.1 of Developing NICE

Field	Content
evidence	guidelines: the manual.
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 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.
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

Table 12: 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	• 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	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. 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).[119] **Inclusion and exclusion criteria** • 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.

Where there is discretion

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 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 13: 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

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.	(granulocyctic 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

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.	(granulocyctic 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

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.	(granulocyctic 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

B.2 Health Economics literature search strategy

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

Table 14: Database date parameters and filters used

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

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.	(granulocyctic 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

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.	(granulocyctic 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.

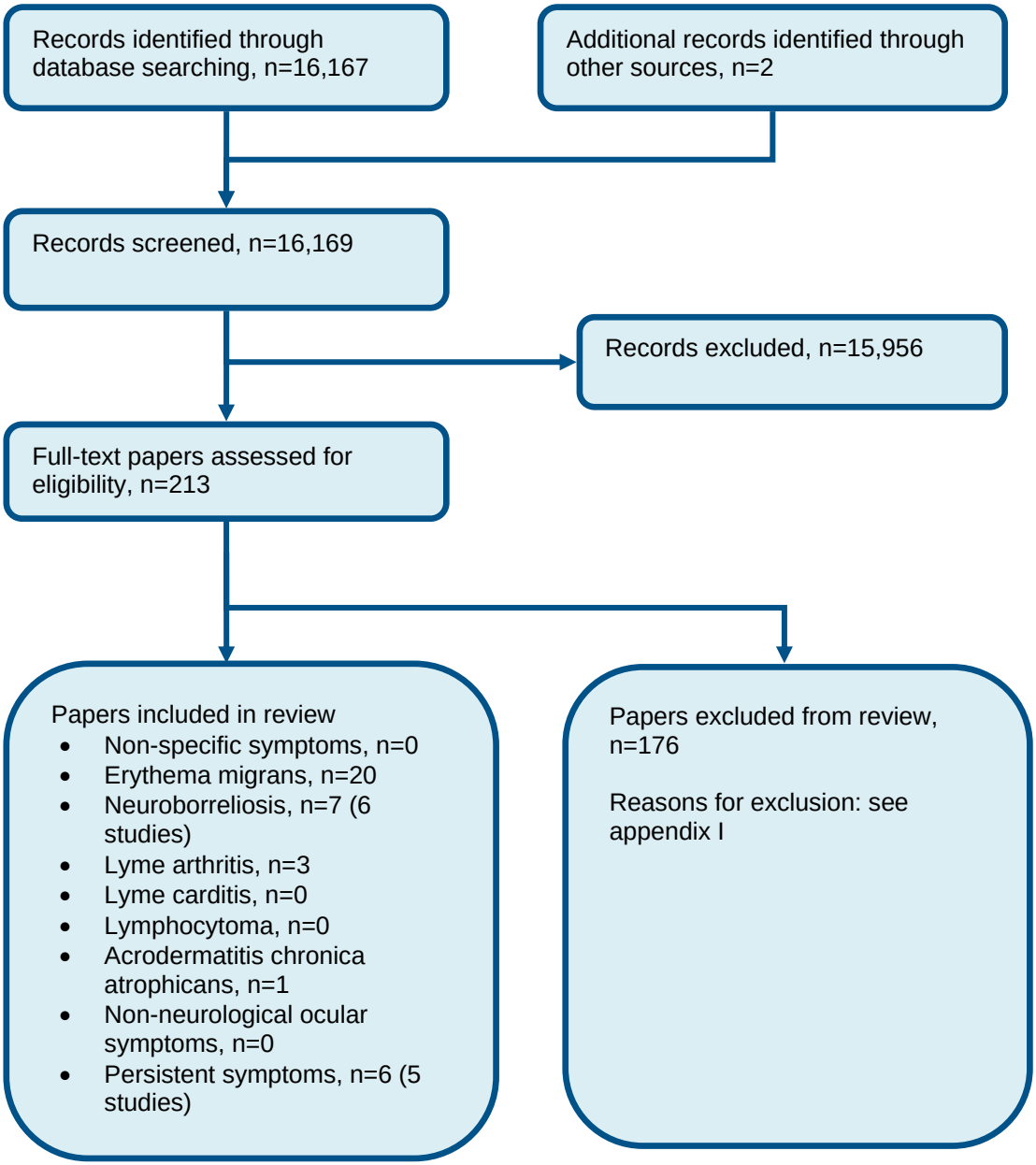
62.	sickness impact profile.ti,ab.
63.	disability adjusted life.ti,ab.
64.	(qal* or qtime* or qwb* or daly*).ti,ab.
65.	(euroqol* or eq5d* or eq 5*).ti,ab.
66.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
67.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
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

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.	((granulocyctic 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

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of the management of specific clinical scenarios for Lyme disease



Appendix D: Clinical evidence tables

Study	Cameron 2008[29]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=86)
Countries and setting	Conducted in the US; Setting: primary care internal medicine practice, USA
Line of therapy	Unclear; mean 2.2 previous courses of antibiotics
Duration of study	Intervention + follow up: 3 months + 3 months
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Adults
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	At least 18 years of age; recurrence of Lyme disease symptoms after previous successful treatment
Exclusion criteria	Inadequate initial antibiotic treatment; allergy to amoxicillin; previous amoxicillin failure; evidence of a new tick-borne infection or another condition that could explain their presentation (new infection presumed if subjects presented with evidence of a new tick bite, EM rash, Bell's palsy, arthritis, meningitis or heart block, or newly positive ELISA or IgM Western blot)
Recruitment/selection of patients	not reported
Age, gender and family origin	Age - Mean (SD): Amoxicillin group: 46 (12), placebo group: 49 (11). Gender (M:F): 41/45. Family origin: 90% White
Further population details	1. Immunocompromised people: Not stated / Unclear 2. Pregnant women: Not stated / Unclear
Indirectness of population	No indirectness: NA
Interventions	(n=52) Intervention 1: Antibiotics - Amoxicillin. Oral Amoxicillin 3g daily. Duration 3 months. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. Previous treatment failure: Previous treatment failure (n=34) Intervention 2: Placebo. Duration 3 months. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. Previous treatment failure: Previous treatment failure
Funding	Other (funded in part by a grant from the Lyme Disease Association)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: AMOXICILLIN versus PLACEBO	

Study	Cameron 2008[29]
Protocol outcome 1: Quality of life - Actual outcome for Adults: SF36 physical component at 6 months; Group 1: mean 8.5 (SD 11); n=31, Group 2: mean 7 (SD 7); n=14; SF36 physical component 0-100 Top=High is good outcome Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 21; Group 2 Number missing: 20 - Actual outcome for Adults: SF36 mental component at 6 months; Group 1: mean 14.4 (SD 6.2); n=31, Group 2: mean 6.2 (SD 11); n=14; SF36 mental component 0-100 Top=High is good outcome Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 21; Group 2 Number missing: 20 Protocol outcome 2: Adverse events - Actual outcome for Adults: any adverse event at 6 months; Group 1: 20/52, Group 2: 12/34 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Cure (resolution of symptoms); Reduction of symptoms; Symptom relapse

Study	Fallon 2008[59]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=37)
Countries and setting	Conducted in the US; Setting: evaluations conducted at the New York State Psychiatric Institute and Columbia University Medical Centre, treatments conducted at patients' homes
Line of therapy	Unclear; mean 2.3 months of prior IV antibiotics, mean 7.2 months of prior oral antibiotics
Duration of study	Intervention + follow up: 24 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: see inclusion criteria
Stratum	Adults: adults
Subgroup analysis within study	Not applicable: NA
Inclusion criteria	History of physician documented EM or US CDC defined manifestations of Lyme disease and a positive or equivocal ELISA confirmed by positive Western blot serology; current positive IgG Western blot using CDC surveillance criteria, assessed using a single reference lab; treatment for Lyme disease with at least 3 weeks

Study	Fallon 2008[59]
	of IV ceftriaxone, completed at least 4 months before study entry; subjective memory impairment that, by participant report, started after the onset of Lyme disease; and objective evidence of memory impairment as documented by the Wechsler Memory Scale-III compared with age, sex and education-adjusted population norms
Exclusion criteria	History of a prior learning disability or medical condition that could confound neuropsychological assessment; cephalosporin allergy or history of a major psychiatric disorder before the onset of Lyme disease
Recruitment/selection of patients	not reported
Age, gender and family origin	Age - Mean (SD): 45.1 (13.2). Gender (M:F): 15/22. Family origin: white
Further population details	1. Immunocompromised people: Not stated / Unclear 2. Pregnant women: Not stated / Unclear
Indirectness of population	No indirectness: NA
Interventions	(n=23) Intervention 1: Antibiotics - Ceftriaxone. IV Ceftriaxone 2g/day. Duration 10 weeks. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. Previous treatment failure: (n=14) Intervention 2: Placebo. IV placebo (0.9% normal saline). Duration 10 weeks. Concurrent medication/care: not reported. Indirectness: No indirectness; Indirectness comment: NA Further details: 1. Previous treatment failure: Previous treatment failure
Funding	Academic or government funding (grant from the National Institutes of Neurological Disorders)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CEFTRIAXONE versus PLACEBO

Protocol outcome 1: Quality of life
- Actual outcome for Adults: Functional status (SF-36) - physical component scale at 12 weeks; Group 1: mean 40.4 (SD 9.4); n=20, Group 2: mean 36 (SD 9.2); n=12; SF-36 physical component 0-100 Top=High is good outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: statistical differences between groups in some rheumatology and neurology exam components, differences in baseline secondary measures not reported; Group 1 Number missing: 3, Reason: 2 thrombus, 1 hemolytic anemia; Group 2 Number missing: 2, Reason: 1 systemic infection, 1 intolerable joint pain requiring narcotic medications
- Actual outcome for Adults: Functional status (SF-36) - physical component scale at 24 weeks; Group 1: mean 42 (SD 10.1); n=20, Group 2: mean 36.8 (SD 10.5); n=12; SF-36 physical component 0-100 Top=High is good outcome
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: statistical differences between groups in some rheumatology

Study	Fallon 2008[59]
	and neurology exam components, differences in baseline secondary measures not reported; Group 1 Number missing: 3, Reason: 2 thrombus, 1 hemolytic anemia; Group 2 Number missing: 2, Reason: 1 systemic infection, 1 intolerable joint pain requiring narcotic medications - Actual outcome for Adults: Functional status (SF-36) - mental component scale at 12 weeks; Group 1: mean 43 (SD 13.7); n=20, Group 2: mean 51.6 (SD 7.2); n=12; SF-36 mental component 0-100 Top=High is good outcome Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: statistical differences between groups in some rheumatology and neurology exam components, differences in baseline secondary measures not reported; Group 1 Number missing: 3, Reason: 2 thrombus, 1 hemolytic anemia; Group 2 Number missing: 2, Reason: 1 systemic infection, 1 intolerable joint pain requiring narcotic medications - Actual outcome for Adults: Functional status (SF-36) - mental component scale at 24 weeks; Group 1: mean 42.1 (SD 15); n=20, Group 2: mean 50.7 (SD 9.2); n=12; SF-36 mental component 0-100 Top=High is good outcome Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: statistical differences between groups in some rheumatology and neurology exam components, differences in baseline secondary measures not reported; Group 1 Number missing: 3, Reason: 2 thrombus, 1 hemolytic anemia; Group 2 Number missing: 2, Reason: 1 systemic infection, 1 intolerable joint pain requiring narcotic medications Protocol outcome 2: Reduction of symptoms - Actual outcome for Adults: Fatigue Severity Scale at 12 weeks; Group 1: mean 4.2 (SD 1.6); n=20, Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: statistical differences between groups in some rheumatology and neurology exam components, differences in baseline secondary measures not reported; Group 1 Number missing: 3, Reason: 2 thrombus, 1 hemolytic anemia; Group 2 Number missing: 2, Reason: 1 systemic infection, 1 intolerable joint pain requiring narcotic medications - Actual outcome for Adults: Fatigue Severity Scale at 24 weeks; Group 1: mean 4.4 (SD 1.6); n=20, Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: statistical differences between groups in some rheumatology and neurology exam components, differences in baseline secondary measures not reported; Group 1 Number missing: 3, Reason: 2 thrombus, 1 hemolytic anemia; Group 2 Number missing: 2, Reason: 1 systemic infection, 1 intolerable joint pain requiring narcotic medications - Actual outcome for Adults: Total symptoms (McGill pain questionnaire - short form) at 12 weeks; Group 1: mean 8.4 (SD 8); n=20, Group 2: mean 7.5 (SD 5.2); n=12; McGill pain questionnaire - short form not reported Top=High is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: statistical differences between groups in some rheumatology and neurology exam components, differences in baseline secondary measures not reported; Group 1 Number missing: 3, Reason: 2 thrombus, 1 hemolytic anemia; Group 2 Number missing: 2, Reason: 1 systemic infection, 1 intolerable joint pain requiring narcotic medications - Actual outcome for Adults: Total symptoms (McGill pain questionnaire - short form) at 24 weeks; Group 1: mean 6.4 (SD 8.4); n=20, Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: statistical differences between groups in some rheumatology and neurology exam components, differences in baseline secondary measures not reported; Group 1 Number missing: 3, Reason: 2 thrombus, 1 hemolytic anemia; Group 2 Number missing: 2, Reason: 1 systemic infection, 1 intolerable joint pain requiring narcotic medications

