National Institute for Health and Care Excellence

Draft for consultation

Vitamin B12 deficiency in over 16s: diagnosis and management

[A] Evidence review for information and support

NICE guideline <number>

Evidence reviews underpinning recommendations 1.1.1 to 1.1.4 in the NICE guideline

July 2023

Draft for Consultation

Developed by NICE

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1.1 Review question

What information and support is needed by people with suspected or confirmed vitamin B12 deficiency caused by a lack of vitamin B12 in their diet, and their families or carers?

1.1.1 Introduction

Providing information and support to people with suspected or confirmed vitamin B12 deficiency and their families and carers will increase understanding and management of the condition. There is currently no national standard for the information and support that should be provided. It is therefore important to identify the unique information and support needs of this group, tailored to the cause of their deficiency.

This review seeks to determine the information, education and support that people with suspected and confirmed vitamin B12 deficiency and their families and carers need by evaluating the qualitative information on the opinions, thoughts, feelings, and experiences of people with vitamin B12 deficiency.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Objective	To identify what information and support is needed by people with suspected or confirmed vitamin B12 deficiency caused by a lack of vitamin B12 in their diet, and their families or carers.
Population and setting	Adults with suspected or confirmed vitamin B12 deficiency caused by a lack of vitamin B12 in their diet, and their families or carers. Strata: • Pregnancy (Mixed population studies will be included in a mixed population stratum but will be downgraded for indirectness. A minimum cut-off of 70% will be used for a study population to fall into a stratum.) Exclusion: people with suspected or confirmed vitamin B12 deficiency due to non-dietary causes.
Context	Establishing what information and support is useful for people with vitamin B12 deficiency caused by a lack of vitamin B12 in their diet and their families or carers will help health and social care professionals to provide appropriate information and support necessary to improve patient outcomes and quality of life.
Review strategy	Synthesis of qualitative research. Results presented in narrative format. Quality of the evidence will be assessed by a GRADE CerQual approach for each review finding.

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 Qualitative evidence

1.1.4.1 Included studies

No studies were identified that explored the information and support required for people with vitamin B12 deficiency because of low vitamin B12 intake from their diet.

1.1.4.2 Excluded studies

For the full list of excluded studies, see Appendix F.

1.1.5 Summary of studies included in the qualitative evidence

No evidence identified.

1.1.6 Summary of the qualitative evidence

No evidence identified.

1.1.7 Economic evidence

The committee agreed that health economic studies would not be relevant to this review question, and so were not sought.

1.2 Review question

What information and support is needed by people with suspected or confirmed vitamin B12 deficiency caused by inadequate absorption of vitamin B12 (including pernicious anaemia), and their families or carers, and when should this be provided?

1.2.1 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 2: PICO characteristics of review question

Objective	To identify what information and support is needed by people with suspected or confirmed vitamin B12 deficiency caused by inadequate absorption of vitamin B12 (including pernicious anaemia), and their families or carers, and when this should be provided.
Population and setting	Inclusion: adults with suspected or confirmed vitamin B12 deficiency caused by inadequate absorption of vitamin B12 (including pernicious anaemia), and their families or carers. Strata: • Pregnancy (Mixed population studies will be included in a mixed population stratum but will be downgraded for indirectness. A minimum cut-off of 70% will be used for a study population to fall into a stratum.) Exclusion: people with suspected or confirmed vitamin B12 deficiency due to a lack of dietary vitamin B12
Context	Establishing what information and support is useful for people with vitamin B12 deficiency caused by inadequate absorption of vitamin B12 (including pernicious anaemia) and their families or carers will help health and social care

	professionals to provide appropriate information and support necessary to improve patient outcomes and quality of life.
Review strategy	Synthesis of qualitative research. Results presented in narrative format. Quality of the evidence will be assessed by a GRADE CerQual approach for each review finding.

1.2.2 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.

1.2.3 Qualitative evidence

1.2.3.1 Included studies

Two qualitative studies were included in the review.[2, 3] These are summarised in Table 3 below. One study provided direct evidence relating to the experiences of patients receiving a diagnosis and treatment for vitamin B12 deficiency caused by inadequate absorption of vitamin B12. The other study provided indirect evidence, including patient safety issues/priorities and messages to healthcare professionals from participants with vitamin B12 deficiency caused by both a lack of vitamin B12 in their diet and due to inadequate absorption of vitamin B12. Key findings from these studies are summarised in the clinical evidence summary below (Table 4). See also the study selection flow chart in below, study evidence tables in Appendix D, and excluded studies lists in Appendix E.

1.2.3.2 Excluded studies

For the full list of excluded studies, see Appendix F.

1.2.4 Summary of studies included in the qualitative evidence

Table 3: Summary of studies included in the evidence review

Study	Design	Population	Research aim	Comments
Seage 2020 [2]	Semi-structured interviews lasting between 27-65 minutes. Transcripts were analysed using Interpretative phenomenological analysis. During analysis, clusters of themes were developed and then analysed in relation to all transcripts. Clusters of themes were developed and then analysed in relation to all transcripts. Recurrence of	N=11 participants aged between 18 and 75 years, English speaking with a formal diagnosis of PA. Participants were recruited from an advert hosted on the Pernicious Anaemia Society's website and social media page.	Capture the lived experience individuals who have received a diagnosis of PA.	Conducted in the UK.

Study	Design	Population	Research aim	Comments
	themes was determined if they appeared in at least half of other transcripts and if so, superordinate themes were constructed. Three superordinate themes were identified.			
Tyler 2021[3]	Patient and public involvement and engagement workshop Various discussions of (a) proposed research, (b) patient safety in B12 deficiency, (c) priorities for health professional education, (d) future research and practice priorities. Lists were drawn up that captured the group's key thematic concerns (patient safety priorities and education priorities) followed by two ranking tasks.	N=12 people with vitamin B12 deficiency/pernicious anaemia, receiving B12 replacement therapy, recruited from a pernicious anaemia charitable organization, university volunteer newsletters and social media (Facebook support group).	To understand and consolidate quality and safety for this patient group concerns and to assess any additional impact of using visual art as a means of expressing quality and safety concerns	Relevance: moderate concerns due to inclusion of all causes of B12 deficiency Conducted in the UK

1 See Appendix D for full evidence tables.

1.2.5 Summary of the qualitative evidence

Table 4: Review findings

Main findings	Statement of finding
Patient Safety Issues/Priorities Tyler 2021[3]	1. Interpretation of test results and inconsistent test results 2. The necessity for symptom-based treatment – less reliance on tests 3. Safety of self-medication 4. Lack of trust in GPs and healthcare professionals 5. GPs variable knowledge about treatments and tests and feelings of disempowerment for patients 6. Diagnosis: GP reluctance to test further, but safety and treatment benefits associated with PA diagnosis 7. Time to diagnosis is too long 8. Postcode lottery 9. Safety of social media as a source of information, advice and support 10. Insufficient information about pre-blood test behaviour (fasting) 11. Ineffective testing following treatment commencement
Patient Messages to Healthcare Professionals [3]	1. Listen to patients when they say treatment is too infrequent 2. Necessity for General Practitioners to recognize and understand symptoms 3. Lack of awareness of the emotional and day-to-day effects of the condition 4. Include tests for B12 levels in standard blood test 5. Listen to patient (don't discount because symptoms are wide ranging, vague and invisible) 6. Understand co-morbidity of B12 deficiency and other conditions (IBS, depression, vitamin deficiencies) 7. Please take condition seriously 8. The effect of social media on patient experience and behaviour 9. Gain greater knowledge of co-factors associated with B12 deficiency 10. Don't discount the patient experience or their own research 11. Recognize that health-care professionals can't know everything about every condition 12. Educate all health-care professionals about B12 deficiency and blood tests 13. Awareness that the UK blood test range is very low (compared to other countries)
Seage 2020[2]	1. The struggle to achieve a diagnosis 2. The significance of a diagnosis 3. Seeking sufficient treatment

Narrative summary of review findings

Direct Evidence

Evidence from people with pernicious anaemia only

Review finding 1: The struggle to achieve a diagnosis

All interviewed participants were not satisfied with the process they underwent to achieve a diagnosis of pernicious anaemia. The paper highlighted that the diagnostic process was too long and resulted in a reduction in both physical and mental wellbeing, causing issues with the relationship between patients and clinicians. Participants felt that the diagnosis of pernicious anaemia was delayed due to clinicians initially assuming that vitamin B12 deficiency was caused by lifestyle factors. Additionally, half of the participants had experienced a misdiagnosis, with many having their symptoms attributed to depression or other psychological conditions.

Explanation of quality assessment: moderate methodological limitations in the contributing study due to the method of recruitment (recruited from charity and social media page) and an unclear relationship between the researcher and the participants. Moderate concerns regarding adequacy due to the finding coming from a single study with a small number of participants. No or minor concerns due to the coherence or relevance of the findings. Overall assessment of confidence was low.

Review finding 2: The significance of a diagnosis

Participants highlighted that despite the difficulty with obtaining a diagnosis of pernicious anaemia, participants valued their diagnosis when they did receive it. Participants felt that receiving a diagnosis allowed them to understand their symptoms and explain them to others. Despite the positive feelings towards receiving a diagnosis, participants felt that they were unable to fully understand pernicious anaemia due to a lack of information about the condition at diagnosis. This was highlighted alongside the widespread appreciation of the impact on daily life that pernicious anaemia can have. Additionally, all participants stated that clinicians had previously understated the impact of pernicious anaemia. The group felt that this underplaying of the severity of the condition led to a breakdown of the patient-clinician relationship, with many patients feeling ignored and losing trust in the NHS. As a result of this, many patients had sought information from alternative sources, with charities and social media support groups proving to be popular sources.

Explanation of quality assessment: moderate methodological limitations in the contributing study due to the method of recruitment (recruited from charity and social media page) and an unclear relationship between the researcher and the participants. Moderate concerns regarding adequacy due to the finding coming from a single study with a small number of participants. No or minor concerns due to the coherence or relevance of the findings. Overall assessment of confidence was low.

Review finding 3: Seeking sufficient treatment

All interview participants felt that their current treatment for pernicious anaemia was inadequate. Participants attributed this to strict adherence to guidelines by clinicians, rather than taking a patient-centred approach whereby treatment is adjusted based on symptoms. Inadequate treatment further led to the breakdown of patient-clinician relationships, with participants expressing that they were made to feel shameful for seeking more regular replacement therapy. The breakdown of trust between patients and clinicians resulted in many choosing to self-inject vitamin B12 against the guidance of clinicians.

Explanation of quality assessment: moderate methodological limitations in the contributing study due to the method of recruitment (recruited from charity and social media page) and an unclear relationship between the researcher and the participants. Moderate concerns regarding adequacy due to the finding coming from a single study with a small number of participants. No or minor concerns due to the coherence or relevance of the findings. Overall assessment of confidence was low.

