National Institute for Health and Care Excellence

Draft for consultation

Vitamin B12 deficiency in over 16s: diagnosis and management

[F] Evidence review for follow up

NICE guideline <number>

Evidence reviews underpinning recommendations 1.6.1 to 1.6.15 and the recommendation for research in the NICE guideline

July 2023

Draft for Consultation

Developed by NICE

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ISBN:

Contents

1. Follow up

1.1. Review question

What is the optimal frequency of follow-up for people with vitamin B12 deficiency, including pernicious anaemia?

1.1.1. Introduction

It is important that people who are diagnosed with vitamin B12 deficiency are followed up to ensure that their treatment is working. There are currently no national guidelines as to the frequency and the components of follow up for people with vitamin B12 deficiency. The most effective frequency and components of follow up are not known. Currently, the frequency and components of follow up are determined by the clinician, considering the reason for the B12 deficiency, treatment offered and a person's response to treatment.

This review seeks to determine the most effective way of following up people with vitamin B12 deficiency. The most appropriate frequency and components of follow up are expected to differ depending on whether a person receives oral or intramuscular treatment, and the evidence will therefore be stratified according to treatment route.

1.1.2. Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Inclusion: Adults with diagnosed vitamin B12 deficiency, including pernicious anaemia. Stratify by: • Treatment route (oral/intramuscular) • Pregnancy/breastfeeding
Intervention	Frequency of follow up: • Up to and including 2 months • 2-3 months (including 3 months) • 3-6 months (including 6 months) • 6 months to 1 year (including 1 year) • Longer than 1 year after start of treatment
Comparisons	• All frequencies compared with each other • No follow up

Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical:
	• quality of life (such as EQ5D, SF36)
	• patient-reported outcomes (PROM scores including some/all symptoms):
	  ○ fatigue
	  ○ sleep
	  ○ peripheral neuropathy
	  ○ cognition

	○ psychiatric symptoms ○ pain • haematological values • complications and adverse events ○ mortality ○ bleeds ○ self-harm ○ nerve damage ○ frailty/falls ○ severe cognitive effects ○ postural hypotension • adherence to treatment • education/work absence
Study design	• Randomised controlled trials • Systematic reviews of RCTs • Non-randomised studies if insufficient RCT evidence is identified (priority will be given to inclusion of non-randomised comparative studies that have controlled/adjusted for confounding factors. If insufficient evidence is identified from studies that have controlled/adjusted for confounding factors, non-randomised comparative studies that have not controlled/adjusted for confounding factors will be considered) Key confounders: symptom severity

1.1.3. Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.4. Effectiveness evidence

1.1.4.1. Included studies

No relevant clinical studies comparing different frequencies of follow up of people with diagnosed vitamin B12 deficiency were identified.

See also the study selection flow chart in Appendix C.

1.1.4.2. Excluded studies

See the excluded studies list in Appendix J.

1.1.5. Summary of studies included in the effectiveness evidence

No included studies.

1.1.6. Summary of the effectiveness evidence

No evidence identified.

1.1.7. Economic evidence

1.1.7.1. Included studies

No health economic studies were included.

1.1.7.2. Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

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

1.1.8. Summary of included economic evidence

None

1.1.9. Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.2. Review question

What should be included in a follow-up review for people with vitamin B12 deficiency, including pernicious anaemia?

1.2.1. Introduction

See section 1.1.1.

1.2.2. Summary of the protocol

For full details see the review protocol in Appendix A.

Table 2: PICO characteristics of review question

Population	Inclusion: Adults with diagnosed vitamin B12 deficiency, including pernicious anaemia. Stratify by: • Treatment route (oral/intramuscular) • Pregnancy/breastfeeding

Interventions	Alone or in combination:
	• Vitamin B12 levels (active and total)
	• Other haematological values
	  ○ MMA
	  ○ full blood count
	  ○ folate
	  ○ ferritin
	  ○ thyroid function
	• Symptom review (including PROM scores, quality of life scores, neurological outcomes, short physical performance battery i.e., walking speed, timed up and go etc.)
	• Assessing diet

Comparisons	• Each other • No follow up review

Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical:
	
	• quality of life (such as EQ5D, SF36)
	• patient-reported outcomes (PROM scores including some/all symptoms):
	  ○ fatigue
	  ○ sleep
	  ○ peripheral neuropathy
	  ○ cognition

	○ psychiatric symptoms ○ pain • haematological values • complications and adverse events ○ mortality ○ bleeds ○ self-harm ○ nerve damage ○ frailty/falls ○ severe cognitive effects ○ postural hypotension • adherence to treatment • education/work absence
Study design	• Randomised controlled trials • Systematic reviews of RCTs • Non-randomised studies if insufficient RCT evidence is identified (priority will be given to inclusion of non-randomised comparative studies that have controlled/adjusted for confounding factors. If insufficient evidence is identified from studies that have controlled/adjusted for confounding factors, non-randomised comparative studies that have not controlled/adjusted for confounding factors will be considered) Key confounders: symptom severity

1.2.3. Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.2.4. Effectiveness evidence

1.2.4.1. Included studies

No relevant clinical studies comparing review of vitamin B12 levels, other haematological values, symptoms, or diet, alone or in combination, with each other, or no follow up were identified.

See also the study selection flow chart in Appendix C.

1.2.4.2. Excluded studies

See the excluded studies list in Appendix J.

1.2.5. Summary of studies included in the effectiveness evidence

No included studies.

1.2.6. Summary of the effectiveness evidence

No evidence identified.

1.2.7. Economic evidence

1.2.7.1. Included studies

No health economic studies were included.

1.2.7.2. Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

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

1.2.8. Summary of included economic evidence

None

1.2.9. Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.2.10. Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 3: Test costs

Resource	Unit costs	Source
Total B12 (cyanocobalamin)	£2.20	Obtained from committee members (average)
Active B12 (holotranscobalamin)	£18.50	Obtained from committee members (average)
MMA (methylmalonic acid)	£30.40	Obtained from committee members (average)
Homocysteine	£35.70	Obtained from committee members (average)

1.3. The committee's discussion and interpretation of the evidence

The committee discussion of the review on what should be included in a follow up review is included in the discussion of the review on frequency of follow up.

1.3.1. The outcomes that matter most

The committee considered quality of life, patient reported outcomes including symptom scores, haematological values, complications and adverse events, adherence to treatment and education/work absence to be the most important outcomes of follow up. All outcomes were considered equally important for decision making and therefore were all rated as critical.

No evidence was identified for any of the outcomes.

1.3.2. The quality of the evidence

No evidence was identified.

1.3.3. Benefits and harms

The committee discussed the varying definitions of a medicine review that are being used in current practice. For example, some medicine reviews are computerised, based on blood test results, whereas others are with the patient. There is also variation in what is included in the review, such as whether symptoms are reviewed.

In the absence of any evidence, the committee agreed based on their experience and expertise that follow up needs are dependent on the type of treatment being received and the clinical presentation of B12 deficiency. Those with more severe symptoms, such as neurological symptoms, haematological abnormalities may require more frequent review until resolved.

From the patient perspective, concerns were expressed that medicines could be stopped when it is still needed if the review is based on test results alone. Blood levels do not always reflect lived experience of the condition, so the person may still be experiencing symptoms despite normal test results. Alternatively, the person may not experience symptoms because the condition is being effectively managed and withdrawing the treatment will cause a relapse in symptoms.

