Vitamin B12 deficiency in over 16s: diagnosis and management

Consultation on draft guideline - Stakeholder comments table
11/07/2023 – 22/08/2023

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ID	Stakeholder	Document	Page No	Line No	Comments	Developer's response
1	1lub-12 UK	Guideline	006	011 – 012	Rec 1.2.3.- Suggest adding to statement "do not rule out a diagnosis … on the absence of anaemia or macrocytosis **or on normal plasma B12 concentrations**".	Thank you for your comment. This recommendation is to help ensure vitamin B12 deficiency is not missed in people who do not have anaemia or macrocytosis. They agreed that there is a common misconception that you cannot have a deficiency without either, or both, of these signs being present. Regarding your point about normal plasma B12 concentrations, a statement has been added to the rationale for the initial test recommendations noting that there is currently no 'gold standard' test for diagnosing vitamin B12 deficiency. This means that while tests can be a diagnostic aid, they cannot be relied on completely to confirm or rule out deficiency. It is also covered indirectly by the recommendations for an indeterminate test result where further testing is recommended.
2	1lub-12 UK	Guideline	010	008	Rec 1.3.8 – Suggest that a sentence is added stating: Reference intervals and cut off limits are method dependent, thus locale values should be employed.	Thank you for your comment. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline however, 1 does not. Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used.
3	1lub-12 UK	Guideline	010	009 – 016	Rec 1.3.8 to 1.3.9- It is unclear in this recommendation whether it is suggested to	Thank you for your comment. We have updated the recommendation to advise using the thresholds to guide

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					take blood concentrations below the indicated threshold as a sufficient criterion for diagnosing vitamin B12 deficiency. In this section on confirmed deficiency, nothing is mentioned on the necessity of the presence of one or more clinical signs and symptoms. It is not clear why the need for a higher threshold for holoTC is extrapolated from pregnancy to breastfeeding time. Indeed, holoTC is physiologically lowered during late pregnancy ONLY, not during the whole pregnancy.	diagnosis. The assumption is that most people would have to have had a sign or symptom to have been tested. Following stakeholder comments the committee agree that there is no need for a higher threshold during pregnancy or breastfeeding and have removed the recommendation from the guideline.
4	2lub-12 UK	Guideline	010	015	Rec 1.3.9 – Suggest adding that folate deficiency also increases homocysteine and should be considered.	Thank you for your comment. We have updated this to make it more specific. The recommendation now states 'Use laboratory reference ranges to interpret plasma homocysteine test results when deciding if vitamin B12 deficiency is likely, but take into account additional factors that may increase plasma homocysteine levels (such as folate deficiency).'
5	2lub-12 UK	Guideline	010	015 - 016	Rec 1.3.9 – Suggest adding that Folate deficiency (as well as B2 and B6 deficiency) also increases homocysteine and should be considered.	Thank you for your comment. This has been added. The recommendation has been updated to state 'Use laboratory reference ranges to interpret plasma homocysteine test results when deciding if vitamin B12 deficiency is likely, but take into account additional factors that may increase plasma homocysteine levels (such as folate deficiency).'

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6	Abbott Laboratories	Guideline	008		BOX 2 Perhaps there could be a note that several risk factors can co-exist and may/would compound the risk for B12 deficiency e.g., Age + Proton Pump Inhibitor + restricted diet etc? It is likely as people age that an increasing number of risk factors would accumulate.	Thank you for your comment. Following stakeholder comments age as a risk factor has been removed from the box. This is because age combined with a symptom and sign would lead to a huge resource impact without evidence to demonstrate it would identify a significant number of people with vitamin B12 deficiency. The committee agreed that while several risk factors could compound the risk for vitamin B12 deficiency there only needs to be one present, along with a symptom or sign, for a test to be recommended. Having multiple factors would not change the requirement for testing.
7	Abbott Laboratories	Guideline	009	008	(In 1.3.2) Active B12 might also be preferable to Total B12 as the initial test for people on the Oral Contraceptive Pill (OCP) or breast feeding? There is some evidence and recommendations that this should be the case e.g., (1) in this guideline (see page 10 line 6 1.3.7 and page 29 line 19, "Factors that can affect initial test results") and (2) *Devalia V, Hamilton MS, Molloy AM and the British Committee for Standards in Haematology. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. Br J Haematol 2014; 166: 496–513*. Suggests that "There is the added advantage of use in pregnancy and in	Thank you for your comment. Whereas the committee agreed that active B12 was the better test during pregnancy it was not clear that this should always be the test for people using oral contraceptives. Total or active B12 are recommended as the initial test so healthcare professionals can use either should they wish. Breastfeeding has been removed from the recommendation because the committee agreed with stakeholders that breastfeeding does not influence total B12 test results.

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					patients on oral contraceptives as the HoloTC fraction of cobalamin does not seem to be subject to the physiological drop seen in total serum cobalamin over the course of pregnancy".	
8	Abbott Laboratories	Guideline	010	018	Perhaps as an alternative to Methyl Malonic Acid (MMA) which is only available on LC-MS/MS (Liquid Chromatography/Mass Spectroscopy-Mass Spectroscopy), which not every lab has access to, Homocysteine (HCY) could be a viable option and could be recommended in the guideline? HCY is more available as this can be run on LC-MS/MS and on immunoassay. Sample tubes are available that can stabilise HCY allowing samples to be taken in primary care if necessary. The major limitation on HCY interpretation is that it is elevated in folate deficiency can be ameliorated (measure folate in the patient, and folate supplementation is becoming more common so fewer people are folate deficient). The use of MMA or HCY was recommended in *Devalia V, Hamilton MS, Molloy AM and the British Committee for*	Thank you for your comment. The committee agreed that there are several practical issues with the homocysteine test. These include the requirement for stabilising tubes if samples cannot be transported immediately to the laboratory on ice, which not all hospitals have, and the requirement of a second blood sample. Results of the homocysteine test are more difficult to interpret in people with folate, B6 or B2 deficiency and in people with renal impairment because these conditions also affect homocysteine levels. In addition, the committee considered the additional cost of the homocysteine test. MMA does not require stabilising tubes and can be performed on the original blood sample taken for the first-line test. Avoiding the need for a second blood sample would speed up the diagnostic process and would involve less burden on the person being tested. Therefore, without evidence to support the use of a more costly test the committee recommend MMA as the test for indeterminate test results.

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					Standards in Haematology. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. Br J Haematol 2014; 166: 496–513 "Plasma tHcy and/or plasma MMA, depending on availability, may be considered as supplementary tests to determine biochemical cobalamin deficiency in the presence of clinical suspicion of deficiency but an indeterminate serum cobalamin level (Grade 2B)." Also, in some circumstances even after MMA is measured, HCY can be a useful test to run to give confirmation or more information on the patient's B12 deficiency/sufficiency status. Could HCY be added to the guideline as a tertiary or additional test?	
9	Abbott Laboratories	Guideline	012	001	1.3.15 Could the guideline suggest homocysteine (HCY) as an option as this may be more widely available than MMA?	Thank you for your comment. The recommendation has been updated to advise investigating other causes as well as considering a repeat of the initial test if they are still experiencing symptoms or signs 3 to 6 months later. MMA has been removed because the committee agreed that most laboratories would not allow for an MMA without testing total or active B12 first.
10	Abbott Laboratories	Guideline	018	018	1.6.18 Could the guideline suggest homocysteine (HCY) as an option as this may be more widely available than MMA?	Thank you for your comment. Plasma homocysteine has been included as a test if serum MMA is unavailable.

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11	Abbott Laboratories	Guideline	028	018	The draft guideline currently says: "The active B12 test is also significantly more costly." As Active B12 is available from at least 4 major suppliers the cost may decrease over time and cost is something that the laboratory could discuss with their supplier. Also, a large part of the cost of testing is related to staff costs and other overheads, so the cost per test difference of Active B12 vs Total B12 may not be that large.	Thank you for your comment. While the committee hope the costs of active B12 will come down in the future any recommendations in the guideline need to reflect the current costs.
12	Abbott Laboratories	Guideline	031	008	The draft guideline currently says: "If more centres decide to use active B12 there will be an increased cost to the NHS because the test is significantly more expensive than a total B12 test." As Active B12 is available from at least four major suppliers the cost may decrease over time and cost is something that the laboratory could discuss with their supplier. Also, a large part of the cost of testing is related to staff costs and other overheads, so the cost per test difference of Active B12 vs Total B12 may not be that large.	Thank you for your comment. While the committee hope the costs of active B12 will come down in the future any recommendations in the guideline need to reflect the current costs.
13	Abbott Laboratories	Guideline	039	006	The draft guideline currently says: "An MMA test should be considered if the person has not previously had one and their symptoms	Thank you for your comment. Where further testing is recommended in follow up, plasma homocysteine has been added as an option if MMA is not available.

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					have not improved, or they have new symptoms." Could the guideline suggest homocysteine (HCY) as an option as this may be more widely available than MMA?	
14	Abbott Laboratories	Evidence Review C	164		**Appendix J – Excluded Studies** *Valente, E., Scott, J. M., Ueland, P. M. et al. (2011) Diagnostic accuracy of holotranscobalamin, methylmalonic acid, serum cobalamin, and other indicators of tissue vitamin B12 status in the elderly. Clinical Chemistry 57(6): 856-63* The Evidence Review C Diagnosis states that this publication is excluded because "- Population not relevant to this review protocol". The population age in the publication is 63 – 97 years old. Why is this not relevant or where other factors used to exclude this study? This publication gives interesting insights into the performance of the assays considered in this guideline, particularly suggesting that "Serum holoTC [Active B12] was the best predictor, with area under the ROC curve(95%CI) 0.90 (0.86–0.93), and this was significantly better (P	Thank you for your comment. The population for this review question was adults with suspected vitamin B12 deficiency. The population in the Valente study was older adults with cognitive impairment. Although cognitive impairment is a possible symptom of vitamin B12 deficiency, there are many other causes, and it was not stated in the study that vitamin B12 deficiency was suspected. The guideline did not include a review question on the effectiveness of vitamin B12 replacement in people with a confirmed or suspected vitamin B12 deficiency.