Study	Fallon 2008[59]
	- Actual outcome for Adults: Visual analogue scale (McGill pain questionnaire - short form) at 12 weeks; Group 1: mean 4 (SD 2.9); n=20, Group 2: mean 3 (SD 2.7); n=12; visual analogue scale not reported Top=High is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: statistical differences between groups in some rheumatology and neurology exam components, differences in baseline secondary measures not reported; Group 1 Number missing: 3, Reason: 2 thrombus, 1 hemolytic anemia; Group 2 Number missing: 2, Reason: 1 systemic infection, 1 intolerable joint pain requiring narcotic medications - Actual outcome for Adults: Visual analogue scale (McGill pain questionnaire - short form) at 24 weeks; Group 1: mean 3.8 (SD 2.9); n=20, Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: statistical differences between groups in some rheumatology and neurology exam components, differences in baseline secondary measures not reported; Group 1 Number missing: 3, Reason: 2 thrombus, 1 hemolytic anemia; Group 2 Number missing: 2, Reason: 1 systemic infection, 1 intolerable joint pain requiring narcotic medications - Actual outcome for Adults: Number of joints with pain at 12 weeks; Group 1: mean 3.3 joints (SD 3); n=20, Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: statistical differences between groups in some rheumatology and neurology exam components, differences in baseline secondary measures not reported; Group 1 Number missing: 3, Reason: 2 thrombus, 1 hemolytic anemia; Group 2 Number missing: 2, Reason: 1 systemic infection, 1 intolerable joint pain requiring narcotic medications - Actual outcome for Adults: Number of joints with pain at 24 weeks; Group 1: mean 3.4 joints (SD 2.7); n=20, Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: statistical differences between groups in some rheumatology and neurology exam components, differences in baseline secondary measures not reported; Group 1 Number missing: 3, Reason: 2 thrombus, 1 hemolytic anemia; Group 2 Number missing: 2, Reason: 1 systemic infection, 1 intolerable joint pain requiring narcotic medications - Actual outcome for Adults: Beck Depression Inventory at 12 weeks; Group 1: mean 11.5 (SD 9); n=20, Group 2: mean 7.4 (SD 7.2); n=12; Beck Depression Inventory 0-63 Top=High is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: statistical differences between groups in some rheumatology and neurology exam components, differences in baseline secondary measures not reported; Group 1 Number missing: 3, Reason: 2 thrombus, 1 hemolytic anemia; Group 2 Number missing: 2, Reason: 1 systemic infection, 1 intolerable joint pain requiring narcotic medications - Actual outcome for Adults: Beck Depression Inventory at 24 weeks; Group 1: mean 11.9 (SD 10.7); n=20, Group 2: mean 6.5 (SD 5.2); n=12; Beck Depression Inventory 0-63 Top=High is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: statistical differences between groups in some rheumatology and neurology exam components, differences in baseline secondary measures not reported; Group 1 Number missing: 3, Reason: 2 thrombus, 1 hemolytic anemia; Group 2 Number missing: 2, Reason: 1 systemic infection, 1 intolerable joint pain requiring narcotic medications - Actual outcome for Adults: Anxiety (Zung Index) at 12 weeks; Group 1: mean 46.7 (SD 10.1); n=20, Group 2: mean 40.5 (SD 9.4); n=12; Zung Anxiety Scale 20-80 Top=High is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: statistical differences between groups in some rheumatology

Study	Fallon 2008[59]
	and neurology exam components, differences in baseline secondary measures not reported; Group 1 Number missing: 3, Reason: 2 thrombus, 1 hemolytic anemia; Group 2 Number missing: 2, Reason: 1 systemic infection, 1 intolerable joint pain requiring narcotic medications - Actual outcome for Adults: Anxiety (Zung Index) at 24 weeks; Group 1: mean 46.3 (SD 11); n=20, Group 2: mean 38.4 (SD 8.2); n=12; Zung Anxiety Scale 20-80 Top=High is poor outcome Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: statistical differences between groups in some rheumatology and neurology exam components, differences in baseline secondary measures not reported; Group 1 Number missing: 3, Reason: 2 thrombus, 1 hemolytic anemia; Group 2 Number missing: 2, Reason: 1 systemic infection, 1 intolerable joint pain requiring narcotic medications - Actual outcome for Adults: Global Symptom Index at 12 weeks; Group 1: mean 57.5 (SD 13.4); n=20, Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: statistical differences between groups in some rheumatology and neurology exam components, differences in baseline secondary measures not reported; Group 1 Number missing: 3, Reason: 2 thrombus, 1 hemolytic anemia; Group 2 Number missing: 2, Reason: 1 systemic infection, 1 intolerable joint pain requiring narcotic medications - Actual outcome for Adults: Global Symptom Index at 24 weeks; Group 1: mean 57.5 (SD 14.1); n=20, Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: statistical differences between groups in some rheumatology and neurology exam components, differences in baseline secondary measures not reported; Group 1 Number missing: 3, Reason: 2 thrombus, 1 hemolytic anemia; Group 2 Number missing: 2, Reason: 1 systemic infection, 1 intolerable joint pain requiring narcotic medications Protocol outcome 3: Adverse events - Actual outcome for Adults: Adverse events at 24 weeks; Group 1: 6/23, Group 2: 1/14 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: NA; Baseline details: statistical differences between groups in some rheumatology and neurology exam components, differences in baseline secondary measures not reported; Group 1 Number missing: 0; Group 2 Number missing: 0
Protocol outcomes not reported by the study	Cure (resolution of symptoms); Symptom relapse

Study	Klempner 2001[81] (Kaplan 2003[74])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=129)
Countries and setting	Conducted in the US; Setting: Dual-centre
Line of therapy	first line
Duration of study	Follow up (post intervention): 180 days

Study	Klempner 2001[81] (Kaplan 2003[74])
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	18 years or older, history of acute Lyme disease acquired in the US, at least 1 of the following: history of single or multiple EM, early neurologic or cardiac symptoms attributed to Lyme disease, radiculoneuropathy, or Lyme arthritis
Exclusion criteria	Hypersensitivity to the study medications, previous parenteral antibiotic treatment for 60 days or more for their current symptoms, active inflammatory synovitis, coexisting condition that could have accounted for their symptoms, unable to discontinue medications that could interfere with the evaluation of their response to the treatment regimen
Recruitment or selection of people	Not reported
Age, gender and family origin	Age - Mean (SD): Antibiotic group: 54 years (14); placebo group: 53 years (13). Gender (M:F): Define. Family origin: 92% white Previous course of antibiotic treatment: 42 people (33%) received intravenous antibiotics, 87 people (67%) received oral antibiotics; mean number of previous antibiotic courses: 2.7 (SD 1.3)
Further population details	1. Immunocompromised people: Not applicable 2. Pregnant women: Not applicable
Indirectness of population	Serious indirectness: People were eligible if they had any specific symptoms (such as EM, neurological symptoms)
Interventions	(n=64) Intervention 1: Polytherapy. 2 g ceftriaxone per day intravenous for 30 days followed by 100 mg doxycycline orally twice per day for 60 days. Duration 90 days. Concurrent medication/care: Not reported (n=65) Intervention 2: Placebo. Dextrose solution intravenous for 30 days followed by oral capsules for 90 days. Duration 90 days. Concurrent medication/care: Not reported
Funding	Equipment / drugs provided by industry
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: POLYTHERAPY versus PLACEBO Protocol outcome 1: Quality of life - Actual outcome: Improvement in SF-36 total score at 180 days; Group 1: 23/57, Group 2: 21/58 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 7; Group 2 Number missing: 7 - Actual outcome: Improvement in SF-36 physical component at 180 days; Group 1: 20/57, Group 2: 15/58	

Study	Klempner 2001[81] (Kaplan 2003[74])
Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 7; Group 2 Number missing: 7 - Actual outcome: Improvement in SF-36 mental component at 180 days; Group 1: 19/57, Group 2: 22/58 Risk of bias: All domain - High, Selection - Low, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 7; Group 2 Number missing: 7 Protocol outcome 2: Adverse events - Actual outcome: Adverse events at 90 days; Group 1: 16/64, Group 2: 11/65 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 3: Reduction of symptoms - Actual outcome for Adults: Auditory verbal learning test total score at 90 days; Group 1: mean 48.3 (SD 9.3); n=64, Group 2: mean 44.1 (SD 11.1); n=65; Rey Auditory Verbal Learning test not reported Top=High is good outcome Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Adults: Auditory verbal learning test total score at 180 days; Group 1: mean 49.6 (SD 11.3); n=64, Group 2: mean 47.6 (SD 10.1); n=65; Rey Auditory Verbal Learning test not reported Top=High is good outcome Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Adults: Symbol digit modalities test (written) at 90 days; Group 1: mean 52.51 (SD 9.3); n=64, Group 2: mean 51.5 (SD 9.7); n=65; Symbol digit modalities test written score not reported Top=High is good outcome Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Adults: Symbol digit modalities test (written) at 180 days; Group 1: mean 52.5 (SD 9.2); n=64, Group 2: mean 53.2 (SD 10.4); n=65; symbol digit modalities test written score not reported Top=High is good outcome Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Adults: Symbol digit modalities test (oral) at 90 days; Group 1: mean 59.5 (SD 12.7); n=64, Group 2: mean 59.2 (SD 12.8); n=65; symbol digit modalities test (oral score) not reported Top=High is good outcome Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Adults: Symbol digit modalities test (oral) at 180 days; Group 1: mean 60.1 (SD 11.8); n=64, Group 2: mean 60.6 (SD 13.2); n=65; symbol digit modalities test (oral score) not reported Top=High is good outcome	

Study	Klempner 2001[81] (Kaplan 2003[74])
Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Adults: Benton visual retention test at 180 days; Group 1: mean 6.8 number correct (SD 2); n=64, Group 2: mean 6.7 number correct (SD 2.07); n=65; Benton visual retention test 0-10 Top=High is good outcome Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Adults: Controlled oral word association test at 90 days; Group 1: mean 41.6 (SD 14.3); n=64, Group 2: mean 44.5 (SD 12.6); n=65; controlled oral word association test not reported Top=High is good outcome Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Adults: Controlled oral word association test at 180 days; Group 1: mean 41.9 (SD 14); n=64, Group 2: mean 45.1 (SD 13.1); n=65; controlled oral word association test not reported Top=High is good outcome Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Adults: Beck depression inventory at 90 day; Group 1: mean 7.8 (SD 6); n=64, Group 2: mean 8.9 (SD 7.1); n=65; Beck depression inventory 0-63 Top=High is poor outcome Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Adults: Beck depression inventory at 180 days; Group 1: mean 8.2 (SD 6.5); n=64, Group 2: mean 8.8 (SD 7.1); n=65; Beck depression inventory 0-63 Top=High is poor outcome Risk of bias: All domain - Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0
Protocol outcomes not reported by the study	Cure (resolution of symptoms); Symptom relapse