In the absence of any evidence on the optimal frequency or composition of follow up reviews, the committee made consensus recommendations based on their experience and expertise. However, they agreed that research is needed on which components of follow up reviews lead to the best outcomes for people receiving vitamin B12 replacement. In particular, they agreed the value in monitoring different haematological parameters, assessing dietary vitamin B12 intake and assessing symptoms needs to be determined for people receiving oral and intramuscular replacement. Therefore, they made a research recommendation.

The committee agreed for most people, an initial follow-up appointment at 3 months would give enough time to ensure treatment is working. However, during pregnancy or breastfeeding, people should be followed up at one month to make sure they are getting the treatment they need to protect both their health and that of their baby.

The committee discussed what should be assessed at the first follow up review. The committee agreed it is important to check that the person is attending appointments for intramuscular injections or taking their tablets as prescribed and receiving the correct dosage

and frequency, as these factors can impact the efficacy of the treatment. The committee cross referred to the recommendations on supporting adherence in the NICE guideline on medicines adherence if there is concern about adherence.

The committee highlighted that although the recommendations on ongoing care and follow up in this guideline provide a guide on when and how often to carry out follow up reviews with people with vitamin B12 deficiency, people should return to their healthcare professional if symptoms are not improving, getting worse or new symptoms develop. The committee agreed it was important not to leave people waiting for their next scheduled follow-up when they could benefit from changes to their treatment. See also the recommendations on information and support for people with vitamin B12 deficiency and signs and symptoms.

The committee agreed that there are differences in the requirements for ongoing care and follow up depending on whether the person is receiving oral or intramuscular replacement. Therefore, separate recommendations were made.

People receiving oral treatment

The committee discussed the appropriate time interval between initiation of treatment and first follow up review. They considered that 3 months would allow adequate time for enough B12 to be absorbed and raise serum levels concentration in the body, which would indicate whether the person is able to absorb the vitamin. Therefore, they agreed that people should be followed up at 3 months.

The committee agreed that vitamin B12 serum concentrations should be retested at the 3 month follow up review to give an indication of whether the person has absorbed enough of the oral replacement. However, the committee agreed this test should only be carried out alongside a review of the person's signs and symptoms, as people may still be experiencing symptoms even if vitamin B12 serum concentrations have moved up to within the reference range and no longer indicate a deficiency.

If the test shows the person still has a deficiency and their symptoms have not improved or new symptoms have developed, the committee considered that this would indicate that the person is unable to absorb enough B12 through their current oral replacement regimen, so increasing the dosage or intramuscular treatment could be considered as an alternative. If the test shows vitamin B12 serum concentrations still suggest a deficiency but their symptoms have improved, the committee agreed it is likely that the oral treatment is working so oral treatment should be continued.

If the test shows vitamin B12 serum concentrations are within or above the reference range for a normal B12 serum concentration and there is symptom improvement, the committee agreed that options are to either continue or stop treatment. Treatment should be continued if the cause of the deficiency has not been addressed. This is because it is likely that the deficiency would return, or the persons symptoms would return. Treatment should be stopped where the cause has been addressed, for example if the person was following dietary advice to increase their vitamin B12 intake or they were no longer taking a medicine that was causing the deficiency. By stopping treatment where it is no longer needed, the committee agreed this would avoid any unnecessary treatment costs.

If the test shows vitamin B12 serum concentrations are within or above the reference range for a normal B12 concentration but the person's symptoms have not improved, or they have new symptoms and the person has previously had an MMA test, the committee agreed that possible options would be to increase the dosage of oral replacement, switch to intramuscular replacement, or to consider alternative diagnoses. The committee also agreed that if the person has not had an MMA test during diagnosis, an MMA test could be considered to check for functional B12 status. If MMA levels suggest that the person still has a vitamin B12 deficiency, the committee agreed that the person could be switched to intramuscular injections or have the dosage of oral replacement increased. If the MMA test is

normal, this would suggest that the symptoms being experienced by the person may be caused by something other than vitamin B12 deficiency and other diagnoses could be explored. However, the committee also pointed out that renal function and advanced age can also cause MMA levels to raise, and this may affect the results. In this situation it is possible to test MMA, give the person intramuscular injections and then retest MMA. If there is a drop in MMA then it suggests that there was a deficiency.

People receiving intramuscular injections

The committee agreed people receiving intramuscular injections should also have a follow up review at 3 months. This is in line with the licenced frequency of injections, so the person should be due for their next injection at 3 months anyway. The committee also considered that by 3 months, people should have noticed an improvement in their symptoms.

The committee highlighted the importance of discussing the person's signs and symptoms with them, as this will guide decisions about changes to treatment and frequency of follow up. The committee agreed that if symptoms have not improved, or new symptoms of deficiency have developed, it may suggest that more frequent injections are needed to help manage these. If this is decided, then a date for the next follow up should be discussed and agreed with the person. The committee noted the variation in the licensed frequency of administration of two to three months. They agreed that if symptoms return before the person's next injection, the frequency of injections could be increased to achieve optimal symptom control.

For people receiving lifelong treatment for an irreversible cause of deficiency, the committee agreed that if symptoms have improved at 3 months, the frequency of follow up could be reduced. The committee considered that it is usual practice for those on long-term medicines to have an annual medicine review and that once stable, the follow up review could align with this.

For people with a reversible cause of deficiency, the committee agreed that if symptoms have improved at 3 months, further treatment and follow up would depend on whether the cause has been addressed. If the cause has not been addressed, the committee agreed that continuing treatment should be considered and a date for the next follow up should be discussed and agreed with the person. This is because it is likely that the deficiency would return, or the persons symptoms would return if treatment was stopped. If the cause has been addressed, the committee agreed that stopping or reducing the frequency of intramuscular treatment should be considered to avoid unnecessary treatment costs. However, the committee highlighted that the person should be advised to return if their symptoms return or new symptoms develop.

The committee agreed there is little benefit in measuring B12 concentration in a person receiving and adhering to intramuscular treatment, because results will reflect the pharmacological dose of vitamin B12 rather than status at tissue level. Therefore, the committee recommended that B12 should not be retested while the person is receiving intramuscular injections.

1.3.4. Cost effectiveness and resource use

Published cost effectiveness evidence

No economic evaluations were identified for this review.

Consideration of cost effectiveness

There was no evidence identified as part of the clinical review. Unit costs of tests were presented to aid the committee with considerations of cost effectiveness. Evidence and patient experiences indicate that haematological values may not truly reflect the condition so

that patients may still have symptoms despite having B12 test results within a normal range. Therefore, for people on oral treatment, the committee raised that it is important to review patient symptoms as well as the haematological test values due to concerns that medicine may be inappropriately stopped. By stopping B12 treatment inappropriately, this could potentially result in further primary care appointments and additional costs of investigations or potential referrals to secondary care.

For people who are on oral treatment but are symptomatic despite having haematological values of total B12/active B12 that indicate they are not deficient, the committee feel that an MMA test should be conducted to investigate whether there is still B12 deficiency which may be due to inadequate absorption. This could result in treatment route being changed to parenteral which is thought by the committee to be more effective in resolving symptoms. The cost of parenteral treatment is lower than oral however this is dependent on the length of treatment and whether there is a loading dose required for parenteral treatment which will influence the costs.