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					<0.0002) than the next best predictors" - (vs the novel Red Blood Cell Cobalamin reference test).	
15	Association for Nutrition	Guideline	General	General	We agree that dietary choices can be a cause or contributor to vitamin B12 deficiency, and supporting individuals to have adequate dietary intakes is beneficial, and in some cases may enable the deficiency to be reversed. It is important those supporting individuals in this respect are suitably qualified and competent to assess current dietary intakes and be able to provide advice on dietary changes to increase B12 intake, which is suitable for any ethical, religious or dietary restrictions the individual may require. UKVRN Registered Nutritionists (ANutr/RNutr) are qualified and competent nutrition professionals whose expertise could be utilised to provide this assessment and support.	Thank you for your comment. The guideline has focused on what treatments should be offered or considered rather than who should deliver them.
16	Association for Nutrition	Guideline	General	General	**Future Research** We agree that additional research into dietary factors that can cause or contribute to vitamin B12 deficiency is important, and this should include investigation into the interaction with other foods/nutrients and medications to explore promoters and	Thank you for your comment. These additional factors were not part of the review protocol therefore they have not been added to the research question.

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					inhibitors to the bioavailability of the dietary B12, along with consideration of dietary pattern and the needs of different population groups (older adults, vegans, vegetarians, cultural diets, IBD etc.). UKVRN Registered Nutritionists specialising in nutrition science research, would be ideally positioned and qualified to undertake this research.	
17	Association for the Study of Obesity	Guideline	007	015 – 017 and Box 1	The statement correctly highlights that B12 deficiency symptoms are nearly always non-specific. It is not common to find peripheral neuropathy or optic neuropathy from B12 deficiency. However, connected to this, there appears to be a growth in private sector B12 treatment / clinics, often giving treatment for non-specific symptoms to people who do not need this. Could a short sentence be added in section 1 to state that in the absence of clear evidence of B12 deficiency there is no benefit from treatment, and it should not be started?	Thank you for your comment. There was a lack of evidence overall for vitamin B12 deficiency and a lot of the recommendations were based on consensus. Stating treatment should not be started without clear evidence of benefit may mean a lot of people do not get the treatment they need.
18	Association for the Study of Obesity	Guideline	008		Box 2 We are pleased to see the inclusion of bariatric operations (for example, Roux-en-Y gastric bypass or sleeve gastrectomy) in the risk factors for vitamin B12 deficiency. This will also capture other procedures that	Thank you for your comment and support for the recommendation.

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					bariatric surgeons are undertaking in the UK such as one anastomosis gastric bypass and single anastomosis duodenal ileal switch.	
19	Association for the Study of Obesity	Guideline	010	017	Thank you for the clarification of when to measure methylmalonic acid (MMA), although many healthcare practitioners in both primary and secondary care are not allowed to request this because of the additional cost.	Thank you for your comment. The committee recommended serum MMA because it is likely to lead to faster diagnosis and treatment, which, in some cases, could avoid unnecessary investigations or avoid a referral to secondary care. Implementing these recommendations will require some reallocation of resources, including some investment in pathology services, so that testing can become more widely available. A resource impact report and tool will be published alongside this guideline.
20	Association for the Study of Obesity	Guideline	011	016 - 018	Thank you for raising that treatment should be started if the person has had bariatric surgery.	Thank you for your support for this recommendation.
21	Association for the Study of Obesity	Guideline	011	023	Thank you for the clarification as there is often confusion amongst healthcare professionals regarding the interpretation of results.	Thank you for your support for the recommendation.
22	Association for the Study of Obesity	Guideline	012	011 - 012	Thank you for this clarification as occasionally some healthcare professionals may insist on an anti-intrinsic factor antibody for people who have had bariatric surgery	Thank you for your comment.

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23	Association for the Study of Obesity	Guideline	013	017 - 021	Thank you for recommending that intramuscular injections should be considered instead of oral vitamin B12 replacement for people who have had bariatric surgery. Although there are some studies looking at oral supplementation, vitamin B12 deficiency may still occur despite high oral doses.	Thank you for your comment and support for the recommendation.
24	Association for the Study of Obesity	Guideline	019	003 - 005	There may be a variable response to intramuscular injections for people who have bariatric surgery, with some patients' levels falling rapid between injections. Without some monitoring after surgery, it can be difficult to determine if the patient is receiving the appropriate frequency of injection or having the injection via the general practice. The first two years of monitoring is provided by the bariatric surgery centre.	Thank you for your comment. The guideline does not cover the recommendations for postoperative management of people following surgery that may lead to a vitamin B12 deficiency. This is best covered by surgical guidelines. The assumption is that this is about preventing a deficiency rather than treating a deficiency that has happened after surgical discharge. This guideline only mentions surgery in the context of people who may present with symptoms of vitamin B12 deficiency.
25	Association for the Study of Obesity	Guideline	034	008 - 010	There are very few studies that have explored oral supplementation in people having bariatric surgery. Those studies are usually short-term with vitamin B12 deficiency still being reported. More research is needed in the bariatric surgery area.	Thank you for your comment. The committee has made a research recommendation on the clinical and cost effectiveness of vitamin B12 replacement for vitamin B12 deficiency, including the dose, frequency and route of administration. This includes stratifying the populations by the cause of deficiency.
26	Association for the Study of Obesity	Guideline	037	011 - 015	Loading doses are mentioned here but not earlier in the guidelines. Following bariatric surgery, it is usual practice to have their	Thank you for your comment. NICE does not generally include dosages in recommendations where they are available in the BNF or SPC. A dosage may be included if

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					first intramuscular injection three months after the procedure. Although this is usually given in written communication, occasionally the general practice healthcare professionals advise the patient that loading doses are needed, creating extra demands on both the practice nurse's and patient's time and additional cost. Could there be an earlier statement in the recommendations to explain when loading doses are needed?	this information is not available, or the committee agrees that there needs to be a change to current recommended dosages, for example because of new evidence. Loading doses are covered in the BNF and therefore not included in the guideline. The guideline did look for clinical evidence relating to the frequency of intramuscular injections however no evidence was identified and the committee made a research recommendation. Loading doses are only mentioned in this section to illustrate the cost of treatment and when intramuscular injections are likely to be cost effective.
27	Association of British Neurologists – Neuromuscular AAG	Guideline	004	005	This language could be clearer: clarify that associated with anti-intrinsic factor or anti gastric-parietal cell antibodies.	Thank you for your comment. The guideline has been updated to acknowledge the difference between autoimmune gastritis and pernicious anaemia and provide a more detailed reason as to why the term 'pernicious anaemia' has not been used. This explains that autoimmune gastritis is sometimes referred to as pernicious anaemia which is a separate condition that can be a consequence of chronic, severe vitamin B12 deficiency, including deficiency caused by autoimmune gastritis. However, pernicious anaemia in its true sense (that is 'a life-threatening anaemia') is now extremely rare because of developments in testing and treatment for, and greater awareness of, vitamin B12 deficiency. For this reason, and to prevent any confusion with autoimmune gastritis, we have not used the term 'pernicious anaemia' in the recommendations.
28	Association of British	Guideline	005	004	This guideline should mention the importance of consideration of folate	Thank you for your comment. Investigating and managing complications related to vitamin B12 deficiency and cofactors

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	Neurologists – Neuromuscular AAG				deficiency and the relationship between B12 and folate, the effect on folate on the tests and should direct the reader to information about subacute combined degeneration of the cord. This is just a comment: In clinical practice in Northern Ireland, you cannot test B12 in isolation, you can only test B12 and folate together, and in my clinical experience this is probably safer as it is then not possible for someone to treat folate deficiency without a knowledge of the B12 result.	were not included as part of the scope of the guideline. Therefore they were not included as part of the guideline reviews and no recommendations have been made related to this. The committee agreed that everyone will still test folate and vitamin B12 together despite there being no mention of folate in this guideline.
29	Association of British Neurologists – Neuromuscular AAG	Guideline	007	001	Suggested clarification: "affects proprioception. Proprioception is the …"	Thank you for your comment. The recommendation has been updated to state 'balance issues and falls caused by impaired proprioception (the ability to sense movement, action and location) and linked to sensory ataxia (which may have been caused by spinal cord damage)'.
30	Association of British Neurologists – Neuromuscular AAG	Guideline	008	001	In "find it difficult to buy or prepare food" consider including people with limited financial resources – this is the commonest reason in my practice.	Thank you for your comment. A bullet point has been added that states 'in people who find it difficult to obtain or afford foods rich in vitamin B12 (for example, people on low income)'.
31	Association of British Neurologists –	Guideline	008	001	There is not sufficient discussion regarding Nitrous Oxide use and a section should be added with more emphasis on the importance. We recommend review of the	Thank you for your comment. The guideline has avoided going into all the detail for vitamin B12 deficiency caused by recreational nitrous oxide use and focused on what test to use and what type of vitamin B12 replacement to offer. The

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	Neuromuscular AAG				ABN Guidelines Paris et al. Association of British Neurologists Clinical Practice Guide 2023, and inclusion of the UK Nitrous Oxide Working Group as a key stakeholder in this guideline development process. This is an increasing problem in clinical practice and enmeshed with the management of B12 deficiency.	ABN guidelines you refer to covers the whole of nitrous oxide induced subacute combined degeneration of the cord, including imaging and acute management in the emergency department. The report was checked to see if any papers met our review protocols that weren't already identified. The committee has not made recommendations relating to the acute management of vitamin B12 deficiency caused by recreational nitrous oxide use because they agreed this would be handled by the emergency department. In this situation factors other than vitamin B12 deficiency are likely to be considered first and any vitamin B12 replacement would need to be considered within this context. Other guidance such as the Royal College of Emergency Medicine's best practice guidelines on Suspected nitrous oxide toxicity in Emergency Departments and guidance from the National Poisons Information Service covers this aspect of care. The UK Nitrous Oxide Working group guidelines appear to cover public health issues whereas this guideline focuses on clinical practice.
32	Association of British Neurologists – Neuromuscular AAG	Guideline	010	015	We recommend that the guideline acknowledge that in my clinical settings processing of homocysteine is imperfect and can lead to false positive testing. Clinicians should use local knowledge of testing processes and consider	Thank you for your comment. We have updated this to make it more specific. The recommendation now states 'Use laboratory reference ranges to interpret plasma homocysteine test results when deciding if vitamin B12 deficiency is likely, but take into account additional factors