Study	Krupp 2003[86]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=56)
Countries and setting	Conducted in the US; Setting: Multi-centre
Line of therapy	first line
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Aged 18-70 years, history of physician-documented EM or CDC-defined late manifestation of Lyme disease confirmed by positive ELISA and WB serology, completion (6 months before study entry) of standard antibiotic treatment for Lyme disease as defined by at least a 3-week course of oral antibiotic therapy or 3 weeks of IV ceftriaxone, current severe fatigue defined by an elevated score (4 or more) on a modified version of the Fatigue Severity Scale
Exclusion criteria	Mental disorder, medical disorder that confounded the assessment of severe fatigue or cognitive loss, cephalosporin allergy, severe psychiatric disorders
Recruitment or selection of people	Not reported
Age, gender and family origin	Age - Mean (SD): Ceftriaxone group: 48.0 years (11.8); placebo group: 47.0 years (9.7). Gender (M:F): 37:19. Family origin: 52 white
Further population details	1. Immunocompromised people: Not stated / Unclear 2. Pregnant women: Not stated / Unclear
Indirectness of population	Serious indirectness: People previously had either EM or late Lyme manifestations
Interventions	(n=28) Intervention 1: Antibiotics - Ceftriaxone. 2 g per day, intravenous. Duration 28 days. Concurrent medication/care: Not reported (n=27) Intervention 2: Placebo. Placebo intravenous. Duration 28 days. Concurrent medication/care: Not reported
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CEFTRIAXONE versus PLACEBO Protocol outcome 1: Reduction of symptoms at Define - Actual outcome: Improvement in fatigue at 6 months; Group 1: 18/28, Group 2: 5/27	

Study	Krupp 2003[86]
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome: FSS-11 score at 6 months; Group 1: mean 4.4 (SD 1.5); n=26, Group 2: mean 5.5 (SD 1.3); n=22; Fatigue Severity Scale 0-77 Top equals High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2; Group 2 Number missing: 5 - Actual outcome: Change in FSS-11 score from baseline at 6 months; Group 1: mean -1.3 (SD 1.4); n=26, Group 2: mean -0.5 (SD 0.93); n=22; Fatigue Severity Scale 0-77 Top equals High is poor outcome Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 2; Group 2 Number missing: 5 - Actual outcome: Improvement in cognitive measure at 6 months; Group 1: 2/26, Group 2: 2/22 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3; Group 2 Number missing: 5 - Actual outcome: A-A score at 6 months; Group 1: mean 3.8 Seconds (SD 1.7); n=26; Group 2: mean 3.4 Seconds (SD 1); n=22 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3; Group 2 Number missing: 5 - Actual outcome: Change in A-A test score from baseline at 6 months; Group 1: mean -0.3 Seconds (SD 1); n=25; Group 2: mean -0.5 Seconds (SD 0.8); n=22 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 3; Group 2 Number missing: 5	
Protocol outcomes not reported by the study	Quality of life; Cure (resolution of symptoms); Symptom relapse; Adverse events

Study	PLEASE trial: Berende 2016[15]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=281)
Countries and setting	Conducted in Netherlands; Setting: Single centre
Line of therapy	first line
Duration of study	Intervention time: 12 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Clinical diagnosis
Stratum	Overall

Study	PLEASE trial: Berende 2016[15]
Subgroup analysis within study	Not applicable
Inclusion criteria	Persistent symptoms attributed to Lyme disease temporarily related to an EM or an otherwise proven case of symptomatic Lyme disease or accompanied by *B. burgdorferi* IgM or IgG antibodies
Exclusion criteria	allergy or intolerance to study drugs or ceftriaxone, more than 5 days of antimicrobial therapy with activity against *Borrelia burgdorferi sensu lato* within previous 4 weeks, presumed diagnosis of neuroborreliosis, known diagnosis of HIV-seropositivity or other immune disorders, positive syphilis serology, liver disease, enrolled in other trials, previously randomised into this study, comorbidity that could account for symptoms of the subject
Recruitment or selection of people	Not reported
Age, gender and family origin	Age - Mean (SD): Doxycycline group: 48.1 years (12.8); clarithromycin group: 48.2 years (13.0); placebo group: 50.0 years (9.7). Gender (M:F): 151:129. Family origin: Doxycycline group: 98% white; clarithromycin group: 96% white; placebo group: 98% white
Further population details	1. Immunocompromised people: Not applicable 2. Pregnant women: Not applicable
Indirectness of population	No indirectness
Interventions	(n=86) Intervention 1: Antibiotics - Doxycycline. 100 mg oral twice daily. Duration 12 weeks. Concurrent medication/care: Open-label intravenous ceftriaxone (2000 mg daily) for 14 days prior to study intervention. Placebo combined with study intervention. (n=96) Intervention 2: Antibiotics - Clarithromycin. 500 mg clarithromycin orally twice daily plus 200 mg hydroxychloroquine orally twice daily. Duration 12 weeks. Concurrent medication/care: Open-label intravenous ceftriaxone (2000 mg daily) for 14 days prior to study intervention. (n=98) Intervention 3: Placebo. Two different placebo capsules orally twice daily. Duration 12 weeks. Concurrent medication/care: Open-label intravenous ceftriaxone (2000 mg daily) for 14 days prior to study intervention.
Funding	Academic or government funding (Netherlands Health Research grant)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DOXYCYCLINE versus CLARITHROMYCIN Protocol outcome 1: Quality of life - Actual outcome for Adults: SF-36 physical component summary score at 14 weeks; 35.0 (95% CI 33.5 to 36.5) versus 35.6 (95% CI 34.2 to 37.1) Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	

Study	PLEASE trial: Berende 2016[15]

Protocol outcome 2: Adverse events

- Actual outcome for Adults: Any drug-related adverse event at 14 weeks; Group 1: 42/86, Group 2: 42/96

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

- Actual outcome for Adults: Discontinued treatment due to adverse events at 14 weeks; Group 1: 3/86, Group 2: 7/96

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: DOXYCYCLINE versus PLACEBO

Protocol outcome 1: Quality of life

- Actual outcome for Adults: SF-36 physical component summary score at 14 weeks; 35.0 (95% CI 33.5 to 36.5) versus 34.8 (95% CI 33.4 to 36.2)

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Adverse events

- Actual outcome for Adults: Any drug-related adverse event at 14 weeks; Group 1: 42/86, Group 2: 34/98

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

- Actual outcome for Adults: Discontinued treatment due to adverse events at 14 weeks; Group 1: 3/86, Group 2: 4/98

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CLARITHROMYCIN versus PLACEBO

Protocol outcome 1: Quality of life at Define

- Actual outcome for Adults: SF-36 physical component summary score at 14 weeks; 35.6 (95% CI 34.2 to 37.1) versus 34.8 (95% CI 33.4 to 36.2)

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Adverse events at Define

- Actual outcome for Adults: Any drug-related adverse event at 14 weeks; Group 1: 42/96, Group 2: 34/98

Study	PLEASE trial: Berende 2016[15]
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 - Actual outcome for Adults: Discontinued treatment due to adverse events at 14 weeks; Group 1: 7/96, Group 2: 4/98 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Cure (resolution of symptoms); Reduction of symptoms; Symptom relapse

Appendix E: Forest plots

E.1 Ceftriaxone (IV) followed by doxycycline (PO) versus placebo

E.1.1 Ongoing Lyme disease symptoms

Figure 2: Improvement in quality of life

Study or Subgroup	Polytherapy Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Klempner 2001	23	57	21	58	100.0%	1.11 [0.70, 1.77]
Total (95% CI)		**57**		**58**	**100.0%**	**1.11 [0.70, 1.77]**
Total events	23		21			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.46 (P = 0.65)

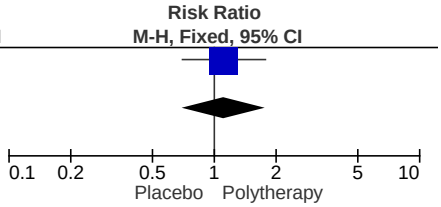


Figure 3: Improvement in SF-36 (physical component)

Study or Subgroup	Polytherapy Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Klempner 2001	20	57	15	58	100.0%	1.36 [0.77, 2.38]
Total (95% CI)		**57**		**58**	**100.0%**	**1.36 [0.77, 2.38]**
Total events	20		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.07 (P = 0.29)

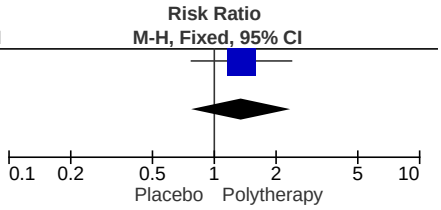


Figure 4: Improvement in SF-36 (mental component)

Study or Subgroup	Polytherapy Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Klempner 2001	19	57	22	58	100.0%	0.88 [0.54, 1.44]
Total (95% CI)		**57**		**58**	**100.0%**	**0.88 [0.54, 1.44]**
Total events	19		22			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.51 (P = 0.61)

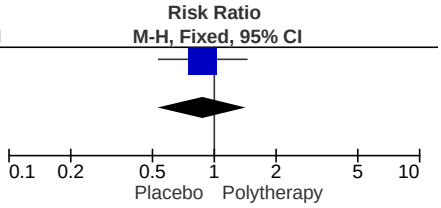


Figure 5: Adverse events

Study or Subgroup	Polytherapy Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Klempner 2001	16	64	11	65	100.0%	1.48 [0.74, 2.93]
Total (95% CI)		**64**		**65**	**100.0%**	**1.48 [0.74, 2.93]**
Total events	16		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.12 (P = 0.26)

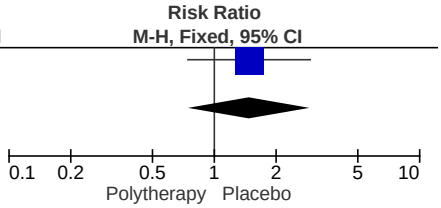


Figure 6: Auditory Verbal Learning Test score at 90 days

Study or Subgroup	Polytherapy Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Klempner2001	48.3	9.3	64	44.1	11.1	65	100.0%	4.20 [0.67, 7.73]
Total (95% CI)			**64**			**65**	**100.0%**	**4.20 [0.67, 7.73]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.33 (P = 0.02)

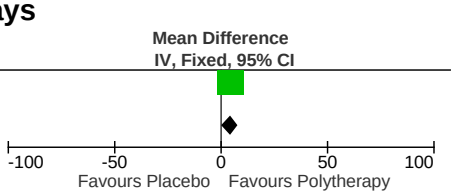


Figure 7: Auditory Verbal Learning Test score at 180 days

Study or Subgroup	Polytherapy Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Klempner2001	49.6	11.3	64	47.6	10.1	65	100.0%	2.00 [-1.70, 5.70]
Total (95% CI)			**64**			**65**	**100.0%**	**2.00 [-1.70, 5.70]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.06 (P = 0.29)

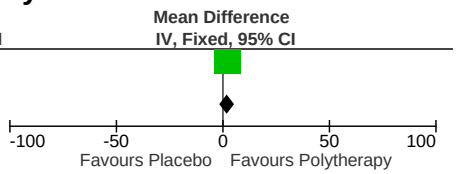


Figure 8: Symbol Digit Modalities Test (written) at 90 days

Study or Subgroup	Polytherapy Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Klempner2001	52.51	9.3	64	51.5	9.7	65	100.0%	1.01 [-2.27, 4.29]
Total (95% CI)			**64**			**65**	**100.0%**	**1.01 [-2.27, 4.29]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.60 (P = 0.55)

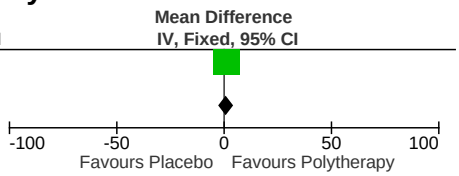


Figure 9: Symbol Digit Modalities Test (written) at 180 days

Study or Subgroup	Polytherapy Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Klempner2001	52.5	9.2	64	53.2	10.4	65	100.0%	-0.70 [-4.09, 2.69]
Total (95% CI)			**64**			**65**	**100.0%**	**-0.70 [-4.09, 2.69]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.41 (P = 0.69)

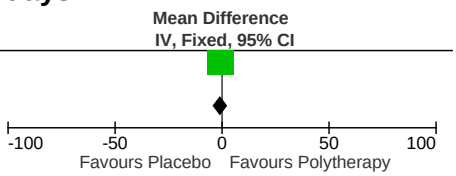


Figure 10: Symbol Digit Modalities Test (oral) at 90 days

Study or Subgroup	Polytherapy Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Klempner2001	59.5	12.7	64	59.2	12.8	65	100.0%	0.30 [-4.10, 4.70]
Total (95% CI)			**64**			**65**	**100.0%**	**0.30 [-4.10, 4.70]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.13 (P = 0.89)