Indirect Evidence

Evidence from mixed population of people with dietary and non-dietary vitamin B12 deficiency

Patient Safety Issues/Priorities

Review finding 1: Interpretation of test results and inconsistent test results

The primary patient safety priority proposed by patients was the need to improve interpretation of test results and reduce inconsistencies in reference ranges. Participants described national and local inconsistencies whereby initiation (and sometimes frequency) of treatment is dependent on reference ranges of test results set by local test centres instead of a national standard test or reference range.

Explanation of quality assessment: serious methodological limitations in the contributing study due to method of recruitment (recruited from charities and social media), unclear relationship between the researcher and participants, lack of information on the analysis strategy and insufficient data to support the finding. Partial relevance due to inclusion of all causes of B12 deficiency. Moderate concerns regarding adequacy due to the finding coming from a single study with a small number of participants included. Overall assessment of confidence was very low.

Review finding 2: The necessity for symptom-based treatment – less reliance on tests

The secondary patient safety priority was linked to the first. Patients felt that general practitioners/healthcare professionals should overcome the issues with test results by adopting a symptom-based approach.

Explanation of quality assessment: serious methodological limitations in the contributing study due to method of recruitment (recruited from charities and social media), unclear relationship between the researcher and participants, lack of information on the analysis strategy and insufficient data to support the finding. Partial relevance due to inclusion of all causes of B12 deficiency. Serious concerns regarding adequacy due to the finding coming from a single study with a small number of participants included and very limited data to support the finding. Overall assessment of confidence was very low.

Review finding 3: The safety of self-medication

Participants stated that they were aware of individuals that chose to self-medicate and felt this was a major safety concern for several reasons and they often did not inform their GPs. Thus, patients might use medicine which is not always obtained from secure sources or following validated advice and as a consequence infections/safety complications associated with injection could occur.

Explanation of quality assessment: serious methodological limitations in the contributing study due to method of recruitment (recruited from charities and social media), unclear relationship between the researcher and participants, lack of information on the analysis strategy and insufficient data to support the finding. Partial relevance due to inclusion of all causes of B12 deficiency. Moderate concerns regarding adequacy due to the finding coming from a single study with a small number of participants included. Overall assessment of confidence was very low.

Review finding 4: Lack of trust in GPs and healthcare professionals

No additional information reported.

Explanation of quality assessment: serious methodological limitations in the contributing study due to method of recruitment (recruited from charities and social media), unclear relationship between the researcher and participants, lack of information on the analysis strategy and insufficient data to support the finding. Partial relevance due to inclusion of all causes of B12 deficiency. Serious concerns regarding adequacy due to the finding coming from a single study with a small number of participants included and no data to support the finding. Overall assessment of confidence was very low.

Review finding 5: GPs variable knowledge about treatments and tests and feelings of disempowerment for patients

No additional information reported.

Explanation of quality assessment: serious methodological limitations in the contributing study due to method of recruitment (recruited from charities and social media), unclear relationship between the researcher and participants, lack of information on the analysis strategy and insufficient data to support the finding. Partial relevance due to inclusion of all causes of B12 deficiency. Serious concerns regarding adequacy due to the finding coming from a single study with a small number of participants included and no data to support the finding. Overall assessment of confidence was very low.

Review finding 6: Diagnosis: GP reluctance to test further, but safety and treatment benefits associated with PA diagnosis

No additional information reported.

Explanation of quality assessment: serious methodological limitations in the contributing study due to method of recruitment (recruited from charities and social media), unclear relationship between the researcher and participants, lack of information on the analysis strategy and insufficient data to support the finding. Partial relevance due to inclusion of all causes of B12 deficiency. Serious concerns regarding adequacy due to the finding coming from a single study with a small number of participants included and no data to support the finding. Overall assessment of confidence was very low.

Review finding 7: Time to diagnosis is too long

No additional information reported.

Explanation of quality assessment: serious methodological limitations in the contributing study due to method of recruitment (recruited from charities and social media), unclear relationship between the researcher and participants, lack of information on the analysis strategy and insufficient data to support the finding. Partial relevance due to inclusion of all causes of B12 deficiency. Serious concerns regarding adequacy due to the finding coming from a single study with a small number of participants included and no data to support the finding. Overall assessment of confidence was very low.

Review finding 8: Postcode lottery

No additional information reported.

Explanation of quality assessment: serious methodological limitations in the contributing study due to method of recruitment (recruited from charities and social media), unclear relationship between the researcher and participants, lack of information on the analysis strategy and insufficient data to support the finding. Partial relevance due to inclusion of all causes of B12 deficiency. Serious concerns regarding adequacy due to the finding coming from a single study with a small number of participants included and no data to support the finding. Overall assessment of confidence was very low.

Review finding 9: Safety of social media as a source of information, advice and support

No additional information reported.

Explanation of quality assessment: serious methodological limitations in the contributing study due to method of recruitment (recruited from charities and social media), unclear relationship between the researcher and participants, lack of information on the analysis strategy and insufficient data to support the finding. Partial relevance due to inclusion of all

causes of B12 deficiency. Serious concerns regarding adequacy due to the finding coming from a single study with a small number of participants included and no data to support the finding. Overall assessment of confidence was very low.

Review finding 10: Insufficient information about pre-blood test behaviour (fasting)

No additional information reported.

Explanation of quality assessment: serious methodological limitations in the contributing study due to method of recruitment (recruited from charities and social media), unclear relationship between the researcher and participants, lack of information on the analysis strategy and insufficient data to support the finding. Partial relevance due to inclusion of all causes of B12 deficiency. Serious concerns regarding adequacy due to the finding coming from a single study with a small number of participants included and no data to support the finding. Overall assessment of confidence was very low.

Review finding 11: Ineffective testing following treatment commencement

No additional information reported.

Explanation of quality assessment: serious methodological limitations in the contributing study due to method of recruitment (recruited from charities and social media), unclear relationship between the researcher and participants, lack of information on the analysis strategy and insufficient data to support the finding. Partial relevance due to inclusion of all causes of B12 deficiency. Serious concerns regarding adequacy due to the finding coming from a single study with a small number of participants included and no data to support the finding. Overall assessment of confidence was very low.

Patient Messages to Healthcare Professionals

Review finding 12: Listen to patients when they say treatment is too infrequent

No additional information reported.

Explanation of quality assessment: serious methodological limitations in the contributing study due to method of recruitment (recruited from charities and social media), unclear relationship between the researcher and participants, lack of information on the analysis strategy and insufficient data to support the finding. Partial relevance due to inclusion of all causes of B12 deficiency. Serious concerns regarding adequacy due to the finding coming from a single study with a small number of participants included and no data to support the finding. Overall assessment of confidence was very low.

Review finding 13: Necessity for General Practitioners to recognize and understand symptoms

No additional information reported.

Explanation of quality assessment: serious methodological limitations in the contributing study due to method of recruitment (recruited from charities and social media), unclear relationship between the researcher and participants, lack of information on the analysis strategy and insufficient data to support the finding. Partial relevance due to inclusion of all causes of B12 deficiency. Serious concerns regarding adequacy due to the finding coming from a single study with a small number of participants included and no data to support the finding. Overall assessment of confidence was very low.

Review finding 14: Lack of awareness of the emotional and day-to-day effects of the condition

No additional information reported.

Explanation of quality assessment: serious methodological limitations in the contributing study due to method of recruitment (recruited from charities and social media), unclear relationship between the researcher and participants, lack of information on the analysis strategy and insufficient data to support the finding. Partial relevance due to inclusion of all causes of B12 deficiency. Serious concerns regarding adequacy due to the finding coming from a single study with a small number of participants included and no data to support the finding. Overall assessment of confidence was very low.

Review finding 15: Include tests for B12 levels in standard blood test

No additional information reported.

Explanation of quality assessment: serious methodological limitations in the contributing study due to method of recruitment (recruited from charities and social media), unclear relationship between the researcher and participants, lack of information on the analysis strategy and insufficient data to support the finding. Partial relevance due to inclusion of all causes of B12 deficiency. Serious concerns regarding adequacy due to the finding coming from a single study with a small number of participants included and no data to support the finding. Overall assessment of confidence was very low.

Review finding 16: Listen to patient (don't discount because symptoms are wide ranging, vague and invisible)

No additional information reported.

Explanation of quality assessment: serious methodological limitations in the contributing study due to method of recruitment (recruited from charities and social media), unclear relationship between the researcher and participants, lack of information on the analysis strategy and insufficient data to support the finding. Partial relevance due to inclusion of all causes of B12 deficiency. Serious concerns regarding adequacy due to the finding coming from a single study with a small number of participants included and no data to support the finding. Overall assessment of confidence was very low.

Review finding 17: Understand co-morbidity of B12 deficiency and other conditions (IBS, depression, vitamin deficiencies)

No additional information reported

Explanation of quality assessment: serious methodological limitations in the contributing study due to method of recruitment (recruited from charities and social media), unclear relationship between the researcher and participants, lack of information on the analysis strategy and insufficient data to support the finding. Partial relevance due to inclusion of all causes of B12 deficiency. Serious concerns regarding adequacy due to the finding coming from a single study with a small number of participants included and no data to support the finding. Overall assessment of confidence was very low.

Review finding 18: Please take condition seriously

No additional information reported.

Explanation of quality assessment: serious methodological limitations in the contributing study due to method of recruitment (recruited from charities and social media), unclear relationship between the researcher and participants, lack of information on the analysis strategy and insufficient data to support the finding. Partial relevance due to inclusion of all causes of B12 deficiency. Serious concerns regarding adequacy due to the finding coming from a single study with a small number of participants included and no data to support the finding. Overall assessment of confidence was very low.

Review finding 19: The effect of social media on patient experience and behaviour

No additional information reported.

Explanation of quality assessment: serious methodological limitations in the contributing study due to method of recruitment (recruited from charities and social media), unclear relationship between the researcher and participants, lack of information on the analysis strategy and insufficient data to support the finding. Partial relevance due to inclusion of all causes of B12 deficiency. Serious concerns regarding adequacy due to the finding coming from a single study with a small number of participants included and no data to support the finding. Overall assessment of confidence was very low.

Review finding 20: Gain greater knowledge of co-factors associated with B12 deficiency

No additional information reported.

Explanation of quality assessment: serious methodological limitations in the contributing study due to method of recruitment (recruited from charities and social media), unclear relationship between the researcher and participants, lack of information on the analysis strategy and insufficient data to support the finding. Partial relevance due to inclusion of all causes of B12 deficiency. Serious concerns regarding adequacy due to the finding coming from a single study with a small number of participants included and no data to support the finding. Overall assessment of confidence was very low.

Review finding 21: Don't discount the patient experience or their own research

No additional information reported.