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					supplementing homocysteine testing with MMA if this a concern.	that may increase plasma homocysteine levels (such as folate deficiency).'
33	Association of British Neurologists – Neuromuscular AAG	Guideline	010	018	In some clinical settings urine but not serum MMA is available. It may be helpful to clarify whether these are equivalent and if there is an option which is preferable.	Thank you for your comment. Evidence for urine MMA was not identified and the committee agreed that this is not a relevant marker for testing in vitamin B12 deficiency. Therefore, the committee have made it clear throughout the guideline that it is serum MMA that is recommended.
34	Association of British Neurologists – Neuromuscular AAG	Guideline	011	001	This language is unclear: clarify that reference ranges are generally higher in people from Black family backgrounds are at risk of not having B12 deficiency detected. NICE should consider recommending that research is undertaken to facilitate more adequate advice.	Thank you for your comment. The findings in the study suggested cut-off for deficiency as 225 ng/L (166 pmol/L). This has been added to the evidence report. However, the committee were aware that this is one study and the result may need to be validated in other populations. Therefore they did not include it in the guideline recommendations. The committee made a recommendation for research on long-term outcomes for people with suspected vitamin B12 deficiency when comparing testing of total B12, active B12, methylmalonic acid (MMA) or homocysteine. This includes a strata (separate analysis) for people with Black ethnicity.
35	Association of British Neurologists – Neuromuscular AAG	Guideline	011	006	Recommend specify **give** treatment, with caveats, rather than consider.	Thank you for your comment. The recommendation is a 'consider' recommendation because there was a lack of evidence in this area, and it is unclear whether these people have a deficiency or another cause for their symptoms. The evidence identified for using MMA or homocysteine as a second-line test was of very low certainty. This was due to serious risk of bias, resulting from a lack of detail surrounding blinding of test results and a 3-month interval between the index test and reference standard. Furthermore, all evidence was downgraded by two increments due to

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						indirectness resulting from incomplete reporting of participant demographics, supplement use, or selection of participants with specific comorbidities, namely macrocytosis and anaemia, and the lack of a gold standard for the diagnosis of vitamin B12 deficiency, which was a limitation of all the diagnostic evidence. These limitations led to very low certainty of the evidence presented, resulting in a consider recommendation as opposed to offer.
36	Association of British Neurologists – Neuromuscular AAG	Guideline	013	007	Consider the following: If there is uncertainty start with IM 1mg hydroxocobalmin while awaiting results of testing for autoimmune gastritis/coeliac disease and then select an appropriate oral dosing depending on the underlying cause. Recommend that a range of oral dosages related to the various underlying causes are suggested by the committee.	Thank you for your comment. Intramuscular injections are recommended for people where malabsorption is the suspected cause of vitamin B12 deficiency. However, there was no evidence to start the dose before test results are received. With regard to oral doses, a recommendation has been added when oral replacement is offered to people with vitamin B12 deficiency caused, or suspected to be caused, by malabsorption which advises prescribing a dosage of at least 1 mg a day. This is because evidence that compared oral vitamin B12 replacement with intramuscular injections used a dosage of 1 mg a day. The committee agreed that usual practice is to offer intramuscular injections and without evidence that lower doses of oral vitamin B12 replacement are effective it was important to specify the dose used in the available evidence. However, for other causes of vitamin B12 deficiency the expectation is that the committee follow the BNF.

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37	Association of British Neurologists – Neuromuscular AAG	Guideline	013	009	Recommend provide a reference to direct the reader to this information.	Thank you for your comment. Following stakeholders' comments this recommendation has been updated to provide more detail. It now states: Explain to people starting treatment with vitamin B12 replacement: • that response to treatment can vary and depends on the cause of the vitamin B12 deficiency • that their symptoms could start to improve within 2 weeks, but this may take up to 3 months • that it can take much longer for symptoms to disappear altogether, and that although their symptoms could get worse initially during treatment, this should improve • when to seek medical help (without waiting for any scheduled appointments) if their symptoms have not improved, get worse or return, or they get new symptoms, after starting treatment.
38	Association of British Neurologists – Neuromuscular AAG	Guideline	015	015	There should be an indication given of the minimum dose that the oral supplement should contain.	Thank you for your comment. A review of the effectiveness of over-the-counter (OTC) supplements was not included as part of the scope of the guideline and therefore no recommendations have been made on whether to suggest them and what dosage to use. The recommendation relating to OTC oral supplements is to highlight which supplements are appropriate. This is because some oral supplements that are labelled as containing vitamin B12 do not contain a form that is appropriate to use as vitamin B12 replacement.
39	Association of British Neurologists	Guideline	019	004	Recommend provide a time interval for repeat testing.	Thank you for your comment. No evidence was identified on monitoring for people with vitamin B12 deficiency and the

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	– Neuromuscular AAG					committee made a research recommendation including what tests should be included.
40	Association of British Neurologists – Neuromuscular AAG	Evidence review A	019	011	Is there work to be done to strengthen the evidence on which this is based before advising? The advice should specifically reassure women with **treated** B12 deficiency only, while this is what it says, it could be clearer.	Thank you for your comment. Other stakeholders also commented on this as well. They suggest that without evidence to support the statement that using nitrous oxide with air (gas and air) during labour is unlikely to make their vitamin B12 deficiency worse, it should not be made. The committee agreed and the recommendation relating to this has been removed from the guideline.
41	Association of British Neurologists – Neuromuscular AAG	Evidence review C	046	General	In some areas serum MMA testing is not available and urine MMA is. Can recommendations about sensitivity specificity and appropriateness of urine MMA testing.	Thank you for your comment. Evidence for urine MMA was not identified and the committee agreed that this is not a relevant marker for testing in vitamin B12 deficiency. Therefore, the committee have made it clear throughout the guideline that it is serum MMA that is recommended.
42	B12 Global Ltd (now B12info Ltd)	Guideline	General	General	Firstly, It's a crying shame that paediatricians and paediatric specialists could not be found to make this a Guideline for children of all ages too, since B12 deficiency does not discriminate and affects all ages and in vitro. Children and their parents are totally at the mercy of professionals who may or may not understand B12deficiency. I'm concerned that the Draft avoids stating treatment regimes. Loading dose and frequency of injections aren't mentioned at	Thank you for your comment. It is unfortunate that paediatrics could not be covered in the guideline. NICE does not generally include dosages in recommendations where they are available in the BNF or SPC. A dosage may be included if this information is not available, or the committee agrees that there needs to be a change to current recommended dosages, for example because of new evidence. Loading doses are covered in the BNF and therefore not included in the guideline. The guideline did look for clinical evidence relating to the frequency of intramuscular injections however no evidence

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					all in 'Managing B12 deficiency'. Already GP Practices have developed their own restrictive protocols for treatment which stretch out the loading dose of 6 injections over two weeks to 4 injections over 4 weeks. This is clearly not in line with NICE CKS Summaries which state - Every other day injections for as long as it takes for symptoms to stop improving for those with neurological symptoms. It needs to be made clear that frequent B12 injections are necessary for recovery from nerve damage caused by lack of B12 and that each patient has a different requirement based on their individual experience. B12 is water soluble and there is no known toxicity. This paper https://onlinelibrary.wiley.com/doi/full/10.1111/hex.13152 shows just how many people feel about their interactions with their doctor regarding B12 deficiency	was identified and the committee made a research recommendation. The study you cite is included as part of the evidence in evidence review A for information and support.
43	B12 Global Ltd (now B12info Ltd)	Guideline	004	020	1.1.2 Information and support B12 injections should not be withheld or delayed pending investigations for other potential causes of symptoms, B12 injections do not interfere with other testing	Thank you for your comment. The information in this recommendation relates to what a healthcare professional explains to the person suspected of vitamin B12 deficiency. The guideline does not make a recommendation for treating without a diagnosis and therefore that statement has not been included. However, the recommendations in the

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					and their administration may well confirm symptom origin to be solely B12 deficiency.	ongoing care and follow up section have been updated to make it clearer that vitamin B12 replacement should be continued if the person has symptoms while thinking about alternative diagnoses.
44	B12 Global Ltd (now B12info Ltd)	Guideline	005	001	1.1.2 Information and support Since B12 deficiency affects all body systems and can cause myriad symptoms, fatigue being a very common symptom. A trial of B12 injections together with co factors and good dietary guidance should be offered if the person includes animal products in their diet and B12 deficiency is not a proven dietary lack.	Thank you for your comment. The guideline recommends that oral Vitamin B12 replacement is considered for people where diet is the suspected or confirmed cause of deficiency, and for a confirmed deficiency when the cause is unknown. Evidence was not available to recommend intramuscular injections over oral in these cases. However, the recommendations on ongoing care and follow up do recommend switching to intramuscular injections in some cases where treatment is not working.
45	B12 Global Ltd (now B12info Ltd)	Guideline	005	003	1.1.2 Information and support This should read 'some' rather than 'most' - B12 deficiency is difficult for a doctor to diagnose. All of the testing for this condition and for pernicious anaemia have limitations and the references are often far too low. Everyone is different and the clinical picture - signs and symptoms and family history is of utmost importance. Signs and symptoms need to be mentioned here. Patient must be treated as individuals and	Thank you for your comment. The committee agreed that a diagnosis could be made for most people with a single test. The bullet point has been updated to state 'a single blood test can be enough to support a diagnosis of vitamin B12 deficiency but some people may need further tests to diagnose the condition'. A trial of injections of vitamin B12 deficiency without a diagnosis was not included as part of the guideline review and no recommendations have been made in this area.