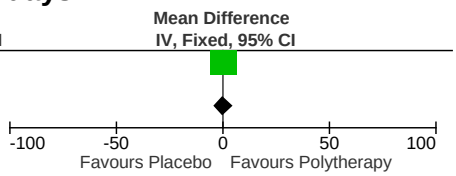


Figure 11: Symbol Digit Modalities Test (oral) at 180 days

Study or Subgroup	Polytherapy Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Klempner2001	60.1	11.8	64	60.6	13.2	65	100.0%	-0.50 [-4.82, 3.82]
Total (95% CI)			**64**			**65**	**100.0%**	**-0.50 [-4.82, 3.82]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.23 (P = 0.82)

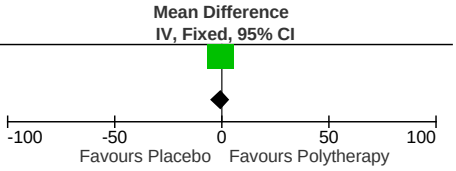


Figure 12: Benton Visual Retention Test at 180 days

Study or Subgroup	Polytherapy Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Klempner2001	6.8	2	64	6.7	2.07	65	100.0%	0.10 [-0.60, 0.80]
Total (95% CI)			**64**			**65**	**100.0%**	**0.10 [-0.60, 0.80]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.28 (P = 0.78)

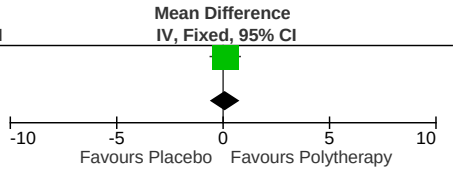


Figure 13: Controlled Oral Word Association Test at 90 days

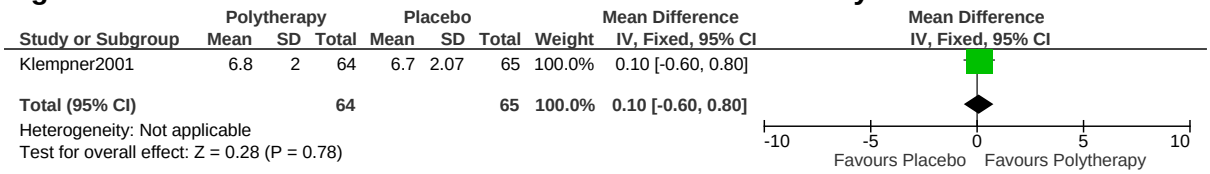


Figure 14: Controlled Oral Word Association Test at 180 days

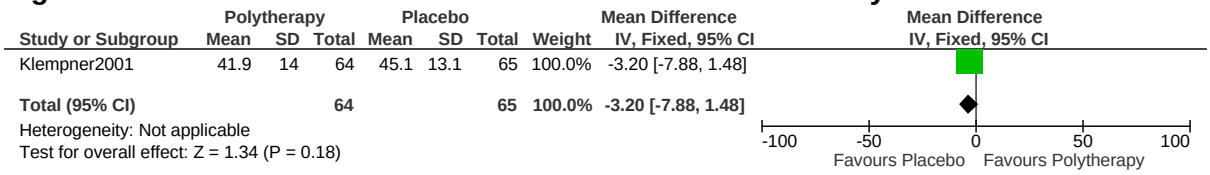


Figure 15: Beck Depression Inventory at 90 days

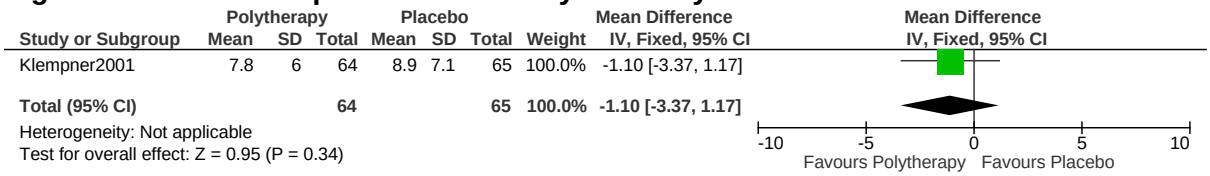
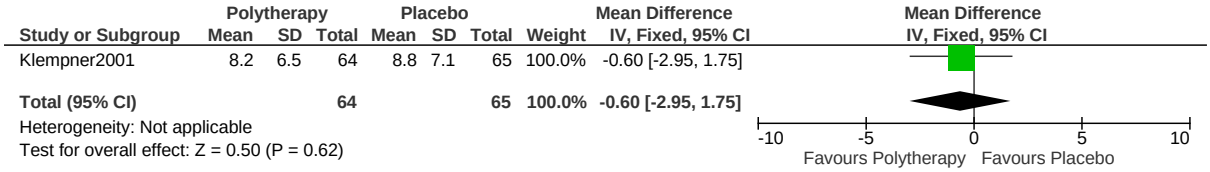


Figure 16: Beck Depression Inventory at 180 days



E.2 Ceftriaxone (IV) versus placebo

E.2.1 Ongoing Lyme disease symptoms

Figure 17: Improvement in fatigue

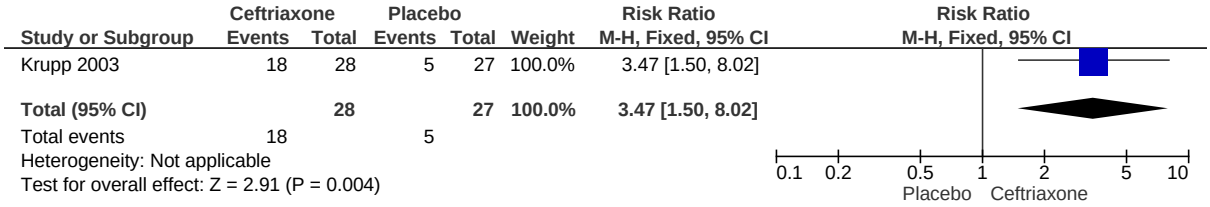


Figure 18: FSS-11 score (final values) at 12 weeks

Study or Subgroup	Ceftriaxone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fallon 2008	4.2	1.6	20	4.8	2	12	100.0%	-0.60 [-1.93, 0.73]
Total (95% CI)			**20**			**12**	**100.0%**	**-0.60 [-1.93, 0.73]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.88 (P = 0.38)

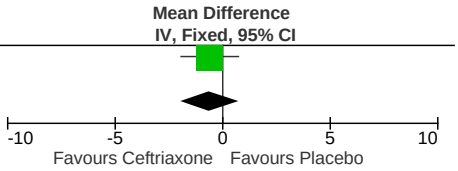


Figure 19: FSS-11 score (final values) at 24 weeks

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fallon 2008	4.4	1.6	20	4.7	1.9	12	27.6%	-0.30 [-1.58, 0.98]
Krupp 2003	4.4	1.5	26	5.5	1.3	22	72.4%	-1.10 [-1.89, -0.31]
Total (95% CI)			**46**			**34**	**100.0%**	**-0.88 [-1.55, -0.21]**

Heterogeneity: Chi² = 1.08, df = 1 (P = 0.30); I² = 7%
Test for overall effect: Z = 2.56 (P = 0.01)

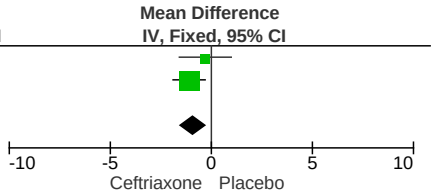


Figure 20: Change in FSS-11 score from baseline

Study or Subgroup	Ceftriaxone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Krupp 2003	-1.3	1.4	26	-0.5	0.93	22	100.0%	-0.80 [-1.46, -0.14]
Total (95% CI)			**26**			**22**	**100.0%**	**-0.80 [-1.46, -0.14]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.36 (P = 0.02)

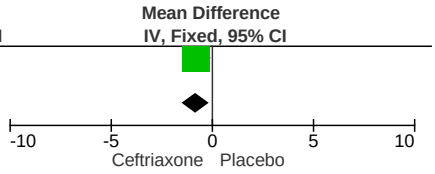


Figure 21: Improvement in cognitive measure

Study or Subgroup	Ceftriaxone Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Krupp 2003	2	26	2	22	100.0%	0.85 [0.13, 5.52]
Total (95% CI)		**26**		**22**	**100.0%**	**0.85 [0.13, 5.52]**
Total events	2		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.17 (P = 0.86)

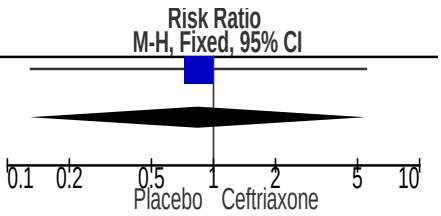


Figure 22: A-A score (final values)

Study or Subgroup	Ceftriaxone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Krupp 2003	3.8	1.7	26	3.4	1	22	100.0%	0.40 [-0.38, 1.18]
Total (95% CI)			**26**			**22**	**100.0%**	**0.40 [-0.38, 1.18]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.01 (P = 0.31)

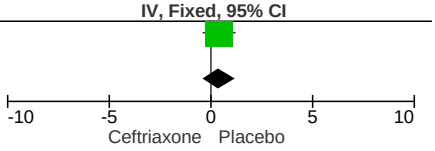


Figure 23: Change in A-A score from baseline

Study or Subgroup	Ceftriaxone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Krupp 2003	-0.3	1	25	-0.5	0.8	22	100.0%	0.20 [-0.32, 0.72]
Total (95% CI)			**25**			**22**	**100.0%**	**0.20 [-0.32, 0.72]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.76 (P = 0.45)

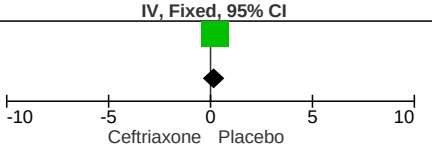


Figure 24: SF36 physical component at 12 weeks

Study or Subgroup	Ceftriaxone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fallon 2008	40.4	9.4	20	36	9.2	12	100.0%	4.40 [-2.24, 11.04]
Total (95% CI)			**20**			**12**	**100.0%**	**4.40 [-2.24, 11.04]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.30 (P = 0.19)

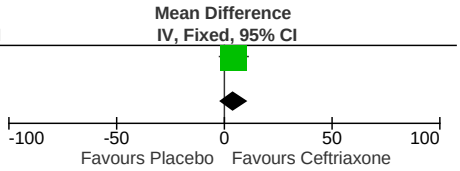


Figure 25: SF36 physical component at 24 weeks

Study or Subgroup	Ceftriaxone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fallon 2008	42	10.1	20	36.8	10.5	12	100.0%	5.20 [-2.21, 12.61]
Total (95% CI)			**20**			**12**	**100.0%**	**5.20 [-2.21, 12.61]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.38 (P = 0.17)

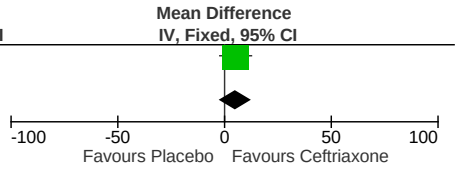


Figure 26: SF36 mental component at 12 weeks

Study or Subgroup	Ceftriaxone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fallon 2008	43	13.7	20	51.6	7.2	12	100.0%	-8.60 [-15.86, -1.34]
Total (95% CI)			**20**			**12**	**100.0%**	**-8.60 [-15.86, -1.34]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.32 (P = 0.02)

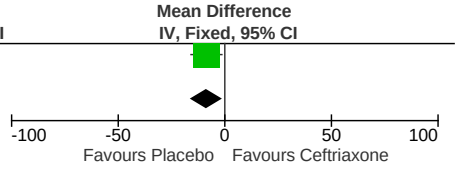


Figure 27: SF36 mental component at 24 weeks

Study or Subgroup	Ceftriaxone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fallon 2008	42.1	15	20	50.7	9.2	12	100.0%	-8.60 [-16.99, -0.21]
Total (95% CI)			**20**			**12**	**100.0%**	**-8.60 [-16.99, -0.21]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.01 (P = 0.04)