Explanation of quality assessment: serious methodological limitations in the contributing study due to method of recruitment (recruited from charities and social media), unclear relationship between the researcher and participants, lack of information on the analysis strategy and insufficient data to support the finding. Partial relevance due to inclusion of all causes of B12 deficiency. Serious concerns regarding adequacy due to the finding coming from a single study with a small number of participants included and no data to support the finding. Overall assessment of confidence was very low.

Review finding 22: Recognize that health-care professionals can't know everything about every condition

No additional information reported.

Explanation of quality assessment: serious methodological limitations in the contributing study due to method of recruitment (recruited from charities and social media), unclear relationship between the researcher and participants, lack of information on the analysis strategy and insufficient data to support the finding. Partial relevance due to inclusion of all causes of B12 deficiency. Serious concerns regarding adequacy due to the finding coming from a single study with a small number of participants included and no data to support the finding. Overall assessment of confidence was very low.

Review finding: 23 Educate all health-care professionals about B12 deficiency and blood tests

No additional information reported.

Explanation of quality assessment: serious methodological limitations in the contributing study due to method of recruitment (recruited from charities and social media), unclear relationship between the researcher and participants, lack of information on the analysis strategy and insufficient data to support the finding. Partial relevance due to inclusion of all causes of B12 deficiency. Serious concerns regarding adequacy due to the finding coming from a single study with a small number of participants included and no data to support the finding. Overall assessment of confidence was very low.

Review finding 24: Awareness that the UK blood test range is very low (compared to other countries)

No additional information reported.

Explanation of quality assessment: serious methodological limitations in the contributing study due to method of recruitment (recruited from charities and social media), unclear relationship between the researcher and participants, lack of information on the analysis strategy and insufficient data to support the finding. Partial relevance due to inclusion of all causes of B12 deficiency. Serious concerns regarding adequacy due to the finding coming from a single study with a small number of participants included and no data to support the finding. Overall assessment of confidence was very low.

See Appendix E for full GRADE CerQUAL tables.

1.2.6 Economic evidence

The committee agreed that health economic studies would not be relevant to this review question, and so were not sought.

1.3 The committee's discussion and interpretation of the evidence

1.3.1 The quality of the evidence

Evidence reporting patient perspectives and experiences of the diagnostic and therapeutic journey in vitamin B12 deficiency was identified from two studies. One study included a direct population, in participants with a diagnosis of pernicious anaemia. All three themes were graded as low-quality evidence. This evidence was downgraded due to methodological limitations because of the targeted recruitment of patients from charities and social media support groups and an unclear relationship between the researcher and the participants. The evidence was also downgraded due to concerns regarding adequacy, as the findings were based on an individual study with a small number of participants.

The other study provided indirect evidence, including patient safety issues/priorities and patient messages to healthcare professionals from participants with all causes of vitamin B12 deficiency. All themes identified in this study were graded as very low quality. Serious methodological limitations were identified due to the targeted recruitment of patients from charities and social media support groups, the unclear relationship between the researcher and participants, lack of information on the analysis strategy and insufficient data to support the findings. Evidence was further downgraded due to the indirectness of the population and due to moderate-serious concerns arising from the adequacy of the data, with a small number of participants included and a small amount of additional supportive text in the paper.

No evidence was identified for pregnant women and pregnant people with suspected or confirmed vitamin B12 deficiency. No evidence was identified on the information and support needs of families and carers of people with vitamin B12 deficiency.

1.3.2 Findings identified in the evidence synthesis

Direct evidence in people with pernicious anaemia identified three major themes from semi-structured interviews. These themes were the struggle to achieve a diagnosis, the significance of a diagnosis, and seeking sufficient treatment.

Indirect evidence in people with all causes of vitamin B12 deficiency identified 24 themes via a patient involvement and engagement workshop. The most frequently voted for patient

safety issues and concerns were interpretation of test results and inconsistent test results; necessity of symptom-based treatment – less reliance on tests; and safety of self-medication. The most frequently voted for patient messages to healthcare professionals were listen to patients when they say treatment is too infrequent; necessity for GPs to recognise and understand symptoms; and lack of awareness of the emotional and day-to-day effects of the condition.

The committee acknowledged the limitations of the evidence presented, with the main limitations being the lack of data presented by the studies to support the findings and the recruitment strategies. It was raised that since the participants of the studies were from social media support groups, they were more likely to be people who had negative experiences of the healthcare system, hence them seeking out a support network. This was taken into account when interpreting the findings, although the committee were in agreement that the majority of the themes identified resonated strongly with their personal experiences of vitamin B12 deficiency.

The overarching theme arising from the themes identified in the included studies was that there is a dissatisfaction with the current process of diagnosing and treating vitamin B12 deficiency. The majority of the themes related to concerns around the diagnostic process used, that being the time taken to receive a diagnosis and the over reliance on objective tests. The committee acknowledged that a lack of awareness of vitamin B12 deficiency is one potential contributor to this. Additionally, it was reiterated that the diagnostic tests currently available for diagnosing vitamin B12 deficiency are subject to limitations. The committee also agreed that given the limitations of vitamin B12 biomarkers, practitioners should take patients symptoms into consideration when making clinical decisions whilst being aware that symptoms of vitamin B12 deficiency can be highly variable.

The committee were mindful of other NICE guidelines on patient experience in adult NHS services, shared decision making, and decision-making and mental capacity. These guidelines include recommendations on knowing the patient as an individual, essential requirements of care, enabling patients to actively participate in their care, putting shared decision making into practice and decision-making with people with cognitive impairment. It was agreed that these apply to vitamin B12 deficiency and should not be repeated in this guideline. Instead, the committee focussed on recommendations specific to vitamin B12 deficiency.

The committee hoped that this guideline will raise awareness of the symptoms and signs of vitamin B12 deficiency among practitioners, leading to cases being identified and referred for testing more quickly. The committee also discussed what information around symptoms and signs would be helpful to give to people with suspected or confirmed deficiency. The committee considered that some symptoms and signs of vitamin B12 deficiency are common, may not affect daily living in isolation and can overlap with other conditions and therefore the person may not attribute them to their deficiency. For people with suspected deficiency, the committee agreed they should be made aware that it can be difficult to find a specific medical cause for some symptoms such as fatigue. The committee agreed that it was important to highlight the variability in presentation and causes of vitamin B12 deficiency so that people with confirmed deficiency are aware of the possible symptoms and signs that they may experience and the degree to which they may be experienced.

Given the limitations of the diagnostic tests, the committee agreed that when vitamin B12 deficiency is suspected, these should be discussed with the person in the context of how it may affect them. The committee were mindful that for most people, B12 testing is useful in achieving a diagnosis and the person should not be made to feel worried or untrusting of the tests. The main points to highlight were considered to be the possibility of the need for additional tests in the case of indeterminate results, and the difficulty in interpreting results in people already taking B12 supplements.

Regarding vitamin B12 replacement, the committee agreed people with confirmed deficiency should be made aware that treatment is effective for most people, but the dose, frequency and route of administration may need to be adjusted to achieve optimal vitamin B12 concentrations and symptom control. For people with causes of deficiency that are irreversible, such as autoimmune gastritis, major gastric resection, bypass (including bariatric procedures) or terminal ileal resection, the committee considered that they should be informed that they will require lifelong treatment to maintain B12 concentrations and symptom control. The committee agreed this is important because it may give the person reassurance that their medicine will not be stopped in the future.

Based on the advice of an expert witness, the committee made a recommendation to explain to pregnant women and pregnant people with vitamin B12 deficiency that the use of nitrous oxide with air (gas and air) during labour is unlikely to make their vitamin B12 deficiency worse. The committee agreed that providing this information would offer reassurance if the person had any concerns.

The committee considered whether a research recommendation would be useful, particularly given the lack of evidence identified for people with vitamin B12 deficiency caused by diet, women and people who are pregnant and breastfeeding and families and carers of people with vitamin B12 deficiency. The committee agreed that although more research would be helpful, there were other areas of higher priority identified for research within the guideline.

1.3.3 Cost effectiveness and resource use

Cost effectiveness evidence was not sought as this is a qualitative review question.

The committee made recommendations about information to give to patients. This is not expected to have a significant resource impact.

1.3.4 Recommendations supported by this evidence review

This evidence review supports recommendations 1.1.1-1.1.4. No research recommendations were made for this topic.

1.4 References

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Appendices

Appendix A – Review protocols

A.1 Review protocol for information and support for people with suspected or confirmed vitamin B12 deficiency caused by a lack of vitamin B12 in their diet

Field	Content
PROSPERO registration number	CRD42022380381
Review title	What information and support is needed by people with suspected or confirmed vitamin B12 deficiency caused by a lack of vitamin B12 in their diet, and their families or carers?
Review question	What information and support is needed by people with suspected or confirmed vitamin B12 deficiency caused by a lack of vitamin B12 in their diet, and their families or carers?
Objective	To identify what information and support is needed by people with suspected or confirmed vitamin B12 deficiency caused by a lack of vitamin B12 in their diet, and their families or carers.
Searches	The following databases (from inception) will be searched: • Embase • MEDLINE • PsychINFO • CINAHL

	Searches will be restricted by: • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews 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).
Condition or domain being studied	Vitamin B12 deficiency caused by a lack of dietary vitamin B12.
Population	Inclusion: adults with suspected or confirmed vitamin B12 deficiency caused by a lack of vitamin B12 in their diet, and their families or carers. Strata: • Pregnancy (Mixed population studies will be included in a mixed population stratum but will be downgraded for indirectness. A minimum cut-off of 70% will be used for a study population to fall into a stratum.)

	Exclusion: people with suspected or confirmed vitamin B12 deficiency due to non-dietary causes.
Phenomena of interest	Perceptions and experiences of people with suspected or confirmed vitamin B12 deficiency caused by a lack of vitamin B12 in their diet, and their families or carers, regarding the information, education and support they find most useful.
Comparator/Reference standard/Confounding factors	Not applicable
Types of study to be included	Inclusion: Qualitative studies (e.g., transcript data collected from focus groups / semi structured interviews) Mixed methods studies that include qualitative methods (qualitative data only will be extracted) Exclusion: Quantitative studies (i.e., closed questionnaire surveys)
Other exclusion criteria	Non-English language studies. Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
Context	Establishing what information and support is useful for people with vitamin B12 deficiency caused by a lack of vitamin B12 in their diet and their families or carers will help health and social care professionals to provide appropriate information and support necessary to improve patient outcomes and quality of life.
Primary outcomes (critical outcomes)	Themes will emerge from the studies and are not predefined.
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).