Recommendations

Regarding the frequency of monitoring, monitoring was proposed at 3 months after starting oral treatment to check that the medicine was providing a response. If there has been improvement, then consider continuing or stopping treatment and follow up in a year or patient led follow up. By reviewing the need for the medicine this will ensure that treatment is appropriate.

For oral treatment, if person is still symptomatic despite B12 levels improving consider MMA testing or switch to parenteral treatment. The benefit of MMA testing or offering parenteral treatment is to potentially identify malabsorption issues which can be overcome by treating with parenteral treatment. This would also reduce the need for further investigations and inappropriate referrals. By confirming that there is a B12 deficiency is present it can then be treated appropriately by parenteral treatment which will provide health gains and offset the cost of the MMA test and the potential inappropriate costs of investigations.

For routine follow up, the committee thought that in practice annual monitoring would take place, or it may be patient led. For people that are on parenteral treatment, the committee thought that there is almost no benefit of testing using total B12 therefore routine testing has not been recommended.

Resource impact

In terms of resource impact, the main change in practice relates to the potential increased use of MMA testing for people on oral B12 treatment who have continuing, or new symptoms related to B12 deficiency. This could potentially have a significant resource impact however the committee expressed the view that the benefit of using MMA testing would outweigh the testing costs. MMA testing costs could be offset by stopping further inappropriate investigations of other causes of symptoms and reducing primary care appointments. The committee also thought that MMA testing would improve people's quality of life by improving symptom control and reducing the risk of B12 deficiency complications and hospitalisations suggesting that MMA testing for monitoring people on oral B12 treatment who have continuing, or new symptoms is likely to be cost-effective. By not offering MMA retesting to people who have previously had an MMA test, this will limit testing and also limit resource impact.

For people receiving oral B12 treatment the recommendation indicates that they should continue treatment up to the 3-month review. During this review, treatment may be advised to be continued or stopped depending on symptom control, potential cause of B12 deficiency and the test results. For some reversible causes of B12 deficiency for example diet related, assuming that the B12 levels for the person are in the reference range, and the person has no symptoms then it would be sensible to stop treatment and provide dietary advice and

advise the person to seek medical attention if symptoms reoccur. Offering longer term treatment when B12 levels are in the reference range and people have no symptoms may not be required, is not usual practice and will have a significant resource impact at an annual cost of £120 per person.

For people who are switched from oral to parenteral treatment due to concerns over low adherence to oral treatment or lack of effectiveness, the switch will be cost saving, as parenteral administration of vitamin B12 is less costly than oral administration. Alternatively, there may be some cases whereby it may appropriate to consider stopping parenteral treatment if there is a reversible cause of B12 deficiency. However, it is important to ensure it is stopped appropriately as the cost saving of ceasing treatment will be cancelled out if a person's B12 symptoms worsen, leading to additional costs incurred by primary care appointments, investigations and potential referrals.

1.3.5. Recommendations supported by this evidence review

This evidence review supports recommendations 1.6.1 to 1.6.15 and the recommendation for research on what should be included in a follow-up review for people with vitamin B12 deficiency, including people with autoimmune gastritis (pernicious anaemia).

1.4. References

1. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [updated January 2022]. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

Appendices

Appendix A Review protocols

A.1 Review protocol for frequency of follow up

ID	Field	Content
0.	PROSPERO registration number	CRD42022363485
1.	Review title	What is the optimal frequency of follow-up for people with vitamin B12 deficiency, including pernicious anaemia?
2.	Review question	What is the optimal frequency of follow-up for people with vitamin B12 deficiency, including pernicious anaemia?
3.	Objective	To determine the most clinically and cost-effective frequency of follow up for people with vitamin B12 deficiency, including pernicious anaemia.
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant.

		The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Vitamin B12 deficiency, including pernicious anaemia.
6.	Population	Inclusion: Adults with diagnosed vitamin B12 deficiency, including pernicious anaemia. Stratify by: • Treatment route (oral/intramuscular) • Pregnancy/breastfeeding
7.	Intervention	Frequency of follow up: • Up to and including 2 months • 2-3 months (including 3 months) • 3-6 months (including 6 months) • 6 months to 1 year (including 1 year) • Longer than 1 year after start of treatment
8.	Comparator	• All frequencies compared with each other • No follow up
9.	Types of study to be included	• Randomised controlled trials • Systematic reviews of RCTs • Non-randomised studies if insufficient RCT evidence is identified (priority will be given to inclusion of non-randomised comparative studies that have controlled/adjusted for confounding factors. If insufficient evidence is identified from studies that have controlled/adjusted for confounding factors, non-randomised comparative studies that have not controlled/adjusted for confounding factors will be considered) Key confounders: symptom severity

10.	Other exclusion criteria	• Non-comparative studies • Non-English language studies • Conference abstracts
11.	Context	NA

12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical:
		
		• quality of life (such as EQ5D, SF36)
		• patient-reported outcomes (PROM scores including some/all symptoms):
		  ○ fatigue
		  ○ sleep
		  ○ peripheral neuropathy
		  ○ cognition
		  ○ psychiatric symptoms
		  ○ pain
		• haematological values
		• complications and adverse events
		  ○ mortality
		  ○ bleeds
		  ○ self-harm
		  ○ nerve damage
		  ○ frailty/falls
		  ○ severe cognitive effects
		  ○ postural hypotension
		• adherence to treatment
		• school/work absence

13.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated.

		10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
14.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: Randomised Controlled Trial: Cochrane RoB (2.0) Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Non-randomised study, including cohort studies: Cochrane ROBINS-I
15.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity

		analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome. The risk of bias across all available evidence was 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/ Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.	
16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • Cause (pernicious anaemia/post-surgical causes/dietary/medicines/unknown/mixed cause) • Dosage • Loading dose	
17.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
18.	Language	English	

19.	Country	England		
20.	Anticipated or actual start date	28/09/2022		
21.	Anticipated completion date	01/11/2023		
22.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
23.	Named contact	5a. Named contact Guideline Development Team NGC 5b Named contact e-mail PerniciousAnaemia@nice.nhs.uk 5e Organisational affiliation of the review		

		National Institute for Health and Care Excellence (NICE)
24.	Review team members	From the National Guideline Centre: Carlos Sharpin [Guideline lead] Maria Smyth [Senior systematic reviewer] Toby Sands [Systematic reviewer] Aamer Jawed [Health economist] Stephen Deed [Information specialist] Katie Tuddenham [Project manager]
25.	Funding sources/sponsor	Development of this systematic review is being funded by NICE.
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: Project documents | Vitamin B12 deficiency, including pernicious anaemia: diagnosis and management | Guidance | NICE
28.	Other registration details	
29.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022363485
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:

		• notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
31.	Keywords		
32.	Details of existing review of same topic by same authors		
33.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
34.	Additional information		
35.	Details of final publication	www.nice.org.uk	

1

A.2 Review protocol for what should be included in a follow up review

2

ID	Field	Content
0.	PROSPERO registration number	CRD42022363492
1.	Review title	What should be included in a follow-up review for people with vitamin B12 deficiency, including pernicious anaemia?