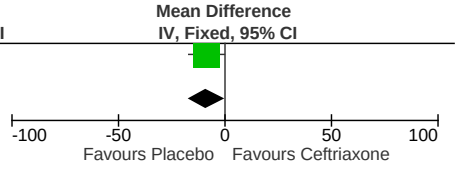


Figure 28: McGill Pain Questionnaire score at 12 weeks

Study or Subgroup	Ceftriaxone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fallon 2008	8.4	8	20	7.5	5.2	12	100.0%	0.90 [-3.68, 5.48]
Total (95% CI)			**20**			**12**	**100.0%**	**0.90 [-3.68, 5.48]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.70)

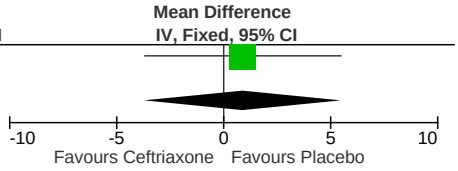


Figure 29: McGill Pain Questionnaire score at 24 weeks

Study or Subgroup	Ceftriaxone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fallon 2008	6.4	8.4	20	8.1	8.2	12	100.0%	-1.70 [-7.62, 4.22]
Total (95% CI)			**20**			**12**	**100.0%**	**-1.70 [-7.62, 4.22]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.56 (P = 0.57)

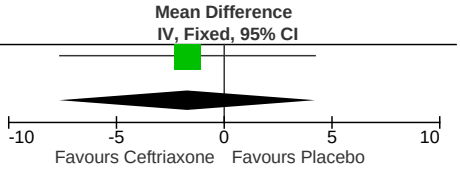


Figure 30: McGill visual analogue scale score at 12 weeks

Study or Subgroup	Ceftriaxone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fallon 2008	4	2.9	20	3	2.7	12	100.0%	1.00 [-0.99, 2.99]
Total (95% CI)			**20**			**12**	**100.0%**	**1.00 [-0.99, 2.99]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.99 (P = 0.32)

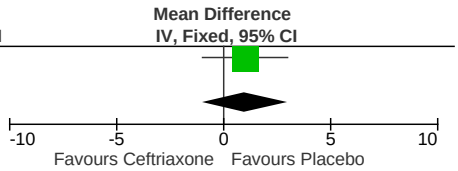


Figure 31: McGill visual analogue scale score at 24 weeks

Study or Subgroup	Ceftriaxone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fallon 2008	3.8	2.9	20	3.8	3.6	12	100.0%	0.00 [-2.40, 2.40]
Total (95% CI)			**20**			**12**	**100.0%**	**0.00 [-2.40, 2.40]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

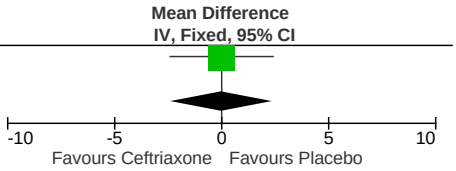


Figure 32: No. of joints with pain at 12 weeks

Study or Subgroup	Ceftriaxone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fallon 2008	3.3	3	20	4.4	6	12	100.0%	-1.10 [-4.74, 2.54]
Total (95% CI)			**20**			**12**	**100.0%**	**-1.10 [-4.74, 2.54]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.59 (P = 0.55)

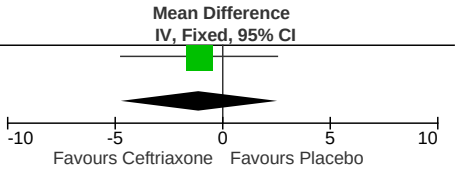


Figure 33: No. of joints with pain at 24 weeks

Study or Subgroup	Ceftriaxone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fallon 2008	3.4	2.7	20	2.6	3.7	12	100.0%	0.80 [-1.60, 3.20]
Total (95% CI)			**20**			**12**	**100.0%**	**0.80 [-1.60, 3.20]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.65 (P = 0.51)

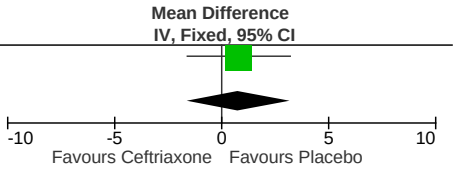


Figure 34: Beck Depression Inventory score at 12 weeks

Study or Subgroup	Ceftriaxone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fallon 2008	11.5	9	20	7.4	7.2	12	100.0%	4.10 [-1.57, 9.77]
Total (95% CI)			**20**			**12**	**100.0%**	**4.10 [-1.57, 9.77]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.42 (P = 0.16)

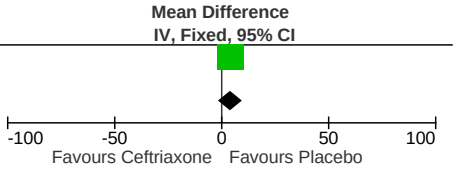


Figure 35: Beck Depression Inventory score at 24 weeks

Study or Subgroup	Ceftriaxone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fallon 2008	11.9	10.7	20	6.5	5.2	12	100.0%	5.40 [-0.14, 10.94]
Total (95% CI)			**20**			**12**	**100.0%**	**5.40 [-0.14, 10.94]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.91 (P = 0.06)

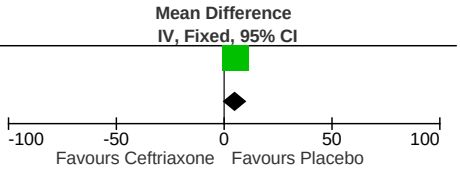


Figure 36: Zung Anxiety Index score at 12 weeks

Study or Subgroup	Ceftriaxone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fallon 2008	46.7	10.1	20	40.5	9.4	12	100.0%	6.20 [-0.72, 13.12]
Total (95% CI)			**20**			**12**	**100.0%**	**6.20 [-0.72, 13.12]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.76 (P = 0.08)

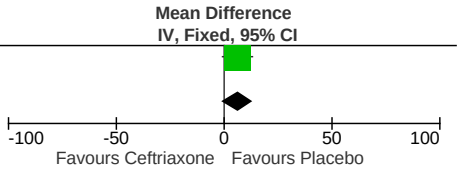


Figure 37: Zung Anxiety Index score at 24 weeks

Study or Subgroup	Ceftriaxone Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Fallon 2008	46.3	11	20	38.4	8.2	12	100.0%	7.90 [1.21, 14.59]
Total (95% CI)			**20**			**12**	**100.0%**	**7.90 [1.21, 14.59]**

Heterogeneity: Not applicable
Test for overall effect: Z = 2.31 (P = 0.02)

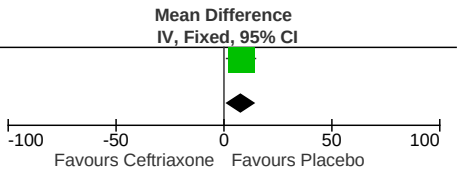


Figure 38: Global symptom index score at 12 weeks

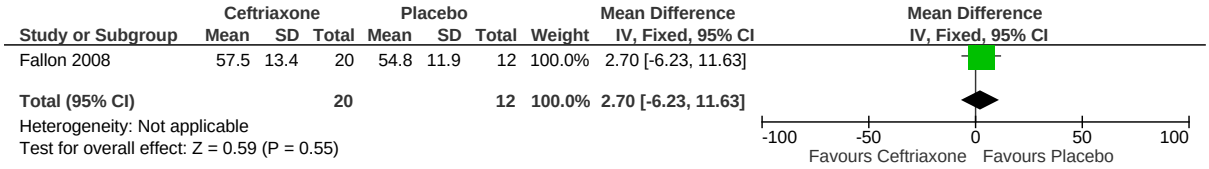


Figure 39: Global symptom index score at 24 weeks

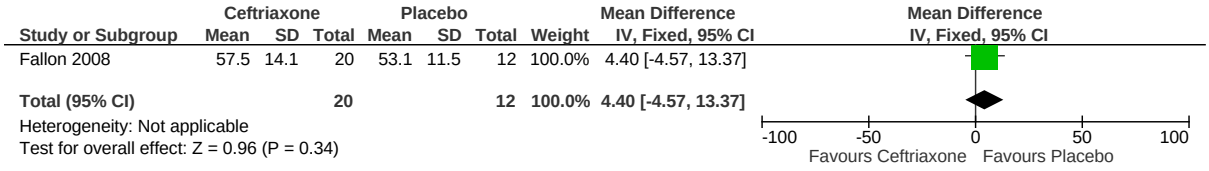
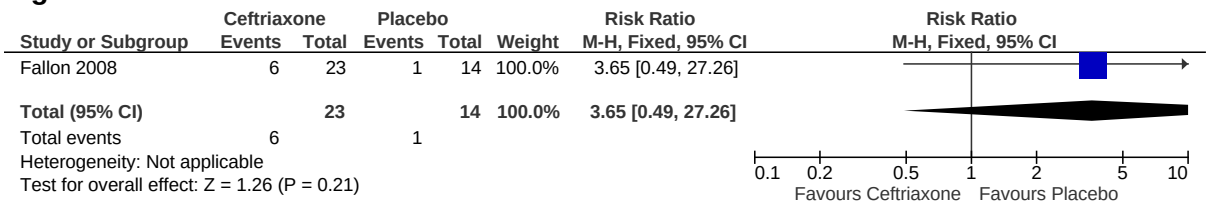


Figure 40: Adverse events



E.3 Ceftriaxone (IV) followed by doxycycline (PO) versus ceftriaxone (IV) followed by clarithromycin (PO) plus hydroxychloroquine

E.3.1 Ongoing Lyme disease symptoms

Figure 41: SF-36 (physical component – final values)

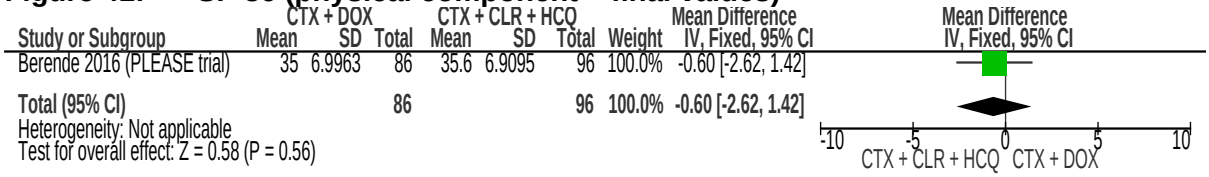


Figure 42: Adverse events

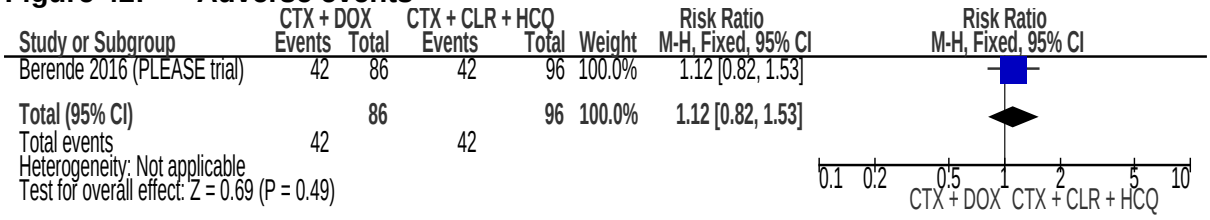
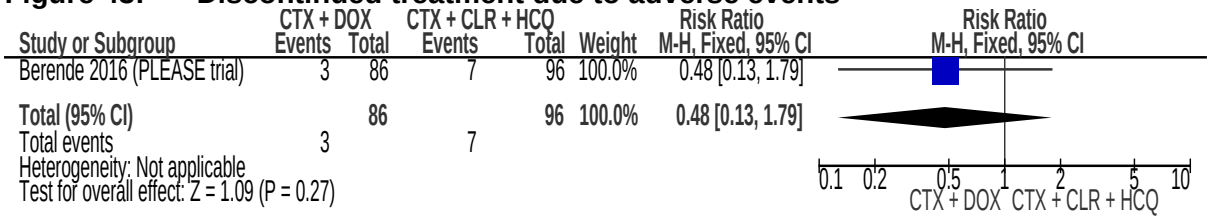