	Additional qualitative studies will be added to the review until themes within the analysis become saturated; i.e. studies will only be included if they contribute towards the development of existing themes or to the development of new themes. The point at which data saturation is reached will be noted within the review. 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.
Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For qualitative reviews, risk of bias is assessed using the Critical Appraisal Skills Programme (CASP) qualitative checklist.
Strategy for data synthesis	The synthesis of qualitative data will follow a thematic analysis approach. Information will be synthesised into main review findings. Results will be presented in a detailed narrative and in table format with summary statements of main review findings. GRADE CERQual will be used to synthesise the qualitative data and assess the certainty of evidence for each review finding.
Analysis of sub-groups	If suggested by the evidence, themes may be reported separately for: • Age (older adults)

<table>
<tr><td></td><td colspan="3">• Disability (mental health disorders)
• Gender reassignment
• Pregnancy and maternity (unless stratified)
• Race (Black, Asian and Minority Ethnic communities)
• Religion or belief (vegan diets)
• Sex</td></tr>
<tr><td rowspan="8">Type and method of review</td><td colspan="2">☐</td><td>Intervention</td></tr>
<tr><td colspan="2">☐</td><td>Diagnostic</td></tr>
<tr><td colspan="2">☐</td><td>Prognostic</td></tr>
<tr><td colspan="2">☒</td><td>Qualitative</td></tr>
<tr><td colspan="2">☐</td><td>Epidemiologic</td></tr>
<tr><td colspan="2">☐</td><td>Service Delivery</td></tr>
<tr><td colspan="2">☐</td><td>Other (please specify)</td></tr>
<tr><td></td><td colspan="3"></td></tr>
<tr><td>Language</td><td colspan="3">English</td></tr>
<tr><td>Country</td><td colspan="3">England</td></tr>
<tr><td>Anticipated or actual start date</td><td colspan="3">02/11/2022</td></tr>
<tr><td>Anticipated completion date</td><td colspan="3">01/11/2023</td></tr>
<tr><td rowspan="3">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>
</table>

	Formal screening of search results against eligibility criteria		
	Data extraction		
	Risk of bias (quality) assessment		
	Data analysis		
Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail PerniciousAnaemia@nice.nhs.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre		
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]		
Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.		

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.	
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	
Other registration details		
Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022380381	
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.	
Keywords		
Details of existing review of same topic by same authors		
Current review status		Ongoing
		Completed but not published

		Completed and published
		Completed, published and being updated
		Discontinued
Additional information		
Details of final publication	www.nice.org.uk	

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A.2 Review protocol for information and support for people with non-dietary vitamin B12 deficiency

2
3

ID	Field	Content
0.	PROSPERO registration number	CRD42022380390
1.	Review title	What information and support is needed by people with suspected or confirmed vitamin B12 deficiency caused by inadequate absorption of vitamin B12 (including pernicious anaemia), and their families or carers, and when should this be provided?
2.	Review question	What information and support is needed by people with suspected or confirmed vitamin B12 deficiency caused by inadequate absorption of vitamin B12 (including pernicious anaemia), and their families or carers, and when should this be provided?
3.	Objective	To identify what information and support is needed by people with suspected or confirmed vitamin B12 deficiency caused by inadequate absorption of vitamin B12 (including pernicious anaemia), and their families or carers, and when this should be provided.
4.	Searches	The following databases (from inception) will be searched: • Embase • MEDLINE

		• PsychINFO • CINAHL Searches will be restricted by: • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews 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 caused by inadequate absorption of vitamin B12 (including pernicious anaemia).
6.	Population	Inclusion: adults with suspected or confirmed vitamin B12 deficiency caused by inadequate absorption of vitamin B12 (including pernicious anaemia), and their families or carers. Strata:

		• Pregnancy (Mixed population studies will be included in a mixed population stratum but will be downgraded for indirectness. A minimum cut-off of 70% will be used for a study population to fall into a stratum.) Exclusion: people with suspected or confirmed vitamin B12 deficiency due to a lack of dietary vitamin B12.
7.	Phenomena of interest	Perceptions and experiences of people with suspected or confirmed vitamin B12 deficiency caused by inadequate absorption of vitamin B12 (including pernicious anaemia), and their families or carers, regarding the information, education and support they find most useful and the point at which this information and support is most useful.
8.	Comparator/Reference standard/Confounding factors	Not applicable
9.	Types of study to be included	Inclusion: Qualitative studies (e.g., transcript data collected from focus groups / semi structured interviews) Mixed methods studies that include qualitative methods (qualitative data only will be extracted) Exclusion: Quantitative studies (i.e., closed questionnaire surveys)
10.	Other exclusion criteria	Non-English language studies. Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	Establishing what information and support is useful for people with vitamin B12 deficiency caused by inadequate absorption of vitamin B12 (including pernicious anaemia) and their families or carers will help health and social care professionals to provide appropriate information and support necessary to improve patient outcomes and quality of life.
12.	Primary outcomes (critical outcomes)	Themes will emerge from the studies and are not predefined.
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).

		Additional qualitative studies will be added to the review until themes within the analysis become saturated; i.e. studies will only be included if they contribute towards the development of existing themes or to the development of new themes. The point at which data saturation is reached will be noted within the review. 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 qualitative reviews, risk of bias is assessed using the Critical Appraisal Skills Programme (CASP) qualitative checklist.
15.	Strategy for data synthesis	The synthesis of qualitative data will follow a thematic analysis approach. Information will be synthesised into main review findings. Results will be presented in a detailed narrative and in table format with summary statements of main review findings. GRADE CERQual will be used to synthesise the qualitative data and assess the certainty of evidence for each review finding.
16.	Analysis of sub-groups	If suggested by the evidence, themes may be reported separately for: • Age (older adults) • Disability (mental health disorders) • Gender reassignment

		• Pregnancy and maternity (unless stratified) • Race (Black, Asian and Minority Ethnic communities) • Religion or belief (vegan diets) • Sex		
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	02/11/2022		
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 National Guideline Centre 5b Named contact e-mail PerniciousAnaemia@nice.nhs.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre		
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	This systematic review is being completed by the National Guideline Centre which receives funding from 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=CRD42022380390	
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

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Appendix B – Literature search strategies

These literature search strategies were used for the following reviews:

- What information and support is needed by people with suspected or confirmed vitamin B12 deficiency caused by a lack of vitamin B12 in their diet, and their families or carers?
- What information and support is needed by people with suspected or confirmed vitamin B12 deficiency caused by inadequate absorption of vitamin B12 (including pernicious anaemia), and their families or carers, and when should this be provided?

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 for patient views were run in Medline (OVID), Embase (OVID), CINAHL Current Nursing and Allied Health Literature (EBSCO) and PsycINFO (OVID). Search filters were applied to the search where appropriate.

Table 5: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 13 December 2022	Qualitative studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 13 December 2022	Qualitative studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
PsycINFO (OVID)	Inception – 13 December 2022	Qualitative studies Exclusions (animal studies, letters, case reports) Human English language
Current Nursing and Allied Health Literature (CINAHL) (EBSCO)	Inception – 13 December 2022	Exclusions (Medline records) Human

Database	Dates searched	Search filter used
		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.	exp Patients/ or exp Family/ or Caregivers/
29.	Consumer Health Information/ or Needs Assessment/ or Patient Education as Topic/ or Patient Education Handout/ or Health Communication/ or Information Dissemination/
30.	((patient* or inpatient* or outpatient* or carer* or client* or user* or customer* or consumer* or caregiver* or care giver* or famil* or parent* or father* or mother* or spouse* or wife or wives or husband* or next of kin or significant other* or partner* or guardian* or relative* or sibling* or sister* or brother* or grandparent* or grandfather* or grandmother*) adj3 (information* or advice or advis* or need* or requirement* or support* or access* or service* or educat* or learn* or teach* or train*)).ti,ab,kf.
31.	((information* or educat*) adj3 (need* or requirement* or support* or seek* or access* or disseminat* or barrier* or service*)).ti,ab,kf.
32.	(support* adj3 (need* or requirement* or assess* or seek* or access* or barrier* or service*)).ti,ab,kf.
33.	"Patient Acceptance of Health Care"/ or exp Patient Satisfaction/

34.	((patient* or inpatient* or outpatient* or carer* or client* or user* or customer* or consumer* or caregiver* or care giver* or famil* or parent* or father* or mother* or spouse* or wife or wives or husband* or next of kin or significant other* or partner* or guardian* or relative* or sibling* or sister* or brother* or grandparent* or grandfather* or grandmother*) adj3 (belief* or attitud* or priorit* or perception* or preferen* or expectation* or choice* or perspective* or view* or satisfact* or experience* or opinion* or preference* or feedback*)).ti,ab,kf.
35.	or/28-34
36.	27 and 35
37.	Qualitative research/ or Narration/ or exp Interviews as Topic/ or exp "Surveys and Questionnaires"/ or Health care surveys/
38.	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
39.	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*).ti,ab.
40.	or/37-39
41.	27 and 40
42.	36 or 41

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 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.	patient/ or family/ or caregivers/
28.	consumer health information/ or needs assessment/ or communication barrier/ or patient education/ or medical information/ or information dissemination/
29.	((patient* or inpatient* or outpatient* or carer* or client* or user* or customer* or consumer* or caregiver* or care giver* or famil* or parent* or father* or mother* or spouse* or wife or wives or husband* or next of kin or significant other* or partner* or guardian* or relative* or sibling* or sister* or brother* or grandparent* or grandfather* or grandmother*) adj3 (information* or advice or advis* or need* or requirement* or support* or access* or service* or educat* or learn* or teach* or train*)).ti,ab,kf.
30.	((information* or educat*) adj3 (need* or requirement* or support* or seek* or access* or disseminat* or barrier* or service*)).ti,ab,kf.
31.	(support* adj3 (need* or requirement* or assess* or seek* or access* or barrier* or service*)).ti,ab,kf.
32.	patient preference/ or patient satisfaction/ or consumer attitude/ or patient attitude/
33.	((patient* or inpatient* or outpatient* or carer* or client* or user* or customer* or consumer* or caregiver* or care giver* or famil* or parent* or father* or mother* or spouse* or wife or wives or husband* or next of kin or significant other* or partner* or guardian* or relative* or sibling* or sister* or brother* or grandparent* or grandfather* or grandmother*) adj3 (belief* or attitud* or priorit* or perception* or preferen* or expectation* or choice* or perspective* or view* or satisfact* or experience* or opinion* or preference* or feedback*)).ti,ab,kf.
34.	or/27-33
35.	26 and 34
36.	health survey/ or exp questionnaire/ or exp interview/ or qualitative research/ or narrative/
37.	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
38.	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*).ti,ab.
39.	or/36-38
40.	26 and 39
41.	35 or 40

1 **PsycINFO (OVID) search terms**

1.	exp vitamin deficiency disorders/
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.	anemia/
4.	((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) adj3 (anemia* or anaemia*)).ti,ab.
5.	intrinsic factor.ti,ab.
6.	or/1-5
7.	Letter/
8.	Case report/