2.	Review question	What should be included in a follow-up review for people with vitamin B12 deficiency, including pernicious anaemia?
3.	Objective	To determine the most clinically and cost-effective elements for inclusion in follow up reviews for people with vitamin B12 deficiency, including pernicious anaemia.
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Vitamin B12 deficiency, including pernicious anaemia.
6.	Population	Inclusion: Adults with diagnosed vitamin B12 deficiency, including pernicious anaemia. Stratify by: • Treatment route (oral/intramuscular) • Pregnancy/breastfeeding

7.	Intervention	Alone or in combination:
		• Vitamin B12 levels (active and total)
		• Other haematological values
		  ○ MMA
		  ○ full blood count
		  ○ folate
		  ○ ferritin
		  ○ thyroid function
		• Symptom review (including PROM scores, quality of life scores, neurological outcomes, short physical performance battery i.e., walking speed, timed up and go etc.)
		• Assessing diet

8.	Comparator	• Each other • No follow up review
9.	Types of study to be included	• Randomised controlled trials • Systematic reviews of RCTs • Non-randomised studies if insufficient RCT evidence is identified (priority will be given to inclusion of non-randomised comparative studies that have controlled/adjusted for confounding factors. If insufficient evidence is identified from studies that have controlled/adjusted for confounding factors, non-randomised comparative studies that have not controlled/adjusted for confounding factors will be considered) Key confounders: symptom severity
10.	Other exclusion criteria	• Non-comparative studies • Non-English language studies • Conference abstracts
11.	Context	NA

12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical:
		
		• quality of life (such as EQ5D, SF36)
		• patient-reported outcomes (PROM scores including some/all symptoms):
		  ○ fatigue
		  ○ sleep
		  ○ peripheral neuropathy
		  ○ cognition
		  ○ psychiatric symptoms
		  ○ pain
		• haematological values
		• complications and adverse events
		  ○ mortality
		  ○ bleeds
		  ○ self-harm
		  ○ nerve damage
		  ○ frailty/falls
		  ○ severe cognitive effects
		  ○ postural hypotension
		• adherence to treatment
		• school/work absence

13.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above.

		A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
14.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: Randomised Controlled Trial: Cochrane RoB (2.0) Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) Non-randomised study, including cohort studies: Cochrane ROBINS-I
15.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness,

		inconsistency and imprecision) will be appraised for each outcome. Publication bias will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome. The risk of bias across all available evidence was 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/ Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.	
16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • Cause (pernicious anaemia/post-surgical causes/dietary/medicines/unknown/mixed cause) • Dosage • Loading dose	
17.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
18.	Language	English	
19.	Country	England	
20.	Anticipated or actual start date	28/09/2022	
21.	Anticipated completion date	01/11/2023	

<table>
<tr><td rowspan="8">22.</td><td rowspan="8">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>☐</td><td>☐</td></tr>
<tr><td>Piloting of the study selection process</td><td>☐</td><td>☐</td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td>☐</td><td>☐</td></tr>
<tr><td>Data extraction</td><td>☐</td><td>☐</td></tr>
<tr><td>Risk of bias (quality) assessment</td><td>☐</td><td>☐</td></tr>
<tr><td>Data analysis</td><td>☐</td><td>☐</td></tr>
<tr><td>23.</td><td>Named contact</td><td colspan="3">5a. Named contact
Guideline Development Team NGC

5b Named contact e-mail
PerniciousAnaemia@nice.nhs.uk

5e Organisational affiliation of the review
National Institute for Health and Care Excellence (NICE)</td></tr>
<tr><td>24.</td><td>Review team members</td><td colspan="3">From the National Guideline Centre:
Carlos Sharpin [Guideline lead]
Maria Smyth [Senior systematic reviewer]</td></tr>
</table>

		Toby Sands [Systematic reviewer] Aamer Jawed [Health economist] Stephen Deed [Information specialist] Katie Tuddenham [Project manager]
25.	Funding sources/sponsor	Development of this systematic review is being funded by NICE.
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: Project documents | Vitamin B12 deficiency, including pernicious anaemia: diagnosis and management | Guidance | NICE
28.	Other registration details	
29.	Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.

31.	Keywords		
32.	Details of existing review of same topic by same authors		
33.	Current review status	☐	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
34.	Additional information		
35.	Details of final publication	www.nice.org.uk	

1 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 2006, abstract-only studies and studies from non-OECD countries or the USA 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).[1] **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 selectively exclude the remaining studies. All studies excluded on the basis of 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 USA 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 2006 or later but that depend on unit costs and resource data entirely or predominantly from before 2006 will be rated as 'Not applicable'. • Studies published before 2006 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

These literature search strategies were used for the following reviews:

- What is the optimal frequency of follow-up for people with vitamin B12 deficiency, including pernicious anaemia?
- What should be included in a follow-up review for people with vitamin B12 deficiency, including pernicious anaemia?

The literature searches for these reviews are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[1]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 4: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 15 December 2022	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 15 December 2022	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
The Cochrane Library (Wiley)	Cochrane Database of Systematic Reviews to Issue 12 of 12, 15 December 2022 Cochrane Central Register of Controlled Trials to Issue 12 of 12, 15 December 2022	Exclusions (clinical trials, conference abstracts)
Epistemonikos	Inception to 15 December 2022	Systematic review

Database	Dates searched	Search filter used
(The Epistemonikos Foundation)		Exclusions (Cochrane reviews)

1 **Medline (Ovid) search terms**

1.	exp Vitamin B 12 Deficiency/
2.	((b12 or b 12 or cobalamin* or c?anocobalamin* or transcobalamin*) adj4 (deficien* or malabsor* or absor* or lack* or diminish* or low* or level* or abnormal* or deficit or disorder* or inadequa* or hypovitaminosis or hypo vitaminosis or avitaminosis)).ti,ab.
3.	exp Macrocytic Anemia/
4.	((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) adj3 (anemia* or anaemia*)).ti,ab.
5.	Intrinsic Factor/
6.	intrinsic factor.ti,ab.
7.	or/1-6
8.	letter/
9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.
16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice or rodent*).ti.
25.	or/18-24
26.	7 not 25
27.	limit 26 to English language
28.	(follow*-up* or followup* or checkup* or check*-up*).ti,ab,kf.
29.	((consultation* or review* or appointment* or test* or retest* or screen* or surveillance or monitor* or measur* or examin* or recall* or visit* or revisit* or evaluat* or assess* or analys* or analyz* or detect*) adj4 (interval* or frequen* or day* or week* or month* or year* or annual* or annum or time* or timing* or regular* or periodic* or ongoing or on-going or continu* or recurr* or repeat* or length or long-term or short-term or duration* or optimal or optimum or standard* or structured or schedule*)).ti,ab,kf.
30.	((symptom* or level*) adj3 (review* or test* or retest* or surveillance or monitor* or measur* or examin* or evaluat* or assess* or analys* or analyz* or detect*)).ti,ab,kf.
31.	((patient* or inpatient* or outpatient*) adj3 (consultation* or review* or appointment* or test* or retest* or screen* or surveillance or monitor* or measur* or examin* or recall* or visit* or revisit* or evaluat* or assess* or analys* or analyz* or detect*)).ti,ab,kf.
32.	or/28-31
33.	27 and 32
34.	randomized controlled trial.pt.