Figure 43: Discontinued treatment due to adverse events



E.4 Ceftriaxone (IV) followed by doxycycline (PO) versus ceftriaxone (IV)

E.4.1 Ongoing Lyme disease symptoms

Figure 44: SF-36 (physical component – final values)

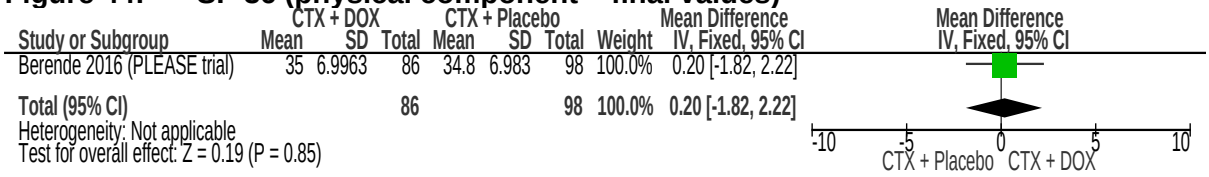


Figure 45: Adverse events

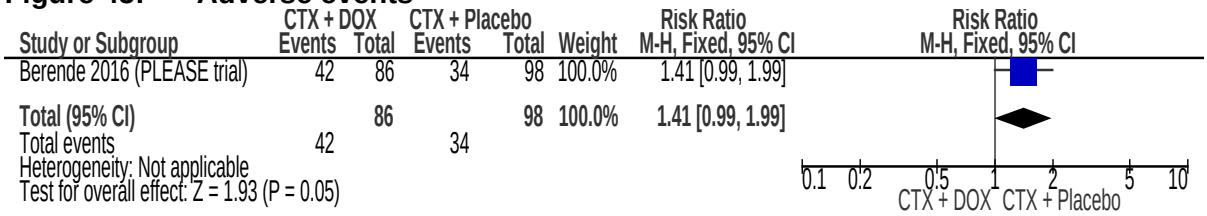
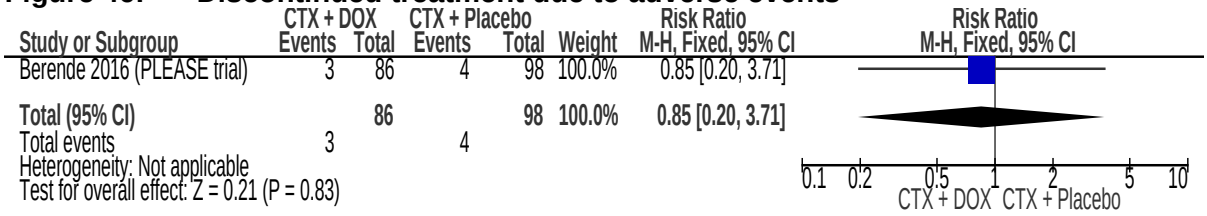


Figure 46: Discontinued treatment due to adverse events



E.5 Ceftriaxone (IV) followed by clarithromycin (PO) plus hydroxychloroquine versus ceftriaxone (IV)

E.5.1 Ongoing Lyme disease symptoms

Figure 47: SF-36 (physical component – final values)

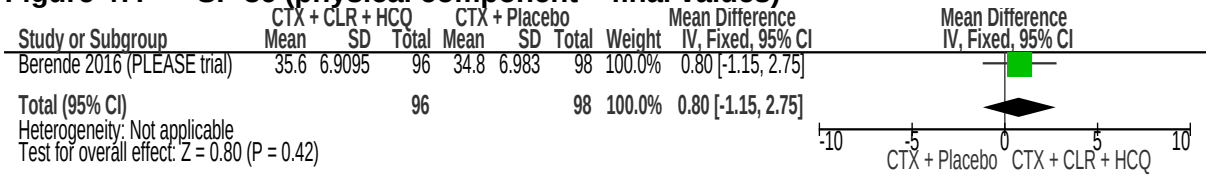


Figure 48: Adverse events

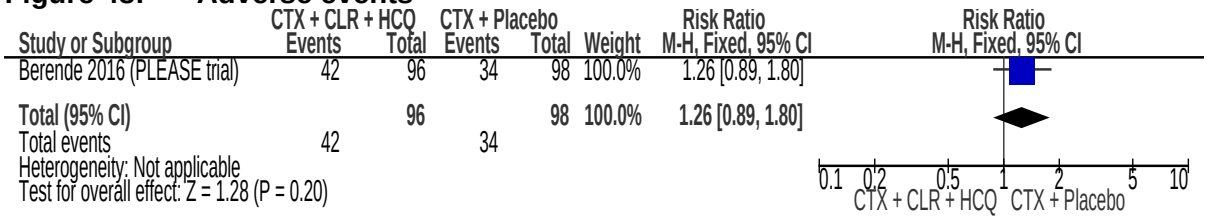
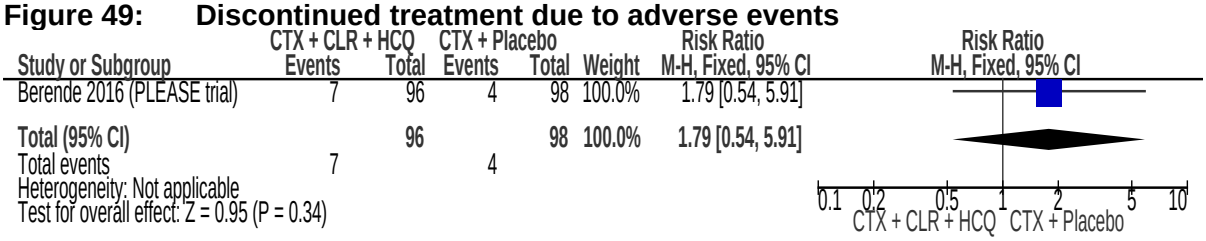


Figure 49: Discontinued treatment due to adverse events



E.6 Amoxicillin (PO) versus placebo

E.6.1 Ongoing Lyme disease symptoms

Figure 50: SF36 physical component

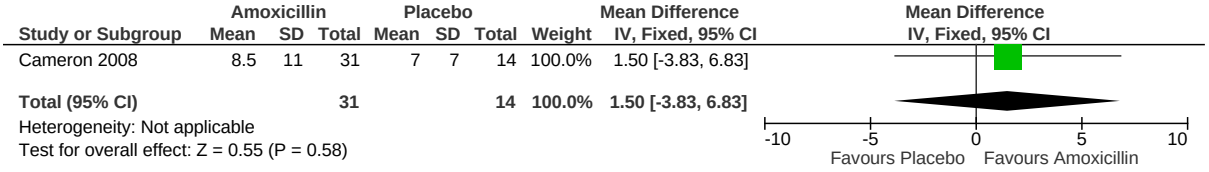


Figure 51: SF36 mental component

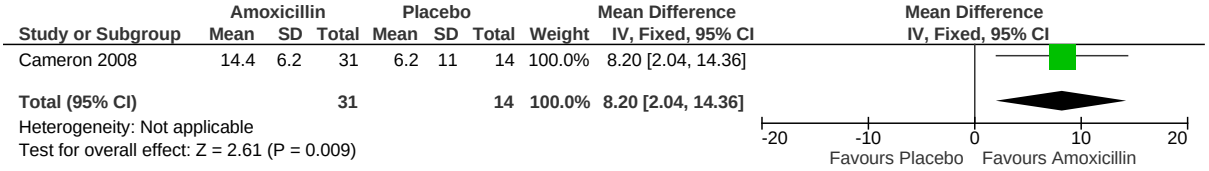
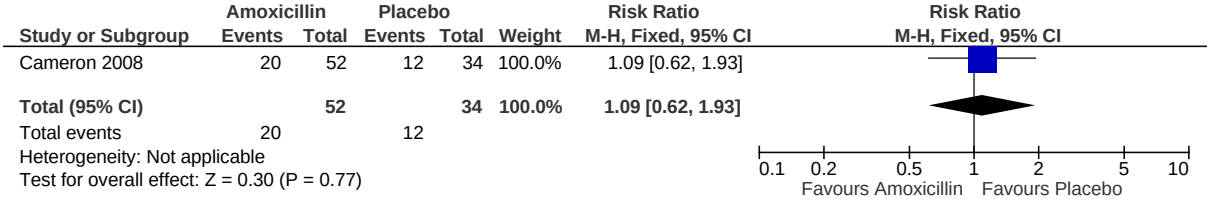


Figure 52: Adverse events



Appendix F:GRADE tables

Table 15: Clinical evidence profile: Ceftriaxone (IV) followed by doxycycline (PO) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone (iv) + doxycycline (po) versus placebo	Control	Relative (95% CI)	Absolute		
Improvement in quality of life												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	23/57 (40.4%)	21/58 (36.2%)	RR 1.11 (0.7 to 1.77)	40 more per 1000 (from 109 fewer to 279 more)	⊕OOO VERY LOW	CRITICAL
Improvement in SF-36 (physical component) at 180 days; 0-100, higher values are beneficial												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20/57 (35.1%)	15/58 (25.9%)	RR 1.36 (0.77 to 2.38)	93 more per 1000 (from 59 fewer to 357 more)	⊕⊕OO LOW	CRITICAL
Improvement in SF-36 (mental component) at 180 days; 0-100, higher values are beneficial												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	19/57 (33.3%)	22/58 (37.9%)	RR 0.88 (0.54 to 1.44)	46 fewer per 1000 (from 174 fewer to 167 more)	⊕OOO VERY LOW	CRITICAL
Adverse events at 90 days												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	16/64 (25%)	11/65 (16.9%)	RR 1.48 (0.74 to 2.93)	81 more per 1000 (from 44 fewer to 327 more)	⊕⊕OO LOW	IMPORTANT

Reduction of symptoms (follow-up 90 days; measured with: Auditory Verbal Learning Test total score; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	64	65	-	MD 4.2 higher (0.67 to 7.73 higher)	⊕OOO VERY LOW	CRITICAL
Reduction of symptoms (follow-up 180 days; measured with: AVLT total score; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	64	65	-	MD 2 higher (1.7 lower to 5.7 higher)	⊕OOO VERY LOW	CRITICAL
Reduction of symptoms (follow-up 90 days; measured with: Symbol Digit Modalities Test written; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	64	65	-	MD 1.01 higher (2.27 lower to 4.29 higher)	⊕⊕OO LOW	CRITICAL
Reduction of symptoms (follow-up 180 days; measured with: SDMT written; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	64	65	-	MD 0.7 lower (4.09 lower to 2.69 higher)	⊕⊕OO LOW	CRITICAL
Reduction of symptoms (follow-up 90 days; measured with: Symbol Digit Modalities Test oral; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	64	65	-	MD 0.3 higher (4.1 lower to 4.7 higher)	⊕⊕OO LOW	CRITICAL
Reduction of symptoms (follow-up 180 days; measured with: Symbol Digit Modalities Test oral; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	64	65	-	MD 0.5 lower (4.82 lower to 3.82 higher)	⊕⊕OO LOW	CRITICAL
Reduction of symptoms (follow-up 180 days; measured with: Benton Visual Retention Test; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	64	65	-	MD 0.1 higher (0.6 lower to 0.8 higher)	⊕⊕OO LOW	CRITICAL

Reduction of symptoms (follow-up 90 days; measured with: Controlled Oral Word Association Test; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	64	65	-	MD 2.9 lower (7.55 lower to 1.75 higher)	⊕OOO VERY LOW	CRITICAL
Reduction of symptoms (follow-up 180 days; measured with: Controlled Oral Word Association Test; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	64	65	-	MD 3.2 lower (7.88 lower to 1.48 higher)	⊕OOO VERY LOW	CRITICAL
Reduction of symptoms (follow-up 90 days; measured with: Beck depression inventory; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	64	65	-	MD 1.1 lower (3.37 lower to 1.17 higher)	⊕⊕OO LOW	CRITICAL
Reduction of symptoms (follow-up 180 days; measured with: Beck depression inventory; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	64	65	-	MD 0.6 lower (2.95 lower to 1.75 higher)	⊕⊕OO LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 16: Clinical evidence profile: Ceftriaxone (IV) versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ceftriaxone (iv) versus placebo**	**Control**	**Relative (95% CI)**	**Absolute**		
Improvement in fatigue												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	18/28 (64.3%)	5/27 (18.5%)	RR 3.47 (1.5 to 8.02)	457 more per 1000 (from 93 more to 1000 more)	⊕⊕⊕⊕ HIGH	CRITICAL