9.	exp Rodents/
10.	or/7-9
11.	6 not 10
12.	limit 11 to (human and English language)
13.	exp Patients/ or Family/ or exp Caregivers/
14.	Health Information/ or exp Needs Assessment/ or Client Education/ or Communication barriers/
15.	((patient* or inpatient* or outpatient* or carer* or client* or user* or customer* or consumer* or caregiver* or care giver* or famil* or parent* or father* or mother* or spouse* or wife or wives or husband* or next of kin or significant other* or partner* or guardian* or relative* or sibling* or sister* or brother* or grandparent* or grandfather* or grandmother*) adj3 (information* or advice or advis* or need* or requirement* or support* or access* or service* or educat* or learn* or teach* or train*)).ti,ab.
16.	((information* or educat*) adj3 (need* or requirement* or support* or seek* or access* or disseminat* or barrier* or service*)).ti,ab.
17.	(support* adj3 (need* or requirement* or assess* or seek* or access* or barrier* or service*)).ti,ab.
18.	Client Satisfaction/ or Client Attitudes/
19.	((patient* or inpatient* or outpatient* or carer* or client* or user* or customer* or consumer* or caregiver* or care giver* or famil* or parent* or father* or mother* or spouse* or wife or wives or husband* or next of kin or significant other* or partner* or guardian* or relative* or sibling* or sister* or brother* or grandparent* or grandfather* or grandmother*) adj3 (belief* or attitud* or priorit* or perception* or preferen* or expectation* or choice* or perspective* or view* or satisfact* or experience* or opinion* or preference* or feedback*)).ti,ab.
20.	or/13-19
21.	12 and 20
22.	qualitative methods/ or exp interviews/ or exp questionnaires/
23.	(qualitative or interview* or focus group* or theme* or questionnaire* or survey*).ti,ab.
24.	(metasynthes* or meta-synthes* or metasummar* or meta-summar* or metastud* or meta-stud* or metathem* or meta-them* or ethno* or emic or etic or phenomenolog* or grounded theory or constant compar* or (thematic* adj3 analys*) or theoretical sampl* or purposive sampl* or hermeneutic* or heidegger* or husserl* or colaizzi* or van kaam* or van manen* or giorgi* or glaser* or strauss* or ricoeur* or spiegelberg* or merleau*).ti,ab.
25.	or/22-24
26.	12 and 25
27.	21 or 26

1 **CINAHL (EBSCO) search terms**

S1.	(MH "Vitamin B12 Deficiency+")
S2.	TI (((b12 or b 12 or cobalamin* or c?anocobalamin* or transcobalamin*) AND (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))) OR AB (((b12 or b 12 or cobalamin* or c?anocobalamin* or transcobalamin*) AND (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)))
S3.	(MH "Anemia, Macrocytic+")

S4.	TI (((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) AND (anemia* or anaemia*))) OR AB (((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) AND (anemia* or anaemia*)))
S5.	TI (intrinsic factor) OR AB (intrinsic factor)
S6.	S1 OR S2 OR S3 OR S4 OR S5
S7.	(MH Patients+) OR (MH Family+) OR (MH Caregivers)
S8.	(MH "Consumer Health Information") OR (MH "Needs Assessment") OR (MH "Patient Education as Topic") OR (MH "Patient Education Handout") OR (MH "Health Communication") OR (MH "Information Dissemination")
S9.	TI (((patient* or inpatient* or outpatient* or carer* or client* or user* or customer* or consumer* or caregiver* or care giver* or famil* or parent* or father* or mother* or spouse* or wife or wives or husband* or next of kin or significant other* or partner* or guardian* or relative* or sibling* or sister* or brother* or grandparent* or grandfather* or grandmother*) AND (information* or advice or advis* or need* or requirement* or support* or access* or service* or educat* or learn* or teach* or train*))) OR AB (((patient* or inpatient* or outpatient* or carer* or client* or user* or customer* or consumer* or caregiver* or care giver* or famil* or parent* or father* or mother* or spouse* or wife or wives or husband* or next of kin or significant other* or partner* or guardian* or relative* or sibling* or sister* or brother* or grandparent* or grandfather* or grandmother*) AND (information* or advice or advis* or need* or requirement* or support* or access* or service* or educat* or learn* or teach* or train*)))
S10.	TI (((information* or educat*) AND (need* or requirement* or support* or seek* or access* or disseminat* or barrier* or service*))) OR AB (((information* or educat*) AND (need* or requirement* or support* or seek* or access* or disseminat* or barrier* or service*)))
S11.	TI ((support* AND (need* or requirement* or assess* or seek* or access* or barrier* or service*))) OR AB ((support* AND (need* or requirement* or assess* or seek* or access* or barrier* or service*)))
S12.	(MH "Patient Satisfaction+")
S13.	TI (((patient* or inpatient* or outpatient* or carer* or client* or user* or customer* or consumer* or caregiver* or care giver* or famil* or parent* or father* or mother* or spouse* or wife or wives or husband* or next of kin or significant other* or partner* or guardian* or relative* or sibling* or sister* or brother* or grandparent* or grandfather* or grandmother*) AND (belief* or attitud* or priorit* or perception* or preferen* or expectation* or choice* or perspective* or view* or satisfact* or experience* or opinion* or preference* or feedback*))) OR AB (((patient* or inpatient* or outpatient* or carer* or client* or user* or customer* or consumer* or caregiver* or care giver* or famil* or parent* or father* or mother* or spouse* or wife or wives or husband* or next of kin or significant other* or partner* or guardian* or relative* or sibling* or sister* or brother* or grandparent* or grandfather* or grandmother*) AND (belief* or attitud* or priorit* or perception* or preferen* or expectation* or choice* or perspective* or view* or satisfact* or experience* or opinion* or preference* or feedback*)))
S14.	S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13
S15.	S6 AND S14

1

Appendix C – Qualitative evidence study selection

Figure 1: Flow chart of qualitative study selection for the review of information and support for people with suspected or confirmed vitamin B12 deficiency caused by a lack of vitamin B12 in their diet

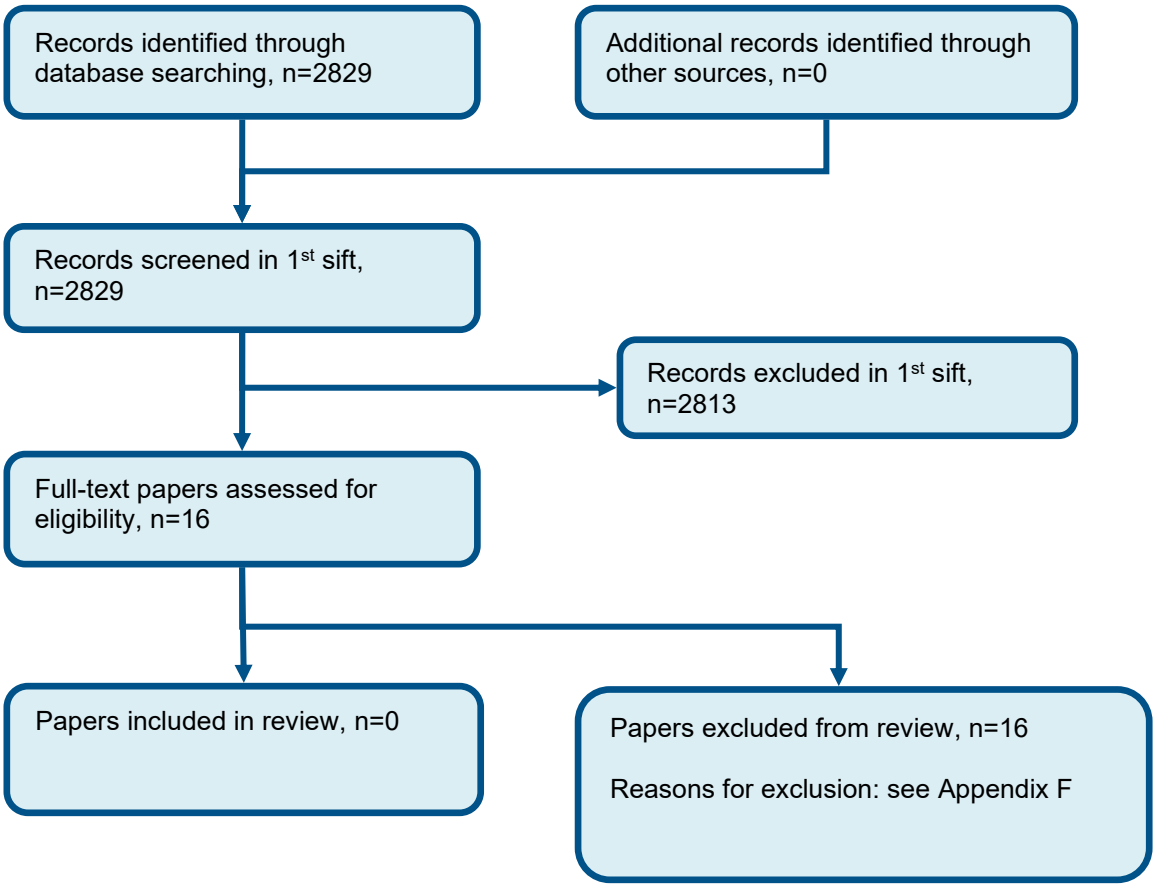
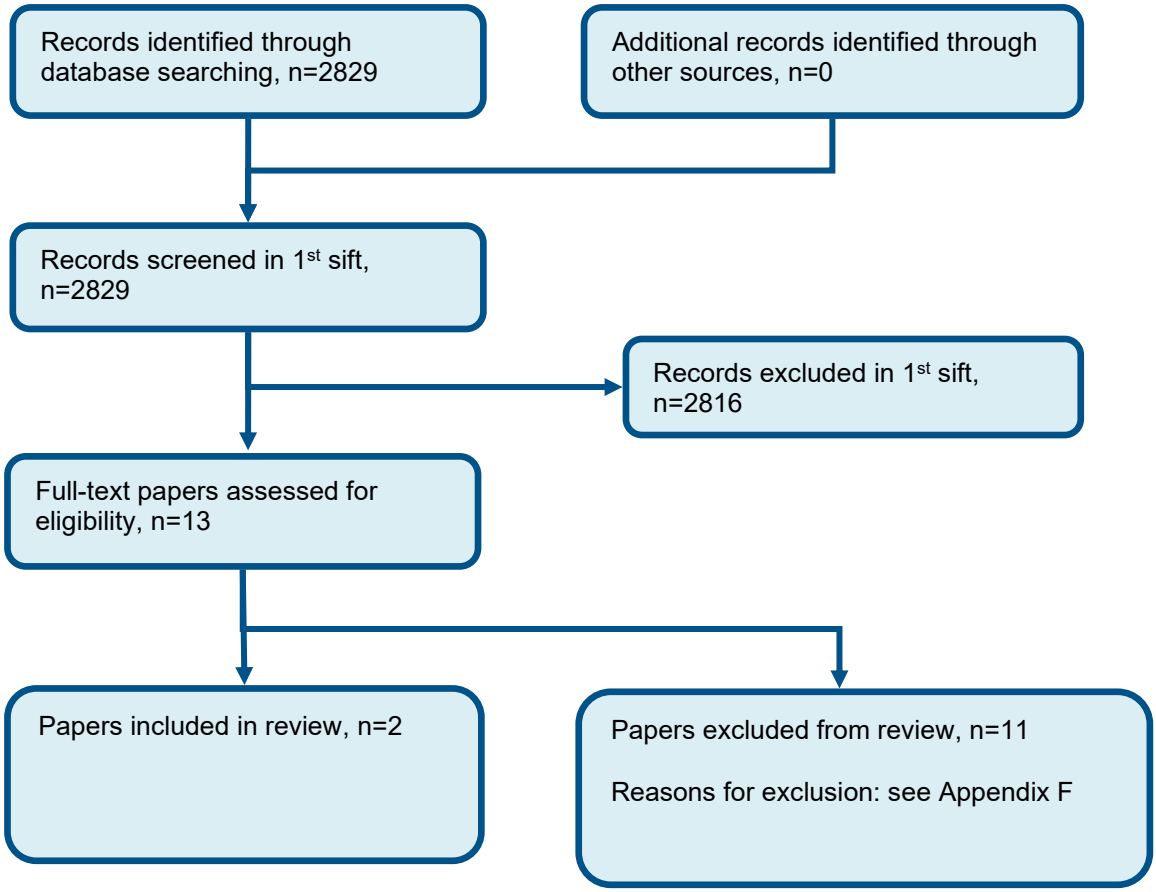