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					trialing B12 injections readily will aid in confirming a diagnosis. B12 injections are safe and inexpensive.	
46	B12 Global Ltd (now B12info Ltd)	Guideline	005	018	1.1.4 Information and support Change the word 'unlikely' for 'likely'. Nitrous oxide inactivates B12 and if the pregnant woman is receiving B12 injections they will need absolutely to be increased in frequency to ensure that no harm comes to either her or the baby.	Thank you for your comment. Several stakeholders commented on this suggesting that without evidence to support this the statement should not be made. The committee agreed and the recommendation relating to this has been removed from the guideline. Recommendations related to pregnant patients on gas and air are covered by MHRA guidance on Nitrous oxide: neurological and haematological toxic effects.
47	B12 Global Ltd (now B12info Ltd)	Guideline	006	008	1.2.2 Recognising B12 deficiency Education is urgently required to for all disciplines of healthcare on vitamin B12 deficiency, its manifestations and testing limitations so that doctors can update previously held, incorrect opinions or beliefs.	Thank you for your comment. The committee hope this guideline will raise awareness of vitamin B12 deficiency among healthcare professionals.
48	B12 Global Ltd (now B12info Ltd)	Guideline	007		1.2.5 Box 1 Signs and symptoms There are many more known and confirmed signs and symptoms than are listed here, for example infertility in men and women, tinnitus, seizures. Please see	Thank you for your comment. The recommendations and box have been updated to make it clear that these are common symptoms and signs. NICE guidelines do not generally link to other organisation guidelines or websites because these may change and NICE has no control over the content. The section on 'Information for the public' on this guideline's web page also provides links to other organisations' websites

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					https://www.b12deficiency.info/signs-and-symptoms/	which provide more detailed advice directly written for people with suspected or confirmed vitamin B12 deficiency.
49	B12 Global Ltd (now B12info Ltd)	Guideline	007	006	1.2.7 Risk factors People who are on oral B12 at this point need to be switched to B12 injections for life. Oral B12 will not help to heal nerves.	Thank you for your comment. These recommendations are about recognising vitamin B12 deficiency rather than treatment. Switching treatment based on the presence of a risk factor was not considered as part of the guideline. There are recommendations on switching treatments depending on the person's response to treatment in the section on ongoing care and follow up.
50	B12 Global Ltd (now B12info Ltd)	Guideline	008		1.2.7 Box 2 Risk Factors The focus on 65 and over often leads doctors to believe that younger people do not have B12 deficiency - The Nitrous oxide statement contradicts 1.1.4 comment, as we know it inactivates B12 in the body. There are a great many common risk factors and causes – Please see https://www.b12deficiency.info/causes/	Thank you for your comment. Following stakeholder comments age as a risk factor has been removed from the box. This is because age combined with a symptom and sign would lead to a huge resource impact without evidence to demonstrate it would identify a significant number of people with vitamin B12 deficiency. Recommendation 1.1.4 has also been removed from the guideline because the committee agreed with stakeholder comments that this statement should not be made without clear evidence that this is the case. Only the most common symptoms and signs were included in the guideline review therefore the recommendations have been restricted to these. The recommendations and box have been updated to make it clear that these are common symptoms and signs.

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51	B12 Global Ltd (now B12info Ltd)	Guideline	009	003	1.3.1 Diagnosing vitamin B12 deficiency – Initial tests Due to the limitations of testing, to remove doubt, why not test both Total and Active B12? As before clinical signs and symptoms must be taken into account. It is critical to check whether B12 has been supplemented prior to testing due to the skewing of results. Fortification of foods, energy drinks as well as B12 supplements can push a severely B12 deficient person 'into range' and thereby affecting true results for months.	Thank you for your comment. No evidence was identified for a combination of tests and therefore these are not recommended. The committee recommend asking people about any B12 supplementation they might be taking so that this can be taken into account when interpreting test results. The recommendation has been updated to include all forms of vitamin B12 supplementation including vitamin B12 tablets, injections or transdermal patches. Assessing the person's dietary intake is included as part of the risk factors in the section on 'When to recognise vitamin B12 deficiency'. This includes the section on recognising vitamin B12 deficiency and has been updated to include food or drinks fortified with vitamin B12.
52	B12 Global Ltd (now B12info Ltd)	Guideline	009	015	1.3.4 Diagnosing vitamin B12 deficiency – Initial tests Shouldn't this be moved up to line 3?	Thank you for your comment. We thought about this but think it is better where it is. This is on the basis that you would need to decide which test to do before actually taking the blood.
53	B12 Global Ltd (now B12info Ltd)	Guideline	009	017	1.3.5 Diagnosing vitamin B12 deficiency – Initial tests Do not delay vitamin B12 treatment if any debilitating B12 deficiency symptom is suspected.	Thank you for your comment. The committee agreed that test results will be returned within 24 hours for most people and within 2 weeks for those having MMA. They did not think it necessary to start treatment before the test results are received except for the circumstances mentioned in the recommendation. The recommendation has been updated to: Do not delay vitamin B12 replacement while waiting for the test results of people with suspected megaloblastic

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						anaemia and neurological symptoms, especially related to sub-acute combined degeneration of the spinal cord.
54	B12 Global Ltd (now B12info Ltd)	Guideline	009	020	1.3.6 Diagnosing vitamin B12 deficiency – Initial tests The dosage here is probably irrelevant as any supplementation will affect blood outcomes. The 50mcg cyanocobalamin tablets can push the B12 blood levels up into range as well as a high dose tablet but both may have no positive effect on symptoms.	Thank you for your comment. The committee agreed it is important to get all the information about any supplements that may be used and therefore it is important to ask about dosage.
55	B12 Global Ltd (now B12info Ltd)	Guideline	010	002	1.3.7 Factors that can affect results View tests with clinical picture in mind.	Thank you for your comment. The committee anticipated that healthcare professionals will view the test results with the clinical picture in mind.
56	B12 Global Ltd (now B12info Ltd)	Guideline	010	010	1.3.8 Thresholds for initial tests The cut off of 180ng/L as being deficient still seems way to low and a worsening from the current guidance which mentions 200ng/L as picking up 95% of those with deficiency. All assay kits are different in the UK and all reference ranges are different too. Some as low as 110ng/L in East lancs – https://www.b12deficiency.info/east-lancashire-nhs-trust-you-win-the-trophy-hands-down-for-dangerously-low-lower-	Thank you for your comment. Several stakeholders commented on the thresholds. Some thought they were too low, others thought they were too high and there was also some support that they are about right. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not. Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The

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					reference-level-for-serum-b12-test-110-914ngl/ and 130 in Cardiff. All patients are different and B12 deficiency diagnosis decided by by blood results on low reference ranges is not remotely helpful. Patients can be severely deficient at levels much higher than180ng/L. Between 200 and 300pg/ml is borderline and requires more testing or investigation depending on the presenting symptoms, the risk factors, and patient history. There are serious concerns about what seem to be arbitrary levels to confirm diagnosis of B12 deficiency.	committee also noted that either active or total B12 are recommended as tests. The committee also recommend considering MMA as a further test for people with an indeterminate active or total B12 test result. This is to capture people who may have a vitamin B12 deficiency when their test result doesn't meet the criteria for deficiency. An indeterminate result covers an active B12 of between 25 and 70 pmol per litre, and a total B12 of between 180 and 350 nanograms (133 and 258 pmol) per litre. The committee has also added a recommendation to use the laboratory's reference ranges to decide if vitamin B12 deficiency is likely when interpreting serum MMA and plasma homocysteine test results.
57	B12 Global Ltd (now B12info Ltd)	Guideline	010	015	1.3.9 Thresholds for initial tests Homocysteine reference range should show that optimal levels are around 6.	Thank you for your comment. We have updated this to make it more specific. The recommendation now states 'Use laboratory reference ranges to interpret plasma homocysteine test results when deciding if vitamin B12 deficiency is likely, but take into account additional factors that may increase plasma homocysteine levels (such as folate deficiency).' The committee did not have the evidence to show the optimal reference ranges and in their experience agreed it would be better to use the laboratory reference ranges.

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58	B12 Global Ltd (now B12info Ltd)	Guideline	011	023	1.3.14 Test results indicating vitamin B12 deficiency is unlikely Unless they are already taking oral supplements which will raise B12 levels in a test, but may not be absorbed by the body to have any meaningful effect whatsoever.	Thank you for your comment. The recommendation following this has been updated to advise investigating other causes. There is also a cross reference to the earlier recommendation on factors that can affect total B12 test results that mentions about taking oral supplements. It also advises considering a repeat of the initial test if the person is still experiencing symptoms or signs 3 to 6 months later.
59	B12 Global Ltd (now B12info Ltd)	Guideline	012	007	1.4.1 Identifying the cause Consider adding serum gastrin testing and parietal cell antibody test too.	Thank you for your comment. The committee agreed that an anti-intrinsic factor antibody test is the best first option to use. It is good at determining that people have a diagnosis if the test is positive. It is also widely available to and used by GPs. Anti-gastric parietal cell gastrin levels or gastrin levels are also recommended if autoimmune gastritis is suspected despite a negative anti-intrinsic factor antibody test. However, evidence was not identified to demonstrate they are more effective than the anti-intrinsic factor antibody test and they are not as widely available.
60	B12 Global Ltd (now B12info Ltd)	Guideline	013	014	1.5.3 Vitamin B12 deficiency caused by malabsorption Offer lifelong vitamin B12 injections for any malabsorption causes of B12 deficiency including genetic polymorphisms.	Thank you for your comment. The recommendations have been updated. Intramuscular injections are offered to people with autoimmune gastritis or who have had a total gastrectomy or complete terminal ileal resection. For all other people with vitamin B12 deficiency because of malabsorption intramuscular injections are considered over oral replacement. The committee agreed that in their experience intramuscular injections are better than oral replacement.