FSS-11 score (follow-up 12 weeks; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20	12	-	MD 0.6 lower (1.93 lower to 0.73 higher)	⊕⊕OO LOW	
FSS-11 score (follow-up 24 weeks; Better indicated by lower values)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	46	34	-	MD 0.88 lower (1.55 to 0.21 lower)	⊕⊕OO LOW	CRITICAL
Change in FSS-11 score from baseline (Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	26	22	-	MD 0.8 lower (1.46 to 0.14 lower)	⊕⊕OO LOW	CRITICAL
Improvement in cognitive measure												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	2/26 (7.7%)	2/22 (9.1%)	RR 0.85 (0.13 to 5.52)	14 fewer per 1000 (from 79 fewer to 411 more)	⊕⊕OO LOW	CRITICAL
A-A score (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	26	22	-	MD 0.4 higher (0.38 lower to 1.18 higher)	⊕⊕⊕O MODERATE	CRITICAL
Change in A-A score from baseline (Better indicated by lower values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	25	22	-	MD 0.2 higher (0.32 lower to 0.72 higher)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life (follow-up 12 weeks; measured with: SF36 physical component; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20	12	-	MD 4.4 higher (2.24 lower to 11.04 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (follow-up 24 weeks; measured with: SF36 physical component; Better indicated by higher values)												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20	12	-	MD 5.2 higher (2.21 lower to 12.61 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (follow-up 12 weeks; measured with: SF36 mental component; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20	12	-	MD 8.6 lower (15.86 to 1.34 lower)	⊕⊕OO LOW	CRITICAL
Quality of life (follow-up 24 weeks; measured with: SF36 mental component; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20	12	-	MD 8.6 lower (16.99 to 0.21 lower)	⊕⊕OO LOW	CRITICAL
Reduction of symptoms (follow-up 12 weeks; measured with: McGill pain questionnaire; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20	12	-	MD 0.9 higher (3.68 lower to 5.48 higher)	⊕OOO VERY LOW	CRITICAL
Reduction of symptoms (follow-up 24 weeks; measured with: McGill pain questionnaire; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20	12	-	MD 1.7 lower (7.62 lower to 4.22 higher)	⊕OOO VERY LOW	CRITICAL
Reduction of symptoms (follow-up 12 weeks; measured with: McGill pain questionnaire visual analogue scale; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20	12	-	MD 1 higher (0.99 lower to 2.99 higher)	⊕⊕OO LOW	CRITICAL
Reduction of symptoms (follow-up 24 weeks; measured with: McGill pain questionnaire visual analogue scale; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20	12	-	MD 0 higher (2.4 lower to 2.4 higher)	⊕OOO VERY LOW	CRITICAL
Reduction of symptoms (follow-up 12 weeks; measured with: no. of joints with pain; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20	12	-	MD 1.1 lower (4.74 lower to 2.54 higher)	⊕OOO VERY LOW	CRITICAL

Reduction of symptoms (follow-up 24 weeks; measured with: no. of joints with pain; Better indicated by lower values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20	12	-	MD 0.8 higher (1.6 lower to 3.2 higher)	⊕OOO VERY LOW	CRITICAL
Reduction of symptoms (follow-up 12 weeks; measured with: Beck depression inventory; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20	12	-	MD 4.1 higher (1.57 lower to 9.77 higher)	⊕⊕OO LOW	CRITICAL
Reduction of symptoms (follow-up 24 weeks; measured with: Beck depression inventory; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20	12	-	MD 5.4 higher (0.14 lower to 10.94 higher)	⊕⊕OO LOW	CRITICAL
Reduction of symptoms (follow-up 12 weeks; measured with: Zung anxiety index; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20	12	-	MD 6.2 higher (0.72 lower to 13.12 higher)	⊕⊕OO LOW	CRITICAL
Reduction of symptoms (follow-up 24 weeks; measured with: Zung anxiety index; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20	12	-	MD 7.9 higher (1.21 to 14.59 higher)	⊕⊕OO LOW	CRITICAL
Reduction in symptoms (follow-up 12 weeks; measured with: SCL-90 Global Symptom Index; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	20	12	-	MD 2.7 higher (6.23 lower to 11.63 higher)	⊕OOO VERY LOW	CRITICAL
Reduction of symptoms (follow-up 24 weeks; measured with: SCL-90 Global Symptom Index; Better indicated by lower values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20	12	-	MD 4.4 higher (4.57 lower to 13.37 higher)	⊕⊕OO LOW	CRITICAL

Adverse events												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/23 (26.1%)	1/14 (7.1%)	RR 3.65 (0.49 to 27.26)	189 more per 1000 (from 36 fewer to 1000 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Table 17: Clinical evidence profile: Ceftriaxone (IV) followed by doxycycline (PO) versus ceftriaxone (IV) followed by clarithromycin (PO) plus hydroxychloroquine

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ceftriaxone plus doxycycline**	**Ceftriaxone plus clarithromycin plus hydroxychloroquine**	**Relative (95% CI)**	**Absolute**		
SF-36 (physical component) at 14 weeks; 15-61 (norm-based T-score), general population score 50 (SD 10), higher values are beneficial												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious imprecision[2]	none	86	96	Not applicable	MD 0.6 lower (2.62 lower to 1.42 higher)	⊕⊕OO LOW	CRITICAL
Adverse events at 14 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	Serious[2]	none	42/86 (48.8%)	42/96 (43.8%)	RR 1.12 (0.82 to 1.53)	53 more per 1000 (from 79 fewer to 232 more)	⊕⊕OO LOW	IMPORTANT
Discontinued treatment due to adverse events at 14 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	3/86 (3.5%)	7/96 (7.3%)	RR 0.48 (0.13 to 1.79)	38 fewer per 1000 (from 63 fewer to 58 more)	⊕OOO VERY LOW	IMPORTANT

[1] People in the clarithromycin group also received hydroxychloroquine
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 18: Clinical evidence profile: Ceftriaxone (IV) followed by doxycycline (PO) versus ceftriaxone (IV)

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone plus doxycycline	Ceftriaxone	Relative (95% CI)	Absolute		
SF-36 (physical component) at 14 weeks; 15-61 (norm-based T-score), general population score 50 (SD 10), higher values are beneficial												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious imprecision[1]	none	86	98	Not applicable	MD 0.2 higher (1.82 lower to 2.22 higher)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events at 14 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	42/86 (48.8%)	34/98 (34.7%)	RR 1.41 (0.99 to 1.99)	142 more per 1000 (from 3 fewer to 343 more)	⊕⊕⊕O MODERATE	IMPORTANT
Discontinued treatment due to adverse events at 14 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	3/86 (3.5%)	4/98 (4.1%)	RR 0.85 (0.2 to 3.71)	6 fewer per 1000 (from 33 fewer to 111 more)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 19: Clinical evidence profile: Ceftriaxone (IV) followed by clarithromycin (PO) plus hydroxychloroquine versus ceftriaxone (IV)

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone plus clarithromycin plus hydroxychloroquine	Ceftriaxone	Relative (95% CI)	Absolute		
SF-36 (physical component) at 14 weeks; 15-61 (norm-based T-score), general population score 50 (SD 10), higher values are beneficial												
1	randomised	no	no serious	serious[1]	serious	none	96	98	Not	MD 0.8 higher	⊕⊕OO	CRITICAL

	trials	serious risk of bias	inconsistency		imprecision[2]				applicable	(1.15 lower to 2.75 higher)	LOW	
Adverse events at 14 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	Serious[2]	none	42/96 (43.8%)	34/98 (34.7%)	RR 1.26 (0.89 to 1.8)	90 more per 1000 (from 38 fewer to 278 more)	⊕⊕OO LOW	IMPORTANT
Discontinued treatment due to adverse events at 14 weeks												
1	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	7/96 (7.3%)	4/98 (4.1%)	RR 1.79 (0.54 to 5.91)	32 more per 1000 (from 19 fewer to 200 more)	⊕OOO VERY LOW	IMPORTANT

[1] People in the clarithromycin group also received hydroxychloroquine
[2] Downgraded by 1 increment if the confidence interval crossed 1 MID or by 2 increments if the confidence interval crossed both MIDs

Table 20: Clinical evidence profile: Amoxicillin (PO) versus placebo

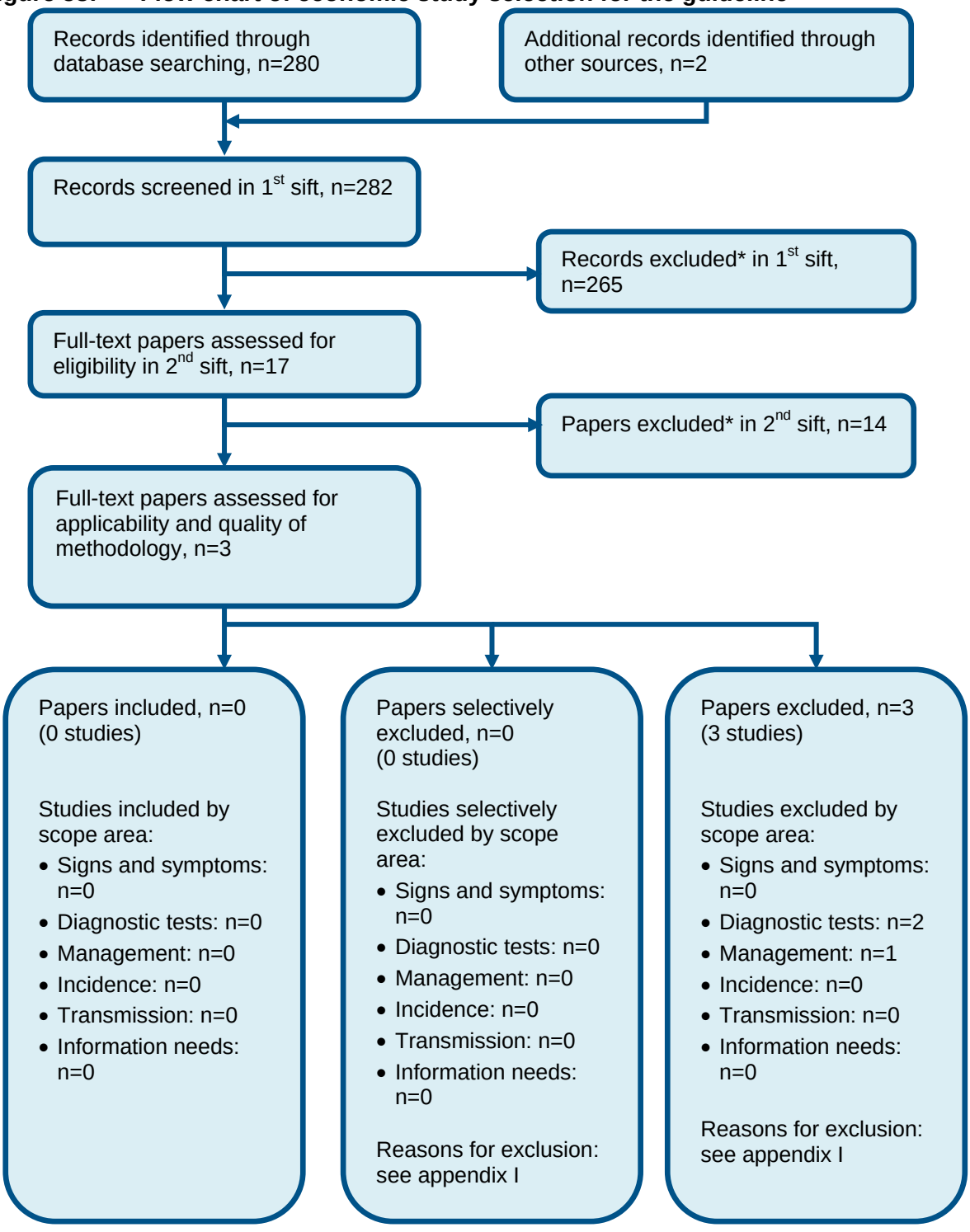
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Amoxicillin (po) versus placebo**	**Control**	**Relative (95% CI)**	**Absolute**		
Quality of life (follow up 6 months; measured with: SF36 physical component; Better indicated by higher values)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	31	14	-	MD 1.5 higher (3.83 lower to 6.83 higher)	⊕OOO VERY LOW	CRITICAL
Quality of life (follow up 6 months; measured with: SF36 mental component; Better indicated by higher values)												
1	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	31	14	-	MD 8.2 higher (2.04 to 14.36 higher)	⊕OOO VERY LOW	CRITICAL

Adverse events												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	20/52 (38.5%)	12/34 (35.3%)	RR 1.09 (0.62 to 1.93)	32 more per 1000 (from 134 fewer to 328 more)	⊕⊕OO LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Appendix G: Health economic evidence selection

Figure 53: Flow chart of economic study selection for the guideline



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

Appendix H: Health economic evidence tables

None.