35.	controlled clinical trial.pt.
36.	randomi#ed.ab.
37.	placebo.ab.
38.	randomly.ab.
39.	clinical trials as topic.sh.
40.	trial.ti.
41.	or/34-40
42.	Meta-Analysis/
43.	Meta-Analysis as Topic/
44.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
45.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
46.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
47.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
48.	(search* adj4 literature).ab.
49.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
50.	cochrane.jw.
51.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
52.	or/42-51
53.	33 and (41 or 52)

1 **Embase (Ovid) search terms**

1.	exp B12 deficiency/
2.	((b12 or b 12 or cobalamin* or c?anocobalamin* or transcobalamin*) adj4 (deficien* or malabsor* or absor* or lack* or diminish* or low* or level* or abnormal* or deficit or disorder* or inadequa* OR or hypovitaminosis or hypo vitaminosis or avitaminosis)).ti,ab.
3.	exp macrocytic anemia/
4.	((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) adj3 (anemia* or anaemia*)).ti,ab.
5.	intrinsic factor/
6.	intrinsic factor.ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	case report/ or case study/
12.	(letter or comment*).ti.
13.	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
14.	or/8-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/

21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/16-23
25.	7 not 24
26.	limit 25 to English language
27.	(follow*-up* or followup* or checkup* or check*-up*).ti,ab,kf.
28.	((consultation* or review* or appointment* or test* or retest* or screen* or surveillance or monitor* or measur* or examin* or recall* or visit* or revisit* or evaluat* or assess* or analys* or analyz* or detect*) adj4 (interval* or frequen* or day* or week* or month* or year* or annual* or annum or time* or timing* or regular* or periodic* or ongoing or on-going or continu* or recurr* or repeat* or length or long-term or short-term or duration* or optimal or optimum or standard* or structured or schedule*)).ti,ab,kf.
29.	((symptom* or level*) adj3 (review* or test* or retest* or surveillance or monitor* or measur* or examin* or evaluat* or assess* or analys* or analyz* or detect*)).ti,ab,kf.
30.	((patient* or inpatient* or outpatient*) adj3 (consultation* or review* or appointment* or test* or retest* or screen* or surveillance or monitor* or measur* or examin* or recall* or visit* or revisit* or evaluat* or assess* or analys* or analyz* or detect*)).ti,ab,kf.
31.	or/27-30
32.	26 and 31
33.	random*.ti,ab.
34.	factorial*.ti,ab.
35.	(crossover* or cross over*).ti,ab.
36.	((doubl* or singl*) adj blind*).ti,ab.
37.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
38.	crossover procedure/
39.	single blind procedure/
40.	randomized controlled trial/
41.	double blind procedure/
42.	or/33-41
43.	Systematic Review/
44.	Meta-Analysis/
45.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
46.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
47.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
48.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
49.	(search* adj4 literature).ab.
50.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
51.	cochrane.jw.
52.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
53.	or/43-52
54.	32 and (42 or 53)

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Vitamin B 12 Deficiency] explode all trees
#2.	((b12 or b 12 or cobalamin* or c?anocobalamin* or transcobalamin*) near/4 (deficien* or malabsor* or absor* or lack* or diminish* or low* or level* or abnormal* or deficit or disorder* or inadequa* or hypovitaminosis or hypo vitaminosis or avitaminosis)):ti,ab

#3.	MeSH descriptor: [Anemia, Macrocytic] explode all trees
#4.	((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) near/3 (anemia* or anaemia*)):ti,ab
#5.	MeSH descriptor: [Intrinsic Factor] this term only
#6.	intrinsic factor:ti,ab
#7.	(or #1-#6)
#8.	conference:pt or (clinicaltrials or trialsearch):so
#9.	#7 not #8
#10.	((follow-up* or followup* or follow* up or checkup* or check-up* or check* up) near/3 (consultation* or review* or appointment* or test* or retest* or screen* or surveillance or monitor* or measur* or examin* or recall* or visit* or revisit* or evaluat* or assess* or analys* or analyz* or detect*)):ti,ab,kw
#11.	((consultation* or review* or appointment* or test* or retest* or screen* or surveillance or monitor* or measur* or examin* or recall* or visit* or revisit* or evaluat* or assess* or analys* or analyz* or detect*) near/4 (interval* or frequen* or day* or week* or month* or year* or annual* or annum or time* or timing* or regular* or periodic* or ongoing or on-going or continu* or recurr* or repeat* or length or long-term or short-term or duration* or optimal or optimum or standard* or structured or schedule*)):ti,ab,kw
#12.	((symptom* or level*) near/3 (review* or test* or retest* or surveillance or monitor* or measur* or examin* or evaluat* or assess* or analys* or analyz* or detect*)):ti,ab,kw
#13.	((patient* or inpatient* or outpatient*) near/3 (consultation* or review* or appointment* or test* or retest* or screen* or surveillance or monitor* or measur* or examin* or recall* or visit* or revisit* or evaluat* or assess* or analys* or analyz* or detect*)):ti,ab,kw
#14.	(or #10-#13)
#15.	#9 and #14

1 **Epistemonikos search terms**

1.	(title:((title:(b12 deficien* OR "B 12 deficien*" OR "cobalamin* deficien*" OR "c?anocobalamin* deficien*" OR "transcobalamin* deficien*" OR "b12 malabsor*" OR "b 12 malabsor*" OR "cobalamin* malabsor*" OR "c?anocobalamin* malabsor*" OR "transcobalamin* malabsor*" OR "b12 anemia*" OR "b 12 anemia*" OR "macrocytic anemia*" OR "megaloblastic anemia*" OR "pernicious anemia*" OR "addison* anemia*" OR "b12 anaemia*" OR "b 12 anaemia*" OR "macrocytic anaemia*" OR "megaloblastic anaemia*" OR "pernicious anaemia*" OR "addison* anaemia*" OR "intrinsic factor") OR abstract:(b12 deficien* OR "B 12 deficien*" OR "cobalamin* deficien*" OR "c?anocobalamin* deficien*" OR "transcobalamin* deficien*" OR "b12 malabsor*" OR "b 12 malabsor*" OR "cobalamin* malabsor*" OR "c?anocobalamin* malabsor*" OR "transcobalamin* malabsor*" OR "b12 anemia*" OR "b 12 anemia*" OR "macrocytic anemia*" OR "megaloblastic anemia*" OR "pernicious anemia*" OR "addison* anemia*" OR "b12 anaemia*" OR "b 12 anaemia*" OR "macrocytic anaemia*" OR "megaloblastic anaemia*" OR "pernicious anaemia*" OR "addison* anaemia*" OR "intrinsic factor")) AND (title:(followup* OR "follow* up*" OR "check* up*" OR checkup* OR retest* OR surveillance OR monitor* OR revisit* OR "patient* review*" OR "symptom* review*") OR abstract:(followup* OR "follow* up*" OR "check* up*" OR checkup* OR retest* OR surveillance OR monitor* OR revisit* OR "patient* review*" OR "symptom* review*"))) OR abstract:((title:(b12 deficien* OR "B 12 deficien*" OR "cobalamin* deficien*" OR "c?anocobalamin* deficien*" OR "transcobalamin* deficien*" OR "b12 malabsor*" OR "b 12 malabsor*" OR "cobalamin* malabsor*" OR "c?anocobalamin* malabsor*" OR "transcobalamin* malabsor*" OR "b12 anemia*" OR "b 12 anemia*" OR "macrocytic anemia*" OR "megaloblastic anemia*" OR "pernicious anemia*" OR "addison* anemia*" OR "b12 anaemia*" OR "b 12 anaemia*" OR "macrocytic anaemia*" OR "megaloblastic anaemia*" OR "pernicious anaemia*" OR "addison* anaemia*" OR "intrinsic factor") OR abstract:(b12 deficien* OR "B 12 deficien*" OR "cobalamin* deficien*" OR "c?anocobalamin* deficien*" OR "transcobalamin* deficien*" OR "b12 malabsor*" OR "b 12 malabsor*" OR "cobalamin* malabsor*" OR "c?anocobalamin* malabsor*" OR "transcobalamin* malabsor*" OR