Figure 2: Flow chart of qualitative study selection for the review of information and support for people with non-dietary vitamin B12 deficiency



Appendix D – Qualitative evidence

D.1 Information and support for people with suspected or confirmed vitamin B12 deficiency caused by a lack of vitamin B12 in their diet

No evidence identified.

D.2 Information and support for people with non-dietary vitamin B12 deficiency

Study	Seage 2020[2]
Aim	Paper title: Receiving a Diagnosis of Pernicious Anaemia: Exploring Experiences of Relationships with Health Professionals Capture the lived experience individuals who have received a diagnosis of PA.
Population	Eligible participants were aged between 18 and 75 years and English speaking with a formal diagnosis of PA. Eleven participants were recruited from an advert hosted on the Pernicious Anaemia Society's website and social media page. The demographics of this group represent the varied backgrounds of those with PA. N= 11 Male/female 1:10 Age, mean (SD): 49.36 (9.50) years Years since PA diagnosis, mean (SD): 6.95 (5.23)
Setting	People with a diagnosis of PA
Study design	Semi-structured interviews
Methods and analysis	Semi-structured interviews explored participant's experience of diagnosis and treatment. Interview durations ranged from 27 to 65 minutes. All interviews were audio-recorded and transcribed verbatim. Transcripts were analysed using IPA. The IPA concerns itself

Study	Seage 2020[2]
	with entering the life world of the participant regarding their social and personal perspectives and experiences through the comprehensive analysis of an individual's accounts. As such, it is idiographic in nature and deals with small sample sizes. During analysis, clusters of themes were developed and then analysed in relation to all transcripts. Clusters of themes were developed and then analysed in relation to all transcripts. Recurrence of themes was determined if they appeared in at least half of other transcripts and if so, superordinate themes were constructed. Three superordinate themes were identified.
Findings	**The Struggle to Achieve a Diagnosis** All participants expressed dissatisfaction with their diagnostic journey; this lengthy process was characterized by a deterioration in physical and psychological health. The challenge of gaining diagnosis resulted in strained relationships with health professionals. On the onset of the condition, it was common for PA symptoms to be attributed to other causes such as lifestyle. There was also experience of misdiagnosis; 5 participants reported that they had received an initial diagnosis of depression. Patients were frequently told that their symptoms were "in their head." This suggestion that symptoms were psychosomatic was often viewed as a judgement of sanity. Madison described the necessity of writing a list of her symptoms to legitimize her experience to her doctor. Many interviewed stated that disbelief of symptom severity had led to a series of visits to health-care providers and in some cases caused the patient to begin to question their own illness experience. All participants described lengthy diagnostic journeys; this was evident even if their symptoms were acknowledged as having a physical cause from the outset. Participants reported being transferred between hospital departments and meeting with multiple clinicians due to a struggle to find medical professionals who were able to make sense of their symptoms.
	The Significance of a Diagnosis Despite the lengthy diagnostic journey, all participants valued receiving the diagnosis of PA. Diagnosis prompted them to adapt and "move on" with their health, having a label for their symptoms legitimized the illness to themselves and others. Despite the personal significance of diagnosis, many patients felt that they had insufficient information to adequately understand PA. Recognition that PA had an impact on daily life was important in developing supportive and meaningful relationships. However, all participants encountered at least one health professional who placed low or no significance on the impact of PA. This trivialization had a negative impact on the patient–health professional relationship. Many patients felt abandoned, and this struggle to be taken seriously lead to a loss of faith in the health-care system. Post-diagnosis, there was a decreased reliance on health professionals with individuals beginning to seek alternative sources of health information. For some, this was a consequence of the negative experiences in primary care. Charities such as PAS and social media support groups were a popular source of alternative support.
	Seeking Sufficient Treatment Each participant reported their current PA treatment was insufficient. A need for replacement B12 was evident through a "lull" toward the end of their treatment cycle, where symptoms would return. Florence described her experience during her 12-week treatment cycle: Health professionals' adherence to British National Formulary treatment guidelines for PA was a cause of grievance. Nine participants described how strict adherence to guidelines had a negative impact on their treatment.

Study	Seage 2020[2]
	Participants claiming treatment insufficiency were often viewed as obsessing over their condition, scrounging for treatment and reported feelings of shame as a result of judgement from their GP. The majority of participants expressed the need for PA treatment be a symptom-led; however, the concept of individual variability was rarely acknowledged within health settings. Most participants expressed desire to collaboratively manage their treatment. When this was not forthcoming from health professionals, they often began to withdraw from this relationship. Self-injection of B12 although outside of current treatment guidelines was common within the sample, with 7 participants engaging in the behaviour. Some participants concealed this self-injecting from their health professionals due to expectations of negative encounters, while others openly disclosed their actions. Many participants turned to self-injection of vitamin B12 as a result of inadequate treatment from their GP. This choice was often treated with disdain by healthcare professionals and led to a breakdown of the relationship between patients and healthcare professionals, with participants expressing fears of negative treatment.
Funding	The author(s) received no financial support for the research, authorship, and/or publication of this article.
Limitations and applicability of evidence	Methodological limitations: Moderate limitations due to selection of participants (recruited from social media and PA society) and due to concerns arising from a lack of consideration of the relationship between the researcher and participants. Applicability: Directly applicable

1

2

Study	Tyler 2021[3]
Aim	Existing evidence highlights a dissatisfaction with current treatment and diagnosis practice and policy in primary care; which is likely to raise quality and safety concerns. This paper reports a patient and public involvement workshop that aimed firstly to understand and consolidate quality and safety for this patient group concerns using numerous verbal and written methods and secondly to assess any additional impact of using visual art as a means of expressing quality and safety concerns.
Population	Participants were contacted and invited to attend the workshop via a regional mailing list from a pernicious anaemia charitable organization, university volunteer newsletters and social media (Facebook support group). Participants were asked to self-identify and email the researcher if they were interested. In order to be included participants must have a diagnosis or be receiving treatment for Vitamin B12 Deficiency or Pernicious Anaemia, there were no restrictions on the causes of B12 deficiency. Twelve participants attended the workshop from a demographically diverse group ranging from teenagers to older adults, multiple ethnicities and both genders were represented. As this was an engagement event and not research demographic data was not collected, and whilst others attended the most highly represented group were Caucasian females aged 25-50. No participants had previous experience of patient and public involvement in vitamin B12 deficiency research.
Setting	A workshop titled ‘B12 Deficiency/Pernicious Anaemia Patient Safety Workshop?’ was held in March 2020. The workshop had four components (a) one-to-one sessions with an artist, using visual art as a means to express experiences of health (b) research/education

Study	Tyler 2021[3]
	priority setting activities in relation to health-care quality and safety (c) comments on research proposals (d) development of a patient and public involvement group for future research.
Study design	Patient and public involvement workshop
Methods and analysis	Participants were informed at the beginning of the workshop that this was a discussion to gather their views on quality and safety, involvement of patients in research. As the workshop aimed to understand quality and safety issues we used many conventional methods for gathering such information in PPIE workshops. This included various discussions: (a) discussions of proposed research, (b) patient safety in B12 deficiency, (c) priorities for health professional education, (d) future research and practice priorities. In terms of priorities for education and patient safety, the discussions were designed to generate the participant's ideas around these topics (rather than to present and discuss existing ideas), the aim was to provide a clean slate for participants to develop their own priorities. Following presentations and discussions on each topic, participants worked in groups of 2-3. Group discussions were facilitated by the host. Following small group discussions, there were opportunities to feedback to the whole group as the facilitator took notes. After two discussions, lists were drawn up that captured the group's key thematic concerns (patient safety priorities and education priorities) followed by two ranking tasks. Participants were each given three stickers and asked to choose the items most important to them (prompts such as 'What would you like future research to address?' 'What would you like health professionals to be educated about/receive training in?' were used to help participants decide. Participants were able to put all stickers on one item or spread them across three.
Findings	**Patient Safety Issues/Priorities** 1. Interpretation of test results and inconsistent test results (8 votes) The primary patient safety priority proposed by patients was the need to improve interpretation of test results and reduce inconsistencies in reference ranges. Participants described national and local inconsistencies whereby initiation (and sometimes frequency) of treatment is dependent on reference ranges of test results set by local test centres instead of a national standard test or reference range 2. The necessity for symptom-based treatment – less reliance on tests (6 votes) General practitioners (GPs)/health-care professionals should overcome this [referring to theme above] by adopting a symptom-based approach. 3. Safety of self-medication (5 votes) Participants stated that they were aware of individuals that chose to self-medicate and felt this was a major safety concern for several reasons and they often did not inform their GPs. Thus, patients might use medication which is not always obtained from secure sources or following validated advice and as a consequence infections/safety complications associated with injection could occur. 4. Lack of trust in GPs and healthcare professionals (5 votes) A lack of trust in health-care professionals was an equally important safety concern [referring to theme above] for this group. 5. GPs variable knowledge about treatments and tests and feelings of disempowerment for patients (3 votes each)