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						However, there was no evidence to suggest that oral replacement could not be effective too. The weaker recommendation to 'consider intramuscular instead of oral vitamin B12 replacement' reflects this. The committee also made a research recommendation in this area to address the uncertainty.
61	B12 Global Ltd (now B12info Ltd)	Guideline	013	017	1.5.4 Vitamin B12 deficiency caused by malabsorption Add gall bladder removal too.	Thank you for your comment. The committee do not agree that gall bladder removal needs to be added because the absence of the gall bladder does not alter B12 homeostasis.
62	B12 Global Ltd (now B12info Ltd)	Guideline	014	001	1.5.5 Vitamin B12 deficiency caused by malabsorption Oral B12 replacement should not be offered based on the person's preference since oral does not help to heal nerves in malabsorption.	Thank you for your comment. Following stakeholder comments the recommendations have been updated. Intramuscular injections are offered to people with autoimmune gastritis or who have had a total gastrectomy or complete terminal ileal resection. For all other people with vitamin B12 deficiency because of malabsorption intramuscular injections are considered over oral replacement.
63	B12 Global Ltd (now B12info Ltd)	Guideline	014	019	1.5.8 Nitrous oxide induced deficiency This should not be a preference it should be the treatment of B12 injections which provides the best chance of nerve healing and recovery.	Thank you for your comment. There is no clear evidence to distinguish which out of oral or intramuscular vitamin B12 replacement was more clinically or cost effective for vitamin B12 deficiency caused by recreational nitrous oxide use. Therefore the committee agreed to recommend either oral or intramuscular vitamin B12 replacement.
64	B12 Global Ltd (now B12info Ltd)	Guideline	014	022	1.5.8 Nitrous oxide induced deficiency Calling treatment of B12 deficiency 'off	Thank you for your comment. Reference to off-label use has been removed from the guideline.

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					label' use when the treatment for nitrous oxide use is B12 injections is surely prohibitive to doctors who may not be aware that B12 injections must be given to ensure best recovery?	
65	B12 Global Ltd (now B12info Ltd)	Guideline	014	024	1.5.9 Nitrous oxide induced deficiency Still provide B12 replacement, while the person is being educated on the harmful effects of nitrous oxide abuse and its complete inactivation of B12.	Thank you for your comment. The committee agree that it is important to provide vitamin B12 replacement as well as to advise the person to stop using nitrous oxide. The aim of the recommendation is that the person would be treated as well as advised to stop.
66	B12 Global Ltd (now B12info Ltd)	Guideline	017	003	1.6.1 Ongoing care and follow up Better information on vitamin B12 deficiency symptoms is required on NHS websites and leaflets at Doctors' surgeries. People need to be made aware that their symptoms could be caused by a B12 deficiency.	Thank you for your comment. The committee hope this guideline will raise awareness of vitamin B12 deficiency.
67	B12 Global Ltd (now B12info Ltd)	Guideline	017	008	1.6.1 Ongoing care and follow up If a patient is taking oral B12 replacement, offer intramuscular B12 injections to establish if better symptom relief is	Thank you for your comment. This recommendation relates to oral vitamin B12 replacement only and is made to check the person's adherence to treatment. It has been moved under that heading to avoid confusion. Where evidence was available, recommendations for intramuscular injections have been made in the section on managing vitamin B12

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					achieved. Currently there appears to be a desire to reduce intramuscular B12 injections. The doctor should allow the patient to make an informed decision and not persuade a patient that oral B12 will be sufficient or that no B12 is required at all.	deficiency. Recommendations are also made to either optimise oral vitamin B12 replacement or switch to intramuscular injections if oral treatment does not appear to help symptoms.
68	B12 Global Ltd (now B12info Ltd)	Guideline	017	017	1.6.3 Follow up appointments for people taking oral replacement This is a pointless and wasteful exercise and gives absolutely no clue as to what is happening at a cellular level for the person. If they are symptomatic a switch to B12 injections should be advised	Thank you for your comment. Following stakeholder comments the recommendation for repeating the initial test for people on oral vitamin B12 replacement has been removed from the guideline.
69	B12 Global Ltd (now B12info Ltd)	Guideline	017	025	1.6.5 Follow up appointments for people taking oral replacement Taking any form of B12 replacement means tests will be skewed, therefore doctors should ignore normal or high tests and diagnose based on observation of symptoms. Increase or decrease the amount of B12 replacement in small increments, e.g. from every 2 days to every 4 days, every 4 days to once a week, once a week to once every two weeks etc. If symptoms return, revert to	Thank you for your comment. Following stakeholder comments the recommendation for repeating the initial test for people on oral vitamin B12 replacement has been removed from the guideline. The ongoing care and follow up recommendations have also been updated to make it clearer that response to treatment should be made by assessing symptoms.

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					previous dose or once every 2 days as preferred by the patient. Having too much B12 in the blood is not an issue but not having insufficient B12 results in symptoms.	
70	B12 Global Ltd (now B12info Ltd)	Guideline	018	013	1.6.7 Follow up appointments for people taking oral replacement A homocysteine test here would be useful.	Thank you for your comment. Plasma homocysteine has been included as a test if serum MMA is unavailable.
71	B12 Global Ltd (now B12info Ltd)	Guideline	018	017	1.6.7 Follow up appointments for people taking oral replacement Add, while maintaining B12 replacement until an alternative diagnosis is confirmed and treatment effective to the satisfaction of the patient. Doctors need to be dissuaded from finding reasons to stop B12 replacement because they have a conscious or unconscious bias..	Thank you for your comment. Following stakeholder comments the recommendation for repeating the initial test for people on oral vitamin B12 replacement has been removed from the guideline. The ongoing care and follow up recommendations have also been updated to make it clearer that response to treatment should be made by assessing symptoms. When further testing with serum MMA (or plasma homocysteine if serum MMA is unavailable) is recommended the committee recommend thinking about an alternative diagnosis and continuing treatment while waiting for the result.
72	B12 Global Ltd (now B12info Ltd)	Guideline	019	008	1.6.12 Follow up appointments for people taking intramuscular replacement At every other day until symptoms stop improving and then as and when the person feels necessary for them.	Thank you for your comment. The recommendation has been updated so it only refers to the frequency of injections and not the dose. The guideline did look for clinical evidence relating to the frequency of intramuscular injections however no evidence

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						was identified and the committee made a research recommendation. Loading doses are covered in the BNF and therefore not included in the guideline. NICE does not generally include dosages in recommendations where they are available in the BNF or SPC. A dosage may be included if this information is not available, or the committee agrees that there needs to be a change to current recommended dosages, for example because of new evidence.
73	B12 Global Ltd (now B12info Ltd)	Guideline	020	001	1.7 Monitoring for gastric cancer in people with autoimmune gastritis There is little to know understanding of how to treat people with autoimmune gastritis within the medical field. Endoscopy is crucial rather than just 'considering it' due to the increased risk of gastric cancer in those with pernicious anaemia and autoimmune gastritis.	Thank you for your comment. We did not have the evidence to make a recommendation that all people should be referred for gastrointestinal endoscopy. Therefore, the strength of the recommendation in this guideline matches the strength of the recommendations on upper gastrointestinal tract cancers in NICE's guideline on suspected cancer.
74	B12 Global Ltd (now B12info Ltd)	Guideline	021	002	Irreversible cause MTRR, MTHFR, COMT and other gene polymorphisms that affect the biochemical methylation processes, B12 absorption, transportation or processing, including transportation across the blood brain barrier. Doctors need to recognise and provide patient guidance on the effects of heavy	Thank you for your comment. The guideline has focused on the main symptoms and risk factors, and which treatment to offer. The effects of gene polymorphisms and heavy metals were not considered as risk factors in the guideline reviews.

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					metal toxicity on methylation and B12 deficiency. This includes the effects of amalgam fillings and mercury emissions from the same on methylation and B12 deficiency.	
75	B12 Global Ltd (now B12info Ltd)	Guideline	027	013	Rec 1.2.1 -1.2.7 Risk factors Birth control pill should be added here.	Thank you for your comment. The committee agreed to limit the risk factors to only the common risk factors. Evidence was not identified to suggest it was a risk factor and therefore the oral contraceptive pill was not included.
76	B12 Global Ltd (now B12info Ltd)	Guideline	027	020	Rec 1.2.1 -1.2.7 Risk factors Nitrous oxide MUST be researched further because of its use in labour.	Thank you for your comment. Recommendations related to nitrous oxide use during labour were not covered in this guideline as they are covered in MHRA guidance on Nitrous oxide: neurological and haematological toxic effects. Therefore no research recommendation has been made in this area.
77	B12 Global Ltd (now B12info Ltd)	Guideline	028	012	Rec 1.3.1 -1.3.15 Initial tests Doctors currently are very reluctant to even test. How is this going to change? Education, training and public health broadcasts, documentaries are required for the message to get through. The publication of updated guidelines will no doubt help, however, there are a lot of doctors out there who's current practice methods will not be easily changed.	Thank you for your comment. The committee hope that this guideline will raise awareness of the condition among healthcare practitioners.

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78	B12 Global Ltd (now B12info Ltd)	Guideline	028	013	Rec 1.3.1 -1.3.15 Initial tests Signs and symptoms of a B12 deficiency should pair with initial diagnostic tests. Understanding about B12 supplementation prior to testing and its affect on results needs to made clear to the GP. No delay to treatment for the patient but adjustment to test in the lab.	Thank you for your comment. Testing is based on the presence of symptoms and signs recommended in section 1.2 of the guideline. The committee has also highlighted the factors that can affect test results. Recommendations to consider further testing with serum MMA are also made for people with an indeterminate test result. The committee agreed that the supplements would affect the active and total B12 results but not the MMA result.
79	B12 Global Ltd (now B12info Ltd)	Guideline	029	021	Rec 1.3.1 -1.3.15 Thresholds for Initial test results How do the current draft B12 test result thresholds compare with other countries such as Germany and Japan? There is an opportunity now to set reasonable B12 test thresholds for early diagnosis.	Thank you for your comment. The committee set the thresholds based on their knowledge of the UK population. The committee noted that there is no universal international threshold with which to define deficiency; it will vary according to how deficiency is diagnosed, the population studied and assay used for each country.
80	B12 Global Ltd (now B12info Ltd)	Guideline	030	027	Rec 1.3.1 -1.3.15 Thresholds for Initial test results A lot of people get used to insignificant symptoms which grow over time and are often attributed to old age by doctors and Consultants. Perhaps a trial of loading doses should be considered as a preventative maintenance measure at certain ages to establish if symptoms of "old age" reduce.	Thank you for your comment. Preventative vitamin B12 replacement was not considered as part of the scope of the guideline. NICE does not generally include dosages in recommendations where they are available in the BNF or SPC. Loading doses are covered in the BNF and therefore not included in the guideline.