	"b12 anemia*" OR "b 12 anemia*" OR "macrocytic anemia*" OR "megaloblastic anemia*" OR "pernicious anemia*" OR "addison* anemia*" OR "b12 anaemia*" OR "b 12 anaemia*" OR "macrocytic anaemia*" OR "megaloblastic anaemia*" OR "pernicious anaemia*" OR "addison* anaemia*" OR "intrinsic factor")) AND (title:(followup* OR "follow* up*" OR "check* up*" OR checkup* OR retest* OR surveillance OR monitor* OR revisit* OR "patient* review*" OR "symptom* review*") OR abstract:(followup* OR "follow* up*" OR "check* up*" OR checkup* OR retest* OR surveillance OR monitor* OR revisit* OR "patient* review*" OR "symptom* review*"))))

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Vitamin B12 deficient population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies.

Table 5: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 16 December 2022	Health economics studies Quality of life studies
	Quality of Life 1946 – 16 December 2022	Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	Health Economics 1 January 2014 – 16 December 2022	Health economics studies Quality of life studies
	Quality of Life 1974 – 16 December 2022	Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31 March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31 March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 16 December 2022	English language

1 **Medline (Ovid) search terms**

1.	exp Vitamin B 12 Deficiency/
2.	((b12 or b 12 or cobalamin* or c?anocobalamin* or transcobalamin*) adj4 (deficien* or malabsor* or absor* or lack* or diminish* or low* or level* or abnormal* or deficit or disorder* or inadequa* or hypovitaminosis or hypo vitaminosis or avitaminosis)).ti,ab.
3.	exp Macrocytic Anemia/
4.	((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) adj3 (anemia* or anaemia*)).ti,ab.
5.	Intrinsic Factor/
6.	intrinsic factor.ti,ab.
7.	or/1-6
8.	letter/
9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.
16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice or rodent*).ti.
25.	or/18-24
26.	7 not 25
27.	limit 26 to English language
28.	quality-adjusted life years/
29.	sickness impact profile/
30.	(quality adj2 (wellbeing or well being)).ti,ab.
31.	sickness impact profile.ti,ab.
32.	disability adjusted life.ti,ab.
33.	(qal* or qtime* or qwb* or daly*).ti,ab.
34.	(euroqol* or eq5d* or eq 5*).ti,ab.
35.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
36.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
37.	(hui or hui1 or hui2 or hui3).ti,ab.
38.	(health* year* equivalent* or hye or hyes).ti,ab.
39.	discrete choice*.ti,ab.
40.	rosser.ti,ab.

41.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
42.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
43.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
44.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
45.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
46.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
47.	or/28-46
48.	Economics/
49.	Value of life/
50.	exp "Costs and Cost Analysis"/
51.	exp Economics, Hospital/
52.	exp Economics, Medical/
53.	Economics, Nursing/
54.	Economics, Pharmaceutical/
55.	exp "Fees and Charges"/
56.	exp Budgets/
57.	budget*.ti,ab.
58.	cost*.ti.
59.	(economic* or pharmaco?economic*).ti.
60.	(price* or pricing*).ti,ab.
61.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
62.	(financ* or fee or fees).ti,ab.
63.	(value adj2 (money or monetary)).ti,ab.
64.	or/48-63
65.	27 and 47
66.	27 and 64
67.	limit 66 to yr="2014 -Current"
68.	65 or 67

1 **Embase (Ovid) search terms**

1.	exp B12 deficiency/
2.	((b12 or b 12 or cobalamin* or c?anocobalamin* or transcobalamin*) adj4 (deficien* or malabsor* or absor* or lack* or diminish* or low* or level* or abnormal* or deficit or disorder* or inadequa* or hypovitaminosis or hypo vitaminosis or avitaminosis)).ti,ab.
3.	exp macrocytic anemia/
4.	((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) adj3 (anemia* or anaemia*)).ti,ab.
5.	intrinsic factor/
6.	intrinsic factor.ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	case report/ or case study/

12.	(letter or comment*).ti.
13.	(conference abstract or conference paper).pt.
14.	or/8-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/16-23
25.	7 not 24
26.	limit 25 to English language
27.	quality adjusted life year/
28.	"quality of life index"/
29.	short form 12/ or short form 20/ or short form 36/ or short form 8/
30.	sickness impact profile/
31.	(quality adj2 (wellbeing or well being)).ti,ab.
32.	sickness impact profile.ti,ab.
33.	disability adjusted life.ti,ab.
34.	(qal* or qtime* or qwb* or daly*).ti,ab.
35.	(euroqol* or eq5d* or eq 5*).ti,ab.
36.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
37.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
38.	(hui or hui1 or hui2 or hui3).ti,ab.
39.	(health* year* equivalent* or hye or hyes).ti,ab.
40.	discrete choice*.ti,ab.
41.	rosser.ti,ab.
42.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
43.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
44.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
45.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
46.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
47.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
48.	or/27-47
49.	health economics/
50.	exp economic evaluation/
51.	exp health care cost/
52.	exp fee/
53.	budget/
54.	funding/
55.	budget*.ti,ab.
56.	cost*.ti.
57.	(economic* or pharmaco?economic*).ti.
58.	(price* or pricing*).ti,ab.

59.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
60.	(financ* or fee or fees).ti,ab.
61.	(value adj2 (money or monetary)).ti,ab.
62.	or/49-61
63.	26 and 48
64.	26 and 62
65.	limit 64 to yr="2014 -Current"
66.	63 or 65

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Vitamin B 12 Deficiency EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Anemia, Macrocytic EXPLODE ALL TREES
#3.	((b12 or b 12 or cobalamin* or c?anocobalamin* or transcobalamin*) adj4 (deficien* or malabsor* or absor* or lack* or diminish* or low* or level* or abnormal* or deficit or disorder* or inadequa* or hypovitaminosis or hypo vitaminosis or avitaminosis))
#4.	((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) adj3 (anemia* or anaemia*))
#5.	(intrinsic factor)
#6.	#1 OR #2 OR #3 OR #4 OR #5