Study	Tyler 2021[3]
	No further detail. 6. Diagnosis: GP reluctance to test further, but safety and treatment benefits associated with PA diagnosis (2 votes) No further detail. 7. Time to diagnosis is too long (2 votes) No further detail. 8. Postcode lottery (2 votes) No further detail. 9. Safety of social media as a source of information, advice and support (1 vote) No further detail. 10. Insufficient information about pre-blood test behaviour (fasting) (0 votes) No further detail. 11. Ineffective testing following treatment commencement (0 votes) No further detail.
	Patient Messages to Healthcare Professionals
	1. Listen to patients when they say treatment is too infrequent (4 votes) Treatment is too infrequent- participants felt that treatment needs to be more frequent and based on symptoms rather that tests. 2. Necessity for General Practitioners to recognize and understand symptoms (4 votes) GPs should better recognize and understand symptoms—participants felt that GPs did not understand their symptoms. 3. Lack of awareness of the emotional and day-to-day effects of the condition (4 votes) Lack of awareness of day-to-day effects of the condition—participants felt that health-care professionals did not understand the scale of the effect of the condition on their quality of life. 4. Include tests for B12 levels in standard blood test (4 votes) Include test for B12 in standard blood test—participants felt that B12 tests should be included in standard blood tests, to identify patients with the condition timely. 5. Listen to patient (don't discount because symptoms are wide ranging, vague and invisible) (3 votes) No further detail. 6. Understand co-morbidity of B12 deficiency and other conditions (IBS, depression, vitamin deficiencies) (3 votes) No further detail. 7. Please take condition seriously (2 votes) No further detail. 8. The effect of social media on patient experience and behaviour (1 vote)

Study	Tyler 2021[3]
	No further detail. 9. Gain greater knowledge of co-factors associated with B12 deficiency (1 vote) No further detail. 10. Don't discount the patient experience or their own research (1 vote) No further detail. 11. Recognize that health-care professionals can't know everything about every condition (0 votes) No further detail. 12. Educate all health-care professionals about B12 deficiency and blood tests (0 votes) No further detail. 13. Awareness that the UK blood test range is very low (compared to other countries) (0 votes) No further detail.
Funding	The project was supported, in part, by The University of Manchester's Faculty of Biology, Medicine and Health's 'Engaging with our Communities' funding. The time of NT, SG, GD-W and MP was funded by the National Institute for Health Research (NIHR) Greater Manchester Patient Safety Translational Research Centre (NIHR Greater Manchester PSTRC).
Limitations and applicability of evidence	Methodological limitations: Serious concerns due to recruitment strategy, unclear relationship between researcher and participants, lack of sufficient data to support the findings Applicability: moderate concerns due to inclusion of all causes of B12 deficiency

1

Appendix E – GRADE-CERQual tables

E.1 Information and support for people with suspected or confirmed vitamin B12 deficiency caused by a lack of vitamin B12 in their diet

Qualitative evidence summary

No evidence identified.

E.2 Information and support for people with non-dietary vitamin B12 deficiency

Qualitative evidence summary

Table 6: Summary of evidence in people with vitamin B12 caused by inadequate absorption of vitamin B12

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
The struggle to achieve a diagnosis					
1	Semi-structured interviews with Interpretative phenomenological analysis	REVIEW FINDING: Participants expressed a dissatisfaction with the time taken to receive a diagnosis and reported that symptoms were frequently dismissed by healthcare professionals.	Limitations	Moderate concerns about methodological limitations[(a)]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Moderate concerns about adequacy[(b)]	
The significance of a diagnosis					
1	Semi-structured intervie	REVIEW FINDING: Participants expressed that they valued their diagnosis as this allowed them to	Limitations	Moderate concerns about methodologic	LOW

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	Design	Finding	Criteria	Rating	Overall assessment of confidence
	ws with Interpretative phenomenological analysis	understand their symptoms and to seek appropriate treatment.		al limitations[(a)]	
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Moderate concerns about adequacy	
Seeking sufficient treatment					
1	Semi-structured interviews with Interpretative phenomenological analysis	REVIEW FINDING: Participants expressed that current treatment is inadequate and too closely adheres to guidelines rather than focussing on the patient and their symptoms.	Limitations	Moderate concerns about methodological limitations[(a)]	LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	No or very minor concerns about relevance	
			Adequacy	Moderate concerns about adequacy[(b)]	

1 [(a)] *One study with moderate limitations; recruitment from charity and social media and unclear relationship*
2 *between the researcher and the participants.*
3 [(b)] *Moderate concerns about adequacy; single study with a small sample size.*

1 **Table 7: Summary of evidence in people with mixed causes of vitamin B12 deficiency**

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Patient safety priorities: interpretation of test results and inconsistent test results					
1	Patient and public involvement and engagement workshop	REVIEW FINDING: The primary patient safety priority proposed by patients was the need to improve interpretation of test results and reduce inconsistencies in reference ranges.	Limitations	Serious concerns about methodological limitations[(a)]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[(b)]	
			Adequacy	Moderate concerns about adequacy[(c)]	
Patient safety priorities: the necessity for symptom-based treatment – less reliance on tests					
1	Patient and public involvement and engagement workshop	REVIEW FINDING: General practitioners (GPs)/health-care professionals should overcome problems with tests by adopting a symptom-based approach.	Limitations	Serious concerns about methodological limitations[(a)]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[(b)]	
			Adequacy	Serious concerns about adequacy[(d)]	
Patient safety priorities: safety of self-medication					
1	Patient and public involvement and	REVIEW FINDING: Self-medication was a major safety concern for several reasons and they often did not inform their GPs.	Limitations	Serious concerns about methodological limitations[(a)]	VERY LOW

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
	engagement workshop		Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[(b)]	
			Adequacy	Moderate concerns about adequacy[(c)]	
Patient safety priorities: lack of trust in GPs and healthcare professionals					
1	Patient and public involvement and engagement workshop	REVIEW FINDING: A lack of trust in health-care professionals was an important safety concern.	Limitations	Serious concerns about methodological limitations[(a)]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[(b)]	
			Adequacy	Serious concerns about adequacy[(d)]	
Patient safety priorities: GPs variable knowledge about treatments and tests and feelings of disempowerment for patients					
1	Patient and public involvement and engagement workshop	REVIEW FINDING: GPs variable knowledge about treatments and tests and feelings of disempowerment for patients	Limitations	Serious concerns about methodological limitations[(a)]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns	

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	Design	Finding	Criteria	Rating	Overall assessment of confidence
				about relevance[(b)]	
			Adequacy	Serious concerns about adequacy[(d)]	
Patient safety priorities: GP reluctance to test further, but safety and treatment benefits associated with PA diagnosis					
1	Patient and public involvement and engagement workshop	REVIEW FINDING: Diagnosis: GP reluctance to test further, but safety and treatment benefits associated with PA diagnosis	Limitations	Serious concerns about methodological limitations[(a)]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[(b)]	
			Adequacy	Serious concerns about adequacy[(d)]	
Patient safety priorities: time to diagnosis is too long					
1	Patient and public involvement and engagement workshop	REVIEW FINDING: Time to diagnosis is too long	Limitations	Serious concerns about methodological limitations[(a)]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[(b)]	
			Adequacy	Serious concerns about adequacy[(d)]	
Patient safety priorities: postcode lottery					

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
1	Patient and public involvement and engagement workshop	REVIEW FINDING: Postcode lottery	Limitations	Serious concerns about methodological limitations[(a)]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[(b)]	
			Adequacy	Serious concerns about adequacy[(d)]	
Patient safety priorities: safety of social media as a source of information, advice and support					
1	Patient and public involvement and engagement workshop	REVIEW FINDING: Safety of social media as a source of information, advice and support	Limitations	Serious concerns about methodological limitations[(a)]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[(b)]	
			Adequacy	Serious concerns about adequacy[(d)]	
Patient safety priorities: insufficient information about pre-blood test behaviour					
1	Patient and public involvement and	REVIEW FINDING: Insufficient information about pre-blood test behaviour	Limitations	Serious concerns about methodological limitations[(a)]	VERY LOW

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	Design	Finding	Criteria	Rating	Overall assessment of confidence
	engagement workshop		Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[(b)]	
			Adequacy	Serious concerns about adequacy[(d)]	
Patient safety priorities: ineffective testing following treatment commencement					
1	Patient and public involvement and engagement workshop	REVIEW FINDING: Ineffective testing following treatment commencement	Limitations	Serious concerns about methodological limitations[(a)]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[(b)]	
			Adequacy	Serious concerns about adequacy[(d)]	
Messages to health-care professionals: listen to patients when they say treatment is too infrequent					
1	Patient and public involvement and engagement workshop	REVIEW FINDING: Treatment needs to be more frequent and based on symptoms rather that tests.	Limitations	Serious concerns about methodological limitations[(a)]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns	

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	Design	Finding	Criteria	Rating	Overall assessment of confidence
				about relevance[(b)]	
			Adequacy	Serious concerns about adequacy[(d)]	
Messages to health-care professionals: necessity for General Practitioners to recognize and understand symptoms					
1	Patient and public involvement and engagement workshop	REVIEW FINDING: GPs should better recognize and understand symptoms—participants felt that GPs did not understand their symptoms.	Limitations	Serious concerns about methodological limitations[(a)]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[(b)]	
			Adequacy	Serious concerns about adequacy[(d)]	
Messages to health-care professionals: lack of awareness of the emotional and day-to-day effects of the condition					
1	Patient and public involvement and engagement workshop	REVIEW FINDING: Participants felt that health-care professionals did not understand the scale of the effect of the condition on their quality of life.	Limitations	Serious concerns about methodological limitations[(a)]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[(b)]	
			Adequacy	Serious concerns about adequacy[(d)]	

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Messages to health-care professionals: include tests for B12 levels in standard blood test					
1	Patient and public involvement and engagement workshop	REVIEW FINDING: B12 tests should be included in standard blood tests, to identify patients with the condition timely.	Limitations	Serious concerns about methodological limitations[(a)]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[(b)]	
			Adequacy	Serious concerns about adequacy[(d)]	
Messages to health-care professionals: listen to patient					
1	Patient and public involvement and engagement workshop	REVIEW FINDING: Don't discount because symptoms are wide ranging, vague and invisible.	Limitations	Serious concerns about methodological limitations[(a)]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[(b)]	
			Adequacy	Serious concerns about adequacy[(d)]	
Messages to health-care professionals: understand co-morbidity of B12 deficiency and other conditions					
1	Patient and public involvement and	REVIEW FINDING: Understand co-morbidity of B12 deficiency and other conditions (IBS, depression, vitamin deficiencies).	Limitations	Serious concerns about methodological limitations[(a)]	VERY LOW