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81	B12 Global Ltd (now B12info Ltd)	Guideline	031	006	Rec - for further research into diagnostoic testing - How the recommendations may affect practice The cost saving in administering B12 will likely be seen in the reduction in costs of other treatments and diagnoses, whilst at the same time providing an excellent public health service and long term economic benefits.	Thank you for your comment. In this section we describe the impact of the practice recommendations rather than the research recommendations. We agree that treatment can potentially reduce costs as well as benefit patients but only if given to those patients that are most likely to benefit. The committee also made a research recommendation in relation to diagnostic tests.
82	B12 Global Ltd (now B12info Ltd)	Guideline	034	021	Rec 1.5.1 -1.5.l6 Medicine induced deficiency This has not been researched enough to make the statement to suggest that there is no difference between oral and intramuscular injections for medicine induced deficiency. If the medicine affects absorption of B12 from food then injections must be preferable.	Thank you for your comment. The sentence reflects the absence of evidence and states there was no evidence to suggest either oral or intramuscular replacement was better. There was no evidence to suggest that oral vitamin B12 replacement would not work and the committee agreed that both options should be offered taking the person's preference into account.
83	B12 Global Ltd (now B12info Ltd)	Guideline	035	029	Rec 1.5.1 -1.5.l6 Dietary deficiency Should add "or intramuscular" after oral on Line 29. This draft still shows an intent on reduced treatment, presumably for cost reasons. The cost of B12 replacement is almost insignificant when compared to the cost to society of someone who is B12 deficient but	Thank you for your comment. This section of the rationale relates to the recommendation when oral vitamin B12 replacement is considered for people with a dietary deficiency. The paragraph further down describes when intramuscular B12 replacement is recommended in this group. The committee agreed that if a person has a dietary vitamin B12 deficiency then oral vitamin B12 replacement should rectify the situation in most cases. If oral treatment does not work, switching to intramuscular injections is

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					either left untreated or treated by other inappropriate means to barely manage symptoms.	recommended in the ongoing care and follow up recommendations. However, the committee also recommend intramuscular vitamin B12 replacement if they have another condition that may deteriorate rapidly, or there are concerns about adherence. There was no evidence to suggest that intramuscular injections are clinically or cost effective as a first line treatment for all people with a dietary vitamin B12 deficiency.
84	B12 Global Ltd (now B12info Ltd)	Guideline	036	001	Rec 1.5.1 -1.5.I6 Dietary deficiency How many experts were canvassed for their opinion. Do any of the experts have first hand knowledge of how debilitating the condition can be? How can the expert make such a general statement that "oral vitamin B12 replacement...of at least 1,000 micrograms a day" be a valid finding for the whole population who might be labeled as dietary deficient. This should be reworded to to include intramuscular B12 or oral B12 according to patient need.	Thank you for your comment. A dose of 1mg was recommended for dietary deficiency in this group because the body can need more vitamin B12 in pregnancy and during breastfeeding. Setting this minimum dose would ensure that enough vitamin is being absorbed. As with other people with a dietary deficiency there was no evidence to suggest it was clinically or cost effective to recommend intramuscular vitamin B12 replacement for all people in this group.
85	B12 Global Ltd (now B12info Ltd)	Guideline	036	007	Rec 1.5.1 -1.5.I6 Dietary deficiency State that treatment should be at a	Thank you for your comment. There was no evidence to recommend the frequency of vitamin B12 replacement. NICE expect healthcare professionals to follow the BNF when prescribing medicines.

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					frequency of every other day until symptoms stop improving	
86	B12 Global Ltd (now B12info Ltd)	Guideline	036	015	Rec 1.5.1 -1.5.I6 Dietary deficiency There is an urgent need to get away from the thinking that injections at 2 or 3 monthly intervals is sufficient for everyone. The thinking should default to every 2 days until symptoms resolve and only then reduce the frequency in small increments. Each person should be listened to and individual injection frequency given according to the patients experience.	Thank you for your comment. NICE does not generally include dosages in recommendations where they are available in the BNF or SPC. A dosage may be included if this information is not available, or the committee agrees that there needs to be a change to current recommended dosages, for example because of new evidence. Loading doses are covered in the BNF and therefore not included in the guideline. The guideline did look for clinical evidence relating to the frequency of intramuscular injections however no evidence was identified and the committee made a research recommendation.
87	B12 Global Ltd (now B12info Ltd)	Guideline	036	026	Rec 1.5.1 -1.5.I6 Unknown causes of vitamin B12 deficiency Will these necessary tests include testing for genetic polymorphisms such as MTRR, MTHFR, COMT, heavy metal toxicity and poisoning such as CO and hydrogen sulphide?	Thank you for your comment. Evidence for testing for genetic polymorphisms such as MTRR, MTHFR, COMT, heavy metal toxicity and poisoning such as CO and hydrogen sulphide was not reviewed in the guideline and therefore no recommendations have been made for their use.
88	B12 Global Ltd (now B12info Ltd)	Guideline	036	029	Rec 1.5.1 -1.5.I6 Self administration Sweeping generalisations are often made in terms of care by members of the medical community. There needs to be more emphasis placed on anecdotal evidence from patients who manage their own care	Thank you for your comment. The guideline review looked for and found no evidence on the effectiveness of self-medication either by intramuscular or subcutaneous injections. There are also no licenced medications for subcutaneous vitamin B12 injections in the UK. The committee agree that self-administration could be beneficial to people with vitamin B12 deficiency, therefore they made a key research recommendation in this area.

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					self administering B12 injections whether it is subcutaneous or intramuscular. Quite often, patients have to take caring for themselves into their own hands due to the lack of knowledge of doctors who restrict treatment which causes delay in recovery and potential permanent harm. Throughout this NICE Draft, the lay person does not appear to be represented in the treatment process which leaves much of this report open to interpretation. Please see : https://research.manchester.ac.uk/en/publications/patient-safety-self-injection-and-b12-deficiency-a-uk-cross-secti	
89	B12 Global Ltd (now B12info Ltd)	Guideline	037	007	Rec 1.5.1 -1.5.l6 How recommendations might affect practice Patients should not be dismissed for having a poor diet. How does the Doctor know if it is diet or malabsorbtion or both that is causing a B12 deficiency? They don't! If B12 deficiency is evident the patient should have the option of either oral or intramuscular replacement. If intramuscular, it should in the first instance be provided every 2 days until symptoms cease. If diet	Thank you for your comment. This section is to explain how the recommendations would be a change to current practice. The section related to diet details that intramuscular injections are not usually prescribed for a dietary deficiency and therefore that may be a change in practice. In the case of dietary deficiency, treatment will usually be required only for a short period and in this circumstance oral B12 will be less costly than intramuscular B12 treatment. There was no evidence to suggest a change in current practice of offering oral vitamin B12 replacement for a dietary

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					is suspected to be the cause or contributing factor, the patient should be offered nutritional guidance on sources or B12 from food, as well as guidance on sources of other vitamins and minerals, including the potential health consequences of synthetic vitamins when compared to the natural version, both in food and supplement form.	deficiency. Should this not resolve symptoms then considering switching treatments is also recommended.
90	B12 Global Ltd (now B12info Ltd)	Guideline	037	014	Rec 1.5.1 -1.5.I6 How recommendations might affect practice On what assumed frequency of B12 injections has the cost effectiveness been calculated? One B12 injection every 3 months should no longer be considered to be the default interval between injections. The recommendation should be once every two days until symptoms resolve and then the frequency reduced gradually until symptoms return or resolve. If symptoms return, revert back to once every two days or an interval at which the patient needs in order to keep symptoms at bay.	Thank you for this comment. The frequency of treatment in the economic analysis for a typical patient, as described in Evidence Review E was one injection every 2 or 3 months with 6 injections in the first month. This was informed by the BNF and the experience of some of the committee members.
91	B12 Global Ltd (now B12info Ltd)	Expert Testimony - Pregnancy and Breast feeding	General	General	Section B Diagnosis 5 Always consider signs and symptoms in addition to blood testing. Treatment 8 The loading dose frequency may need to be continued, do not assume 8 - 12 weeks will suffice.	Thank you for your comment. This is an expert witness testimony and is provided in the guideline for information.

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92	B12 Global Ltd (now B12info Ltd)	Expert Testimony - Pregnancy and Breast feeding	General	General	Treatment 10 - consider that there may be other causes alongside dietary lack.	Thank you for your comment. This is an expert witness testimony and is provided in the guideline for information. Therefore it has not been updated. However, your views are reflected in recommendation 1.5.11 related to dietary deficiency where the committee recommend readers to 'be aware that diet (for example, a vegetarian or vegan diet) may not be the cause, or the only cause, of a person's vitamin B12 deficiency'.
93	B12 Global Ltd (now B12info Ltd)	Expert Testimony - Pregnancy and Breast feeding	General	General	Nitrous oxide 11 - It WILL be an issue and B12 injections will need to be frequent after birth.	Thank you for your comment. This is an expert witness testimony and is provided in the guideline for information. Several stakeholders commented on the statement about nitrous oxide use during labour, suggesting that without evidence to support this the statement should not be made. The committee agreed and the recommendation relating to this has been removed from the guideline.
94	B12 Global Ltd (now B12info Ltd)	Expert Testimony - Pregnancy and Breast feeding	General	General	Nitrous oxide 13. The response of the expert shows she is not an expert in B12 deficiency - B12 injections should be given before and frequently afterwards to ensure mother and breastfed baby are accessing B12.	Thank you for your comment. This is an expert witness testimony and is provided in the guideline for information. Therefore it has not been updated. However, the use of injections was discussed and the committee agreed that for a dietary vitamin B12 deficiency oral replacement would be suitable treatment. The committee do not agree that intramuscular vitamin B12 injections should be given to all mothers before and after the

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						birth. If the cause of the deficiency is malabsorption then intramuscular vitamin B12 replacement is recommended as with other populations. Where there is a dietary deficiency then a dose of at least 1 mg a day of oral vitamin B12 replacement is recommended.
95	B12 Global Ltd (now B12info Ltd)	Expert Testimony - Pregnancy and Breast feeding	General	General	Other comments 15 Perhaps it's time to advocate routine testing - especially if poor mental health is a factor.	Thank you for your comment. This is an expert witness testimony and is provided in the guideline for information. Routine testing was not within the scope of the guideline.
96	B12 Global Ltd (now B12info Ltd)	Expert Testimony - Pregnancy and Breast feeding	General	General	Additionally, mothers who present with post natal depression following birth should all be screened for B12 and folate deficiency.	Thank you for your comment. This is an expert witness testimony and is provided in the guideline for information. Screening for vitamin B12 deficiency was not within the scope of the guideline.
97	B12 Global Ltd (now B12info Ltd)	Methods	General	General	The research samples do not show an accurate cross-section of people who actually have vitamin B12 deficiency. Studies focus on over 60's. Yet, B12 deficiency occurs in all ages and both sexes. The many causes of B12 deficiency may occur at different stages of life, such as, coeliac disease, Crohn's disease, prescribed medicines, eating disorders, gastric operations and nitrous oxide abuse	Thank you for your comment. The committee were aware that the evidence for vitamin B12 deficiency was limited. They agreed that treatment should be effective in all age groups and without evidence to suggest otherwise made the recommendations apply to all adults and are not just restricted to older people.