Appendix I: Excluded studies

I.1 Excluded clinical studies

Table 21: Studies excluded from the clinical management reviews

Reference	Reason for exclusion
Aberer 2006[1]	Excluded due to an incorrect intervention
Abrutyn 1989[2]	Excluded due to an incorrect study design
Agger 1992[3]	Excluded due to an incorrect study design
Agus 1995[4]	Excluded due to an incorrect study design
Agwuh 2006[5]	Excluded due to an incorrect study design
Ahmed 2005[6]	Excluded due to an incorrect study design
Ahmed 2013[7]	Excluded due to an incorrect study design
Alarcon 1994[8]	Excluded due to an incorrect study design
Andiman 1986[9]	Excluded due to an incorrect study design
Anonymous 1991[10]	Excluded due to an incorrect study design
Arvikar 2015[11]	Excluded due to an incorrect study design
Auwaerter 2004[12]	Excluded due to an incorrect study design
Bennet 2003[13]	Excluded due to an incorrect study design
Berende 2014[14]	Excluded due to an incorrect study design
Berger 1988[17]	Excluded due to an incorrect study design
Berger 1986[16]	Excluded due to an incorrect study design
Bernardino 2009[18]	Excluded due to an incorrect study design
Bhate 2011[19]	Excluded due to an incorrect study design
Bjark 2016[20]	Not available
Borg 2005[23]	Excluded due to an incorrect study design
Bratton 2008[24]	Excluded due to an incorrect study design
Bremell 2014[25]	Excluded due to an incorrect study design
British Infection Association 2011[26]	Excluded due to an incorrect study design
Butler 1978[27]	Excluded due to an incorrect population
Cadavid 2016[28]	Excluded due to an incorrect study design
Canadian Paediatric Society 1992[30]	Excluded due to an incorrect study design
Chen 1999[32]	Excluded due to an incorrect outcome
Choo-Kang 2010[33]	Excluded due to an incorrect study design
Christian 1992[34]	Excluded due to an incorrect study design
Cimmino 1992[36]	Excluded due to an incorrect study design
Cimmino 1997[35]	Excluded due to an incorrect study design
Cimperman 1999[37]	Excluded due to an incorrect study design
Coblyn 1981[38]	Excluded due to an incorrect study design
Committee on Infectious Diseases 1991[40]	Excluded due to an incorrect study design
Cuisset 2008[41]	Excluded due to an incorrect study design
Dattwyler 1996[43]	Excluded due to an incorrect comparison
Dattwyler 1987[44]	Excluded due to an incorrect study design
Dattwyler 1988[45]	Excluded due to an incorrect population
Dattwyler 2005[46]	Excluded due to an incorrect population
Dersch 2015[48]	Excluded due to an incorrect study design

Reference	Reason for exclusion
Dersch 2016[51]	Excluded due to an incorrect study design
Dersch 2014[49]	Excluded due to an incorrect study design
Dersch 2017[50]	Not available
Dhoot 2011[52]	Excluded due to an incorrect study design
Dinser 2005[53]	Excluded due to an incorrect study design
Dotevall 1988[54]	Excluded due to an incorrect study design
Eliassen 2017[55]	Excluded due to an incorrect study design
Eliassen 2017[56]	Excluded due to an incorrect intervention
Eppes 2003[57]	Excluded due to an incorrect study design
Esposito 2013[58]	Excluded due to an incorrect study design
Fallon 1999[60]	Excluded due to an incorrect intervention
Galev 2005[61]	Excluded due to an incorrect study design
Garkowski 2017[62]	Systematic review
Gasser 1996[64]	Not available
Gasser 1995[65]	Excluded due to an incorrect study design
Gasser 1995[63]	Excluded due to an incorrect study design
Gerber 1996[66]	Excluded due to an incorrect intervention
Gillies 2015[67]	Excluded due to an incorrect study design
Goodwin 1990[68]	Excluded due to an incorrect study design
Hansen 1992[69]	Excluded due to an incorrect intervention
Hassler 1990[70]	Excluded due to an incorrect population
Horton 2017[71]	Conference abstract
Hu 2001[72]	Excluded due to an incorrect study design
Inboriboon 2010[73]	Excluded due to an incorrect study design
Karkkonen 2001[75]	Excluded due to an incorrect study design
Karlsson 1996[76]	Excluded due to an incorrect outcome
Kersten 1995[77]	Excluded due to an incorrect study design
Kilic Muftuoglu 2016[78]	Excluded due to an incorrect study design
Klempner 2013[80]	Excluded due to an incorrect study design
Korenberg 1996[82]	Excluded due to an incorrect intervention
Kowalski 2010[84]	Excluded due to an incorrect outcome
Kowalski 2011[83]	Excluded due to an incorrect study design
Krbkova 1996[85]	Excluded due to an incorrect comparison
Kuhn 2012[87]	Excluded due to an incorrect study design
Laasila 2003[88]	Excluded due to an incorrect population
Lantos 2013[89]	Excluded due to an incorrect study design
Lauhio 1994[90]	Excluded due to an incorrect population
Lauhio 1991[91]	Excluded due to an incorrect population
Lempner 2002[79]	Excluded due to an incorrect study design
Liegner 1992[92]	Excluded due to an incorrect study design
Lipsker 2002[93]	Excluded due to an incorrect study design
Ljostad 2008[94]	Study abstract
Loewen 1999[95]	Excluded due to an incorrect study design
Loewen 2000[96]	Excluded due to an incorrect study design
Luft 1988[98]	Excluded due to an incorrect outcome

Reference	Reason for exclusion
Luft 1989[97]	Excluded due to an incorrect population
Maraspin 1995[104]	Excluded due to an incorrect study design
Maraspin 1996[99]	Excluded due to an incorrect study design
Maraspin 1999[100]	Excluded due to an incorrect study design
Maraspin 2002[101]	Excluded due to an incorrect study design
Maraspin 1999[102]	Excluded due to an incorrect study design
Maraspin 2002[103]	Excluded due to an incorrect population
Marks 2016[105]	Excluded due to an incorrect study design
McGill 1965[106]	Excluded due to an incorrect population
Meyerhoff 2002[107]	Excluded due to an incorrect study design
Meyerhoff 2016[108]	Excluded due to an incorrect study design
Millner 1996[109]	Excluded due to an incorrect outcome
Millner 1996[110]	Excluded due to an incorrect outcome
Morales 2000[111]	Excluded due to an incorrect study design
Muellegger 1995[113]	Excluded due to an incorrect study design
Muellegger 1996[112]	Excluded due to an incorrect comparison
Mullegger 1991[114]	Excluded due to an incorrect outcome
Nadelman 1993[116]	Excluded due to an incorrect study design
Nadelman 2001[115]	Excluded due to an incorrect population
Naglo 1989[117]	Excluded due to an incorrect study design
Neumann 1987[120]	Excluded due to an incorrect study design
Nimmrich 2014[122]	Excluded due to an incorrect study design
Nowakowski 2000[123]	Excluded due to an incorrect study design
Nowakowski 1995[124]	Excluded due to an incorrect study design
Ogrinc 2006[125]	Excluded due to an incorrect population
Oksi 1999[126]	Excluded due to an incorrect study design
Oksi 2007[127]	Excluded due to an incorrect population
Oksi 1998[128]	Excluded due to an incorrect population
Peltomaa 1998[129]	Excluded due to an incorrect comparison
Pena 1999[130]	Excluded due to an incorrect study design
Perronne 2015[131]	Not available
Pfister 1988[132]	Excluded due to an incorrect outcome
Pirila 1951[135]	Excluded due to an incorrect study design
Plorer 1993[136]	Excluded due to an incorrect study design
Plotkin 1991[137]	Excluded due to an incorrect study design
Puchalska 1996[138]	Excluded due to an incorrect study design
Puri 2015[139]	Excluded due to an incorrect comparison
Puri 2015[140]	Excluded due to an incorrect study design
Rebman 2015[141]	Excluded due to an incorrect study design
Renaud 2004[142]	Excluded due to an incorrect study design
Rohacova 1996[143]	Excluded due to an incorrect comparison
Rose 1994[144]	Excluded due to an incorrect study design
Rose 1996[145]	Excluded due to an incorrect intervention
Rubin 1992[146]	Excluded due to an incorrect study design
Salazar 2005[147]	Excluded due to an incorrect intervention

Reference	Reason for exclusion
Salazar 1993[148]	Excluded due to an incorrect study design
Sanchez 2016[149]	Excluded due to an incorrect study design
Sandstrom 1989[150]	Excluded due to an incorrect study design
Schmidt 1995[151]	Excluded due to an incorrect study design
Selby 2008[152]	Excluded due to an incorrect study design
Shadick 1994[153]	Excluded due to an incorrect study design
Shadick 1999[154]	Excluded due to an incorrect study design
Shemenski 2016[155]	Excluded due to an incorrect study design
Shoemaker 2006[156]	Excluded due to an incorrect intervention
Sjowall 2012[158]	Excluded due to an incorrect intervention
Sjowall 2011[157]	Excluded due to an incorrect study design
Skogman 2003[160]	Excluded due to an incorrect intervention
Skogman 2008[159]	Excluded due to an incorrect study design
Skoldenberg 1988[161]	Excluded due to an incorrect study design
Smith 2002[162]	Excluded due to an incorrect study design
Solomon 1998[163]	Excluded due to an incorrect intervention
Spathling 1992[164]	Article not in English
Stanek 1999[165]	Excluded due to an incorrect study design
Steere 1980[169]	Excluded due to an incorrect study design
Steere 1983[170]	Excluded due to an incorrect study design
Steere 1987[166]	Excluded due to an incorrect study design
Steurer 2016[171]	Article not in English
Stricker 2011[172]	Excluded due to an incorrect study design
Stricker 2010[173]	Excluded due to an incorrect study design
Strle 1996[174]	Excluded due to an incorrect outcome
Strle 1996[175]	Excluded due to an incorrect outcome
Strle 1992[176]	Excluded due to an incorrect study design
Strle 1993[177]	Excluded due to an incorrect outcome
Stupica 2015[179]	Excluded due to an incorrect comparison
Stupica 2011[178]	Excluded due to an incorrect comparison
Suarez-Magdalena 2017[180]	Not available
Thompson 2012[181]	Excluded due to an incorrect study design
Thorstrand 2002[182]	Excluded due to an incorrect study design
Thyresson 1949[183]	Excluded due to an incorrect study design
Torbahn 2016[184]	Excluded due to an incorrect study design
Tory 2010[185]	Excluded due to an incorrect comparison
Tseng 2017[186]	Excluded due to an incorrect outcome
Valesova 1996[187]	Excluded due to an incorrect comparison
Vazquez 2003[189]	Excluded due to an incorrect study design
Vazquez-Lopez 2016[188]	Excluded due to an incorrect study design
Wahlberg 1994[190]	Excluded due to an incorrect intervention
Weber 1988[192]	Excluded due to an incorrect study design
Weber 1987[191]	Excluded due to an incorrect population
Weissenbacher 2005[193]	Excluded due to an incorrect intervention
White 2013[194]	Excluded due to an incorrect study design

Reference	Reason for exclusion
Zochling 1996[195]	Excluded due to an incorrect study design

I.2 Excluded health economic studies

Table 22: Studies excluded from the health economic review

Reference	Reason for exclusion
None	None