Study design and sample size		Finding	Quality assessment		
Number of studies contributing to the finding	Design		Criteria	Rating	Overall assessment of confidence
	engagement workshop		Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[(b)]	
			Adequacy	Serious concerns about adequacy[(d)]	
Messages to health-care professionals: please take condition seriously					
1	Patient and public involvement and engagement workshop	REVIEW FINDING: Please take condition seriously.	Limitations	Serious concerns about methodological limitations[(a)]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[(b)]	
			Adequacy	Serious concerns about adequacy[(d)]	
Messages to health-care professionals: the effect of social media on patient experience and behaviour					
1	Patient and public involvement and engagement workshop	REVIEW FINDING: The effect of social media on patient experience and behaviour.	Limitations	Serious concerns about methodological limitations[(a)]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns	

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	Design	Finding	Criteria	Rating	Overall assessment of confidence
				about relevance[(b)]	
			Adequacy	Serious concerns about adequacy[(d)]	
Messages to health-care professionals: gain greater knowledge of co-factors associated with B12 deficiency					
1	Patient and public involvement and engagement workshop	REVIEW FINDING: Gain greater knowledge of co-factors associated with B12 deficiency.	Limitations	Serious concerns about methodological limitations[(a)]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[(b)]	
			Adequacy	Serious concerns about adequacy[(d)]	
Messages to health-care professionals: don't discount the patient experience or their own research					
1	Patient and public involvement and engagement workshop	REVIEW FINDING: Don't discount the patient experience or their own research.	Limitations	Serious concerns about methodological limitations[(a)]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[(b)]	
			Adequacy	Serious concerns about adequacy[(d)]	

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	**Design**	**Finding**	**Criteria**	**Rating**	**Overall assessment of confidence**
Messages to health-care professionals: recognize that health-care professionals can't know everything about every condition					
1	Patient and public involvement and engagement workshop	REVIEW FINDING: Recognize that health-care professionals can't know everything about every condition.	Limitations	Serious concerns about methodological limitations[(a)]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[(b)]	
			Adequacy	Serious concerns about adequacy[(d)]	
Messages to health-care professionals: educate all health-care professionals about B12 deficiency and blood tests					
1	Patient and public involvement and engagement workshop	REVIEW FINDING: Educate all health-care professionals about B12 deficiency and blood tests.	Limitations	Serious concerns about methodological limitations[(a)]	VERY LOW
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[(b)]	
			Adequacy	Serious concerns about adequacy[(d)]	
Messages to health-care professionals: awareness that the UK blood test range is very low (compared to other countries)					
1	Patient and public involve	REVIEW FINDING: Awareness that the UK blood test range is very low (compared to other countries).	Limitations	Serious concerns about methodologic	VERY LOW

Study design and sample size			Quality assessment		
Number of studies contributing to the finding	Design	Finding	Criteria	Rating	Overall assessment of confidence
	ment and engagement workshop			al limitations[(a)]	
			Coherence	No or very minor concerns about coherence	
			Relevance	Moderate concerns about relevance[(b)]	
			Adequacy	Serious concerns about adequacy[(d)]	

(a) One study with serious limitations; recruitment from charity and social media, unclear relationship between researcher and participants, lack of information on analysis strategy or sufficient data to support the findings
(b) One study with moderate concerns about relevance; included all causes of vitamin B12 deficiency
(c) One study with moderate concerns about adequacy; insufficient data presented to support the finding
(d) One study with serious concerns about adequacy; no data presented to support the finding and small sample size

Appendix F – Excluded studies

F.1 Information and support for people with suspected or confirmed vitamin B12 deficiency caused by a lack of vitamin B12 in their diet

Clinical studies

Table 8: Studies excluded from the qualitative review

Study	Code [Reason]
Al Mufarej, S., Alharshan, R., Alismail, A. et al. (2019) Awareness of the importance and deficiency of vitamin B12 among Saudi population. International Journal of Pharmaceutical Research and Allied Sciences 8(4): 187-191	- Population not relevant to this review protocol
Aravena, Javiera, Zubarew, Tamara, Bedregal, Paula et al. (2020) Vegetarian diets in first year university students. Revista chilena de pediatria 91(5): 705-710	- Population not relevant to this review protocol

Study	Code [Reason]
Arazo-Rusindo, M.C., Zuniga, R.N., Cortes-Segovia, P. et al. (2022) Nutritional status and serum levels of micronutrients in an elderly group who participate in the program for complementary food in older people (PACAM) from the metropolitan region, Santiago de Chile. Nutrients 14(1): 3	- Study design not relevant to this review protocol
Argyrakopoulou, G., Konstantinidou, S.K., Dalamaga, M. et al. (2022) Nutritional Deficiencies Before and After Bariatric Surgery: Prevention and Treatment. Current Nutrition Reports 11(2): 95-101	- Study design not relevant to this review protocol
Austin, K.; Bonnes, S.; Daniel, H. (2019) Controversy in Nutrition Recommendations for Short Bowel Syndrome: How Type of SBS Impacts Response. Current Gastroenterology Reports 21(12): 64	- Study design not relevant to this review protocol
Carmel, Ralph (2008) How I treat cobalamin (vitamin B12) deficiency. Blood 112(6): 2214-21	- Study design not relevant to this review protocol
Cordero, Jose F; Do, Ann; Berry, R J (2008) Review of interventions for the prevention and control of folate and vitamin B12 deficiencies. Food and nutrition bulletin 29(2suppl): 188-95	- Study design not relevant to this review protocol
Hooper, Martyn, Hudson, Peter, Porter, Fiona et al. (2014) Patient journeys: diagnosis and treatment of pernicious anaemia. British journal of nursing (Mark Allen Publishing) 23(7): 376-81	- Study design not relevant to this review protocol
Kwong, Jeff C, Carr, David, Dhalla, Irfan A et al. (2005) Oral vitamin B12 therapy in the primary care setting: a qualitative and quantitative study of patient perspectives. BMC family practice 6(1): 8	- No relevant themes identified
Lander, Rebecca L., Hambidge, K. Michael, Westcott, Jamie E. et al. (2019) Pregnant Women in Four Low-Middle Income Countries Have a High Prevalence of Inadequate Dietary Intakes That Are Improved by Dietary Diversity. Nutrients 11(7): 1560-1560	- Study design not relevant to this review protocol
Ortet-Walker, Ariadna; Ponsford, Ayla; McIntosh, Bryan (2019) Communicating with patients using a new vitamin B12 deficiency leaflet. British journal of nursing (Mark Allen Publishing) 28(22): 1450-1454	- Study design not relevant to this review protocol

Study	Code [Reason]
Rivera, Juan A, Sotres-Alvarez, Daniela, Habicht, Jean-Pierre et al. (2004) Impact of the Mexican Program for Education, Health, and Nutrition (Progresa) on Rates of Growth and Anemia in Infants and Young Children: A Randomized Effectiveness Study. JAMA: Journal of the American Medical Association 291(21): 2563-2570	- Study design not relevant to this review protocol
Seage, Catherine Heidi (2018) Living with pernicious anaemia: exploring the link between anticipated stigma and wellbeing. Journal of Psychosomatic Research 113: 72-73	- Not a peer-reviewed publication
Seage, Catherine Heidi; Glover, Emily; Mercer, Jenny (2020) Receiving a Diagnosis of Pernicious Anemia: Exploring Experiences of Relationships With Health Professionals. Journal of patient experience 7(5): 766-770	- Study includes people with non-dietary vitamin B12 deficiency
Seage, Catherine Heidi and Semedo, Lenira (2021) How Do Patients Receiving Prescribed B12 Injections for the Treatment of PA Perceive Changes in Treatment During the COVID-19 Pandemic? A UK-Based Survey Study. Journal of patient experience 8: 2374373521998842	- No relevant themes identified
Tyler, Natasha, Giles, Sally, Daker-White, Gavin et al. (2021) A patient and public involvement workshop using visual art and priority setting to provide patients with a voice to describe quality and safety concerns: Vitamin B12 deficiency and pernicious anaemia. Health expectations : an international journal of public participation in health care and health policy 24(1): 87-94	- Study includes people with non-dietary vitamin B12 deficiency

F.2 Information and support for people with non-dietary vitamin B12 deficiency

Table 9: Studies excluded from the qualitative review

Study	Code [Reason]
Anonymous (2003) Information from your family doctor. Vitamin B12. American family physician 67(5): 993-4	- Not a peer-reviewed publication

Study	Code [Reason]
Hooper, Martyn, Hudson, Peter, Porter, Fiona et al. (2014) Patient journeys: diagnosis and treatment of pernicious anaemia. British journal of nursing (Mark Allen Publishing) 23(7): 376-81	- Study design not relevant to this review protocol
Kernich, Catherine A (2006) Patient and family fact sheet. Vitamin B12 deficiency and the nervous system. The neurologist 12(3): 169-70	- Full text paper not available
Kwong, Jeff C, Carr, David, Dhalla, Irfan A et al. (2005) Oral vitamin B12 therapy in the primary care setting: a qualitative and quantitative study of patient perspectives. BMC family practice 6(1): 8	- No relevant themes identified
MacDONALD, JANE (2016) B12 supplementation: Making the switch. Canadian Nurse 112(6): 32-33	- Not a peer-reviewed publication
Ortet-Walker, Ariadna; Ponsford, Ayla; McIntosh, Bryan (2019) Communicating with patients using a new vitamin B12 deficiency leaflet. British journal of nursing (Mark Allen Publishing) 28(22): 1450-1454	- Study design not relevant to this review protocol
Seage, Catherine Heidi (2018) Living with pernicious anaemia: exploring the link between anticipated stigma and wellbeing. Journal of Psychosomatic Research 113: 72-73	- Study design not relevant to this review protocol
Seage, Catherine Heidi and Semedo, Lenira (2021) How Do Patients Receiving Prescribed B12 Injections for the Treatment of PA Perceive Changes in Treatment During the COVID-19 Pandemic? A UK-Based Survey Study. Journal of patient experience 8: 2374373521998842	- No relevant themes identified
Staley, Kristina, Ahmadi, Kourosh R, Carter, Karyl et al. (2022) Research priorities in pernicious anaemia: James Lind Alliance Priority Setting Partnership. BMJ open 12(8): e065166	- No relevant themes identified
Sukumar, Nithya and Saravanan, Ponnusamy (2019) Investigating vitamin B12 deficiency. BMJ (Clinical research ed.) 365: l1865	- Study design not relevant to this review protocol
Tyler, Natasha, Hodkinson, Alexander, Ahlam, Naeem et al. (2022) Patient safety, self-injection, and B12 deficiency: a UK cross-sectional survey. The British journal of general	- Study design not relevant to this review protocol

Study	Code [Reason]
practice : the journal of the Royal College of General Practitioners 72(725): e891-e898	