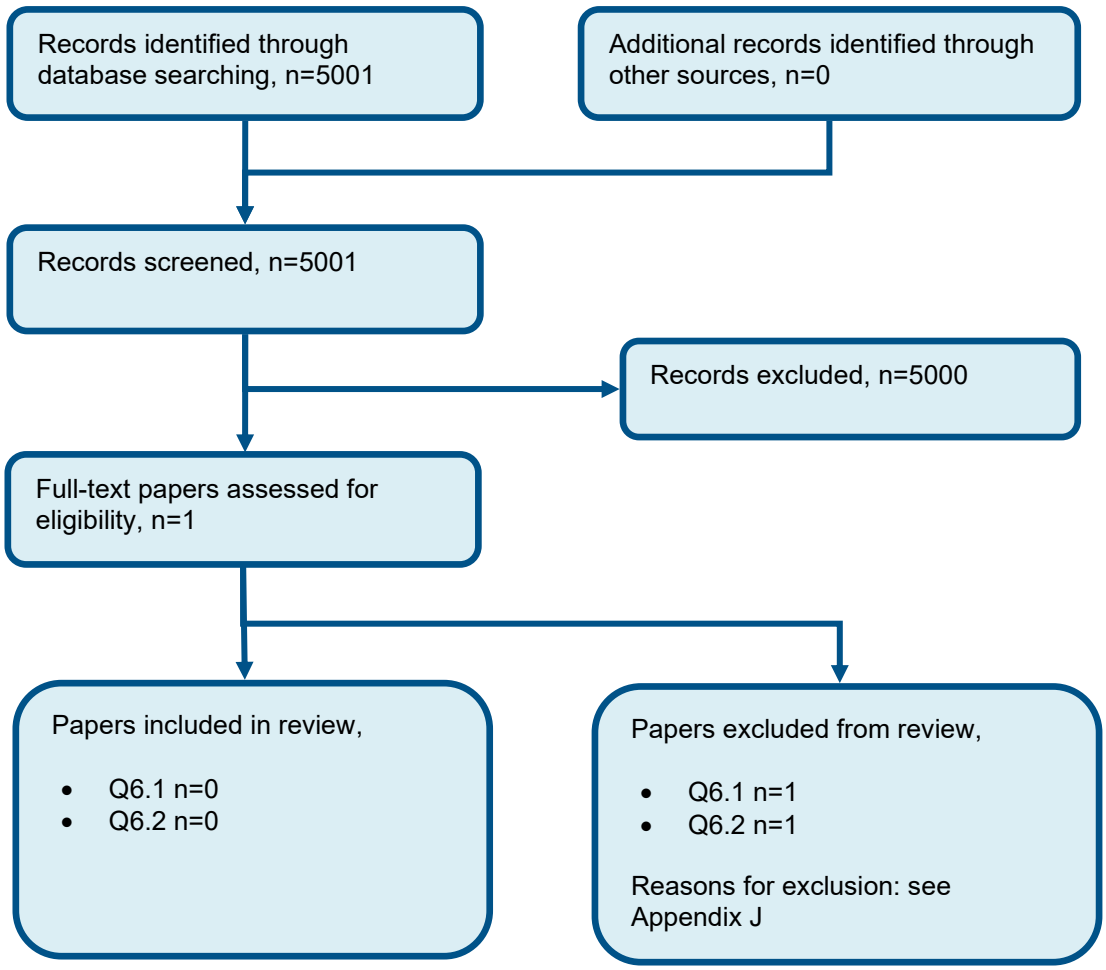
INAHTA search terms

1.	(Anemia, Pernicious)[mh] OR (Vitamin B 12 Deficiency)[mh] OR (pernicious anemia) OR (pernicious anemia) OR (B12) OR (B 12)

Appendix C Effectiveness evidence study selection

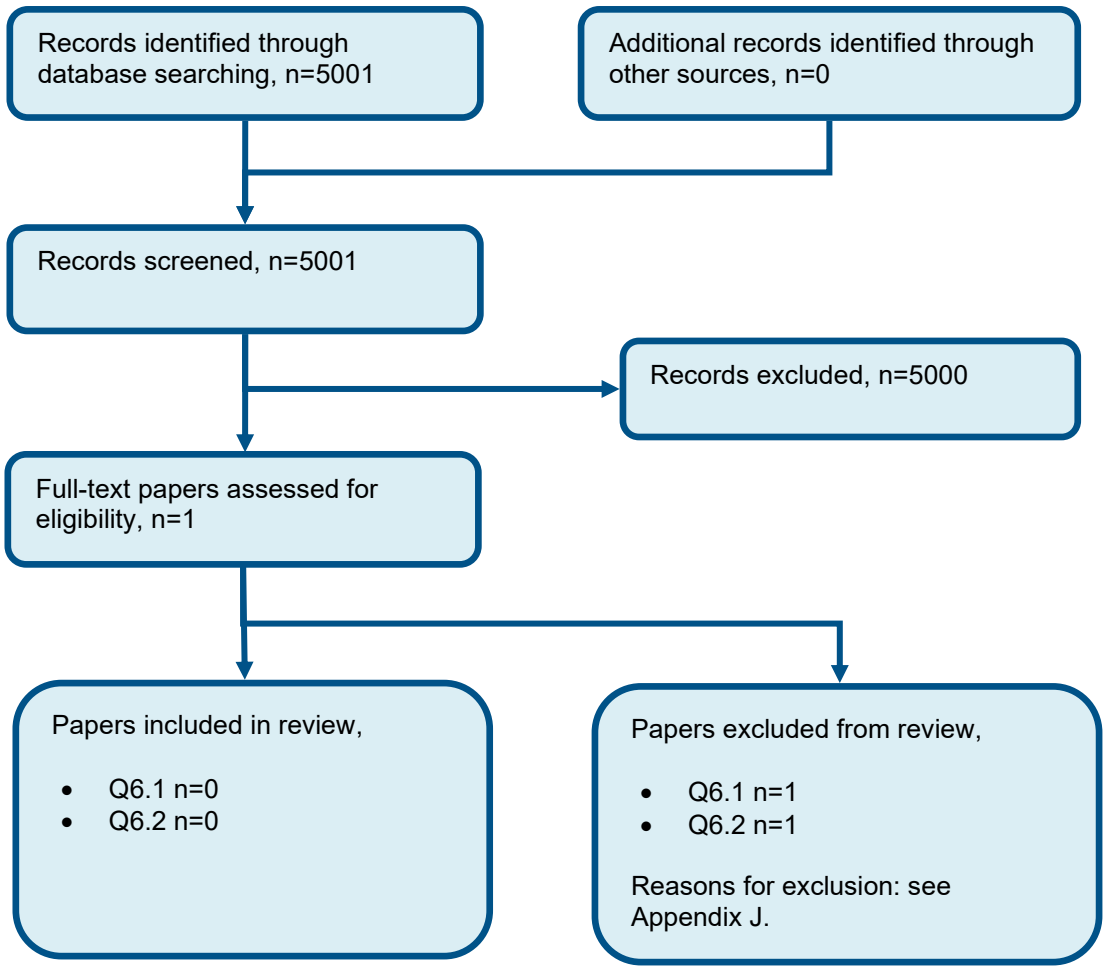
C.1 Frequency of follow up

Figure 1: Flow chart of clinical study selection for the review of frequency of follow up



C.2 What should be included in a follow up review

Figure 2: Flow chart of clinical study selection for the review of follow up reviews



Appendix D Effectiveness evidence

D.1 Frequency of follow up

No evidence identified.

D.2 What should be included in a follow up review

No evidence identified.

Appendix E Forest plots

E.1 Frequency of follow up

No forest plots.

E.2 What should be included in a follow up review

No forest plots.