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					are examples where the 'population ' includes children and teenagers. B12 deficiency can take many years to diagnose due to lack of education for all clinicians, therefore, due to misdiagnoses, mismanagement and mistreatment, many people are excluded from the studies and research. This is a huge problem. Where is the data collection and studies on this aspect of B12 deficiency?	
98	Beckman Coulter (UK) Ltd	Guideline	010	010	The committee acknowledges in Evidence Review C (Pg 45 'Thresholds for test results') the lack of standardisation of Vitamin B12 assays, the consequent significant differences in reference ranges recommended between test manufacturers and the fact that the evidence 'didn't clearly support any particular cut-offs'. In view of this perhaps a sentence could be added to the guideline to indicate that the proposed thresholds may not be suitable for all assays and that locally validated thresholds for confirmed deficiency may be more suitable in some laboratories.	Thank you for your comment. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not. Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests.
99	Beckman Coulter (UK) Ltd	Guideline	010	021-022	The committee acknowledges in Evidence Review C (Pg 45 'Thresholds for test results') the lack of standardisation of	Thank you for your comment. Several stakeholders commented on the thresholds. Some thought they were too

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					Vitamin B12 assays, the consequent significant differences in reference ranges recommended between test manufacturers and the fact that the evidence 'didn't clearly support any particular cut-offs'. In view of this perhaps a sentence could be added to the guideline to indicate that the proposed thresholds may not be suitable for all assays and that locally validated thresholds for indeterminate test results may be more suitable in some laboratories.	low, others thought they were too high and there was also some support that they are about right. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not. Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests. The committee also recommend considering MMA as a further test for people with an indeterminate active or total B12 test result. This is to capture people who may have a vitamin B12 deficiency when their test result doesn't meet the criteria for deficiency. An indeterminate result covers an active B12 of between 25 and 70 pmol per litre, and a total B12 of between 180 and 350 nanograms (133 and 258 pmol) per litre. The committee has also added a recommendation to use the laboratory's reference ranges to decide if vitamin B12 deficiency is likely when interpreting serum MMA and plasma homocysteine test results.

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100	Beckman Coulter (UK) Ltd	Guideline	011	026	The committee acknowledges in Evidence Review C (Pg 45 'Thresholds for test results') the lack of standardisation of Vitamin B12 assays, the consequent significant differences in reference ranges recommended between test manufacturers and the fact that the evidence 'didn't clearly support any particular cut-offs'. In view of this perhaps a sentence could be added to the guideline to indicate that the proposed thresholds may not be suitable for all assays and that locally validated thresholds for deficiency unlikely may be more suitable in some laboratories.	Thank you for your comment. Several stakeholders commented on the thresholds. Some thought they were too low, others thought they were too high and there was also some support that they are about right. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not. Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests. The committee also recommend considering MMA as a further test for people with an indeterminate active or total B12 test result. This is to capture people who may have a vitamin B12 deficiency when their test result doesn't meet the criteria for deficiency. An indeterminate result covers an active B12 of between 25 and 70 pmol per litre, and a total B12 of between 180 and 350 nanograms (133 and 258 pmol) per litre. The committee has also added a recommendation to use the laboratory's reference ranges to decide if vitamin B12 deficiency is likely when interpreting serum MMA and plasma homocysteine test results.

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101	Birmingham Quality	Guideline	009	012	1.3.3 **Again, we are in classic Catch 22 mode**. Homocysteine is not widely measured. There are different clinical situations where different levels are appropriate, but in the Lipid/Heart disease arena we are talking about 10 Laboratories measuring Homocysteine in UK NEQAS. I would be surprised if POCT systems were anywhere good enough. There isn't the data out there to support the theoretical benefits of using homocysteine, MMA or indeed HoloTC. There are pockets of data, but the numbers/values are just laboratory-specific and might not transfer.	Thank you for your comment. Following stakeholder comments the committee have recommended using either homocysteine or serum MMA when testing for vitamin B12 deficiency suspected to be caused by recreational nitrous oxide use. The recommendation has also been updated to state that if homocysteine is the chosen test then the person should be referred to phlebotomy services in secondary care. The committee recommend these tests because they agreed that total and active B12 are not suitable tests for people who use nitrous oxide recreationally. This is because the substance inactivates the B12 molecule, so the person's active or total B12 concentrations would appear to be normal even when they have a deficiency.
102	Birmingham Quality	Guideline	010	010	1.3.8 Threshold for initial test results. I have concerns about 'accuracy', and assay performance generally, with any analyte/measurand (even where there is an internationally agreed reference material or method) where a mixture is being measured **and** the different assay system in use by hospital laboratories have different specificities **and** so consequently the	Thank you for your comment. Several stakeholders commented on the thresholds. Some thought they were too low, others thought they were too high and there was also some support that they are about right. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not. Therefore, they have added the caveat that where there is

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					numerical results they produce are different. In the UK, Total B12 is analysed primarily on 6 analysers from 4 international Diagnostic companies. At the cut-off concentration quoted at 350 ng/L there can be a difference of +/-30% between methods. Data from UK NEQAS from 2023 indicates that on a native, un-manipulated specimen, with a consensus mean of 348 ng/L the +/-2SD range of results reported would be between 256 and 440 ng/L. At the lower cut-off of 180 ng/L, while there is less variation between methods, there is still one method that is 38% lower. The +/-2SD range at 185 ng/L is between 115 and 255 ng/L.	substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests. The committee also recommend considering MMA as a further test for people with an indeterminate active or total B12 test result. This is to capture people who may have a vitamin B12 deficiency when their test result doesn't meet the criteria for deficiency. An indeterminate result covers an active B12 of between 25 and 70 pmol per litre, and a total B12 of between 180 and 350 nanograms (133 and 258 pmol) per litre. The committee has also added a recommendation to use the laboratory's reference ranges to decide if vitamin B12 deficiency is likely when interpreting serum MMA and plasma homocysteine test results.
103	Birmingham Quality	Guideline	010	017	1.3.10 I believe the **Indeterminate** category may have its origins from UK NEQAS data more than 15 years ago. However, it is not an interpretation category that is being commonly used in the UK, if	Thank you for your comment. Several stakeholders commented on the thresholds. Some thought they were too low, others thought they were too high and there was also some support that they are about right. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted

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					the data from ~ 350 analysers, ~ 180 Laboratories is to be believed. Data from the last few years from hundreds of Laboratories, shows that the empirical cut-off between **Low** and **Normal** interpretations is ~ 180 ng/L *[which despite my reservations above does fit in with NICE quoted cut-off]*. However, at a concentration of ~ 265 ng/L, which is midway between 180 and 350 of this putative **Indeterminate** category range, less than 5% of Laboratories would categorise this result as being Indeterminate. The highest ever % Indeterminate classification for any specimen was just over 10% and this was on a specimen with a consensus mean of approximately 200 ng/L. Despite its theoretical attractiveness, Indeterminate is just not being used as a category by UK Laboratories.	that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not. Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests. The committee also recommend considering MMA as a further test for people with an indeterminate active or total B12 test result. This is to capture people who may have a vitamin B12 deficiency when their test result doesn't meet the criteria for deficiency. An indeterminate result covers an active B12 of between 25 and 70 pmol per litre, and a total B12 of between 180 and 350 nanograms (133 and 258 pmol) per litre. The committee has also added a recommendation to use the laboratory's reference ranges to decide if vitamin B12 deficiency is likely when interpreting serum MMA and plasma homocysteine test results.

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104	Birmingham Quality	Guideline	010	025	1.3.10 MMA and Active B12. The number of UK Laboratories measuring Active B12 (HoloTC) is only ~10% of those measuring Total B12 (~18 Laboratories; 36 Analysers). Despite the test now being available on analysers from several Diagnostic companies (it was only Abbott for many years) the number of users has **not** grown over the last 10 years. At a notional concentration of 33 pmol/L HoloTC, the between Laboratory agreement would only be ~ 17%, though would be a respectable 7% for within-method agreement from the latest Abbott analyser. Following Covid-19, the number of UK-based MMA users returning results to UK NEQAS fell away to zero. There will be several Laboratories measuring MMA but there is no robust data from a range of Laboratories to support the theoretical advantage of using a HoloTC/MMA combination. I wish that there was.	Thank you for your comment. The committee thought carefully before making the recommendations and took cost effectiveness into account. Economic modelling showed that MMA is likely to be cost effective for people with a B12 measurement in the indeterminate range. Implementing these recommendations will require some reallocation of resources, including investment in pathology services, so that testing can become more widely available in primary care. A resource impact report and tool will be published alongside this guideline.
105	British Dietetic Association -	Guideline	013	017-021	The recommendation that intramuscular vitamin B12 injections should be considered in preference to oral vitamin B12	Thank you for your comment and support for the recommendation.