Appendix F GRADE and/or GRADE-CERQual tables

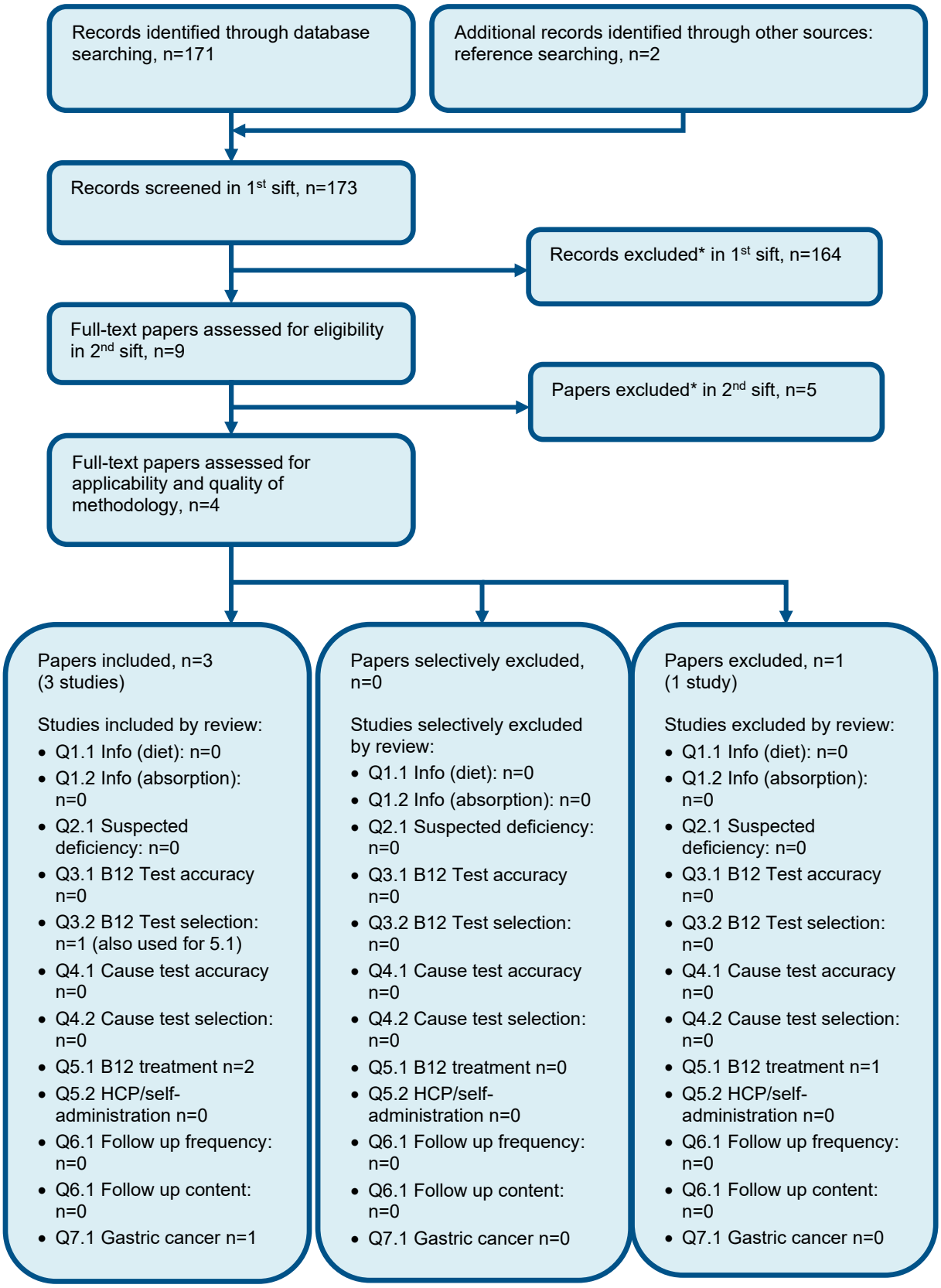
F.1 Frequency of follow up

No GRADE tables.

F.2 What should be included in a follow up review

No GRADE tables.

Appendix G Economic evidence study selection



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

Appendix H Economic evidence tables

H.1 Frequency of follow up

None

H.2 What should be included in a follow up review

None

Appendix I Health economic model

I.1 Frequency of follow up

No original economic modelling undertaken.

I.2 What should be included in a follow up review

No original economic modelling undertaken.

Appendix J Excluded studies

J.1 Clinical studies

J.1.1 Frequency of follow up

Table 6: Studies excluded from the clinical review

Study	Code [Reason]
Del Alamo, M., Sanchez, A.I., Serrano, M.L. et al. (2018) Monitoring strategies for clinical trials in primary care: An independent clinical research perspective. Basic and Clinical Pharmacology and Toxicology 123(supplement4): 25-26	- Study design (conference abstract)

J.1.2 What should be included in a follow up review

Table 7: Studies excluded from the clinical review

Study	Code [Reason]
Del Alamo, M., Sanchez, A.I., Serrano, M.L. et al. (2018) Monitoring strategies for clinical trials in primary care: An independent clinical research perspective. Basic and Clinical Pharmacology and Toxicology 123(supplement4): 25-26	- Study design (conference abstract)

J.2 Health Economic studies

None.

Appendix K Recommendation for research – full details

K.1 Recommendation for research

What should be included in a follow-up review for people with vitamin B12 deficiency, including people with autoimmune gastritis?

K.1.1 Why this is important

It is important that people with diagnosed vitamin B12 deficiency are followed up to ensure that their treatment is working. However, there is variation in follow up and no evidence on the most effective components of follow up reviews was identified. Therefore, research into which components lead to the best outcomes for people with vitamin B12 deficiency is needed.

K.1.2 Rationale for the recommendation for research

Importance to 'patients' or the population	Identifying the most effective components of follow up reviews for people with vitamin B12 deficiency will help to ensure that their condition is managed optimally.
Relevance to NICE guidance	Follow up reviews were considered in this guideline and there is a lack of evidence. Further research would inform future guideline updates.
Relevance to the NHS	The outcome would affect the components of follow up reviews for people with vitamin B12 deficiency provided by the NHS.
National priorities	Not applicable
Current evidence base	No evidence was identified on the most effective components of follow up reviews.
Equality considerations	None known

K.1.3 Modified PICO table

Population	People with diagnosed vitamin B12 deficiency, including autoimmune gastritis. Stratify by: • Treatment route (oral/intramuscular) • Pregnancy/breastfeeding

Intervention	Alone or in combination:
	• Vitamin B12 levels (active and total)
	• Other haematological values
	  ○ MMA
	  ○ full blood count
	  ○ folate
	  ○ ferritin
	  ○ thyroid function
	• Symptom review (including PROM scores, quality of life scores, neurological outcomes,

	short physical performance battery i.e., walking speed, timed up and go etc.) • Assessing diet
Comparator	• Each other
Outcome	• quality of life (such as EQ5D, SF36) • patient-reported outcomes (PROM scores including some/all symptoms): ○ fatigue ○ sleep ○ peripheral neuropathy ○ cognition ○ psychiatric symptoms ○ pain • haematological values • complications and adverse events ○ mortality ○ bleeds ○ self-harm ○ nerve damage ○ frailty/falls ○ severe cognitive effects ○ postural hypotension • adherence to treatment • school/work absence
Study design	Randomised controlled trial
Timeframe	Long term
Additional information	The ideal study design to answer this type of research question would be a randomised controlled trial. However, there may be practical challenges such as securing funding for a long-term trial. The next best design would be a comparative observational cohort study, controlling for confounding factors such as symptom severity.

1