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	Obesity Specialist Committee				replacement for people who have had bariatric surgery, will help support patients receiving this through their general practice and aid adherence. Apart from the bariatric population, we are not aware that those living with obesity are at greater risk of B12 deficiency providing that they are consuming a nutritionally balanced diet or perhaps because of long-term use of Metformin. However we recommend further research into prevalence of deficiency in this population group.	Prevalence of vitamin B12 deficiency was not a review in the guideline so no research recommendations have been made in this area.
106	British Dietetic Association – Obesity Specialist Committee	Guideline	008		Box 2 We are pleased to see the inclusion of bariatric surgical procedures as not all healthcare professionals are aware that many bariatric surgical procedures such as the Roux-en-Y gastric bypass and sleeve gastrectomy increase the risk of vitamin B12 deficiency.	Thank you for your comment and support for the recommendation.
107	British Dietetic Association – Obesity Specialist Committee	Guideline	010	017	It is helpful to identify when to measure methylmalonic acid (MMA), however, this test is not widely available within primary or secondary care.	Thank you for your comment. The committee recommended serum MMA because it is likely to lead to faster diagnosis and treatment, which, in some cases, could avoid unnecessary investigations or avoid a referral to secondary care.

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					It is good to see that the cost benefits of more advanced tests to determine if there is deficiency has been recommended.	Implementing these recommendations will require some reallocation of resources, including some investment in pathology services. A resource impact report and tool will be published alongside this guideline.
108	British Dietetic Association [on behalf of the BDA Paediatric Specialist Group, BDA Maternal and Fertility Nutrition Specialist Group and BDA Oncology Specialist Group]	Guideline	General	General	We would recommend linking in with NICE guidelines for diabetes to highlight the risk of b12 deficiency with metformin use.	Thank you for your comment. We have not linked to the NICE guidelines for diabetes as there is no information in these on the risk of vitamin B12 deficiency and diabetes. The risk is highlighted in the BNF which links to MHRA safety advice and the expectation is that clinicians refer to the BNF when prescribing medicines.
109	British Dietetic Association [on behalf of the BDA Paediatric Specialist Group, BDA	Guideline	008	003	Box 2 In the second bullet point, food allergy to milk, fish and/or eggs should be included as an example of diets that are low in animal-food sources, pertaining to risk of B12 deficiency.	Thank you for your comment. Food allergy has been added as a bullet point in box 2. More detail has also been added to the rationale for the recommendations on managing dietary vitamin B12 deficiency covering your points.

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	Maternal and Fertility Nutrition Specialist Group and BDA Oncology Specialist Group]					
110	British Dietetic Association [on behalf of the BDA Paediatric Specialist Group, BDA Maternal and Fertility Nutrition Specialist Group and BDA Oncology Specialist Group]	Guideline	008	003	Box 2 People following a diet that is low in animal food, may still take enough B12 via fortified food; we recommend changing this to "without the regular use of supplements or B12 fortified food".	Thank you for your comment. A bullet point has been added to the recommendation to state in people who do not consume food or drinks fortified with vitamin B12.
111	British Dietetic Association	Guideline	008	003	Box 2 We recommend specifying that supplements of B12 should be taken as	Thank you for your comment. The aim of this recommendation is to identify whether the person is taking supplements rather than recommending what should be

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	[on behalf of the BDA Paediatric Specialist Group, BDA Maternal and Fertility Nutrition Specialist Group and BDA Oncology Specialist Group]				10mcg per day or at least 2mg per week (Garton 2017).	taken. Evidence was not reviewed to specify the dosage of oral supplements and where they are mentioned in the section on managing dietary vitamin B12 deficiency the committee only specified which forms of vitamin B12 should be used. This was because they were aware that some forms of vitamin B12 supplements do not contain enough or the right type of vitamin B12.
112	British Dietetic Association [on behalf of the BDA Paediatric Specialist Group, BDA Maternal and Fertility Nutrition Specialist Group and BDA Oncology	Guideline	008	General	Box 2 It is helpful to see a list of risk factors with radiotherapy to the abdomen and pelvis included. When listing surgery, bariatric surgery is given a large focus which is understandable. While we understand you cannot make an extensive list, oncology surgery such as total gastrectomy, oesophago-gastrectomy, partial or subtotal gastrectomy should be noted.	Thank you for your comment. The committee agreed that oncology would be covered by 'previous gastrointestinal surgery' which includes both benign and malignant surgery.

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	Specialist Group]					
113	British Dietetic Association [on behalf of the BDA Paediatric Specialist Group, BDA Maternal and Fertility Nutrition Specialist Group and BDA Oncology Specialist Group]	Guideline	008	General	Box 2 Under risk factors we could not see infection such as Helicobacter pylori which we know if infected can significantly impact on patients B12 levels.	Thank you for your comment. Helicobacter Pylori/other parasitic infestations as risk factors were not included as part of the review and therefore no recommendations have been made relating to them. Only the most common symptoms and signs were included in the guideline review therefore the recommendations have been restricted to these. The recommendations and box have been updated to make it clear that these are common symptoms and signs.
114	British Dietetic Association [on behalf of the BDA Paediatric Specialist Group, BDA Maternal and Fertility	Guideline	009	017	1.3.5 We recommend adding "people who are pregnant or `" to the list of people who should not delay B12 replacement, as B12 is a vital nutrient for foetal and infant neurological development.	Thank you for your comment. The committee agreed it is important to establish if there is a diagnosis first and that it would not take long for test results to come back. Starting treatment before the test results come back is recommended during pregnancy if they are considered for an MMA test. This is because it could take longer to get this test result back.

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	Nutrition Specialist Group and BDA Oncology Specialist Group]					
115	British Dietetic Association [on behalf of the BDA Paediatric Specialist Group, BDA Maternal and Fertility Nutrition Specialist Group and BDA Oncology Specialist Group]	Guideline	014 - 015	001	1.5.10 We recommend adding "Ask about their intake of B12 fortified foods, e.g., some breakfast cereals, yeast extract, some plant-based dairy alternatives"	Thank you for your comment. The recommendation has been updated to state 'ask what they eat or drink including any foods or drinks that contain vitamin B12.' The rationale has also been updated in relation to this to state that 'as well as meat, fish and dairy products sources of vitamin B12 include yeast extract and foods fortified with vitamin B12 such as some breakfast cereals.'
116	British Dietetic Association [on behalf of the BDA	Guideline	015	028	1.5.14 We recommend adding "If a person has B12 deficiency linked to their diet and they are pregnant or breastfeeding, they should	Thank you for your comment. Referral to a dietician was not included as part of the scope of the guideline and no recommendations have been made related to this.

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	Paediatric Specialist Group, BDA Maternal and Fertility Nutrition Specialist Group and BDA Oncology Specialist Group]				be referred to a dietitian or registered nutritionist for dietary advice"	
117	British Dietetic Association [on behalf of the BDA Paediatric Specialist Group, BDA Maternal and Fertility Nutrition Specialist Group and BDA Oncology Specialist Group]	Membership List	General	General	It is great to see a wide MDT involved in the development of these guidelines. These are some thorough and well set out guidelines that the BDA oncology group fully support.	Thank you for your support.

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118	British Medical Association	Guideline	General	General	This draft guideline is overly wordy, does not make any attempt to simplify concepts through flow charts, and is unnecessarily complex. It also relies on a large number of tests being done in primary care and over reliance on GPs to become specialists when symptoms are not improving.	Thank you for your comment. The guideline has been updated following stakeholder comments. We have revised some wording to ensure it is as clear, concise and user-friendly as possible. There is now a table for the diagnostic thresholds rather than long worded recommendations. There is also a visual summary to aid with the recommendations for ongoing care and follow up. Most of the tests recommended can be requested by GPs through their laboratories. However, where they cannot it has been made clear in the recommendations that specialist input will be required.
119	British Medical Association	Guideline	General	General	The guidance is vague in parts which seems to push clinical uncertainty back to GPs – good guidance should support GPs to navigate this uncertainty, not introduce it.	Thank you for your comment. The guideline has been updated following stakeholder comments. We have revised some wording to ensure it is as clear, concise and user-friendly as possible. There is now a table for the diagnostic thresholds rather than long worded recommendations. There is also a visual summary to aid with the recommendations for ongoing care and follow up. The recommendations are based on the available evidence which was unfortunately lacking, this limited the committee's ability to make more directive recommendations in a lot of cases. However the committee also made some research recommendations to help address some of the uncertainty.
120	British Medical Association	Guideline	009	003	Will GPs have access to active B12 testing vs total?	Thank you for your comment. The committee agreed that using active B12 would not require a change in practice for GP surgeries because it can be carried out on the same serum sample as for total B12. They agreed that in their

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					We would like clarification to whom GPs should for homocysteine levels – is it Haematology?	experience, active B12 is a more accurate test than total B12. However, they recommended either total or active B12 to reflect the lack of evidence demonstrating this and the lack of availability of active B12 at all laboratories. The committee has added a recommendation to use the laboratory reference ranges for interpreting homocysteine and MMA.
121	British Medical Association	Guideline	010	002	It would be helpful to have greater clarity on what is meant by using caution and how to interpret the results in pregnancy.	Thank you for your comment. Following stakeholder comments the recommendation has been updated and pregnancy has been removed.
122	British Medical Association	Guideline	010	015	If there is access to homocysteine in primary care and GPs are expected to request the test, this statement is unacceptable: When interpreting homocysteine test results, use clinical judgement to determine what reference range to use GPs have no expertise in homocysteine levels so would not be able to use clinical judgement, therefore could not do the test.	Thank you for your comment. We have updated this to make it more specific. The recommendation now states 'Use laboratory reference ranges to interpret plasma homocysteine test results when deciding if vitamin B12 deficiency is likely, but take into account additional factors that may increase plasma homocysteine levels (such as folate deficiency).' We have also updated the recommendation to make it clear that the person should be referred to hospital phlebotomy when homocysteine is used as the test.

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123	British Medical Association	Guideline	010	018	Is MMA testing available in Primary Care? This is too vague and it should be a recommendation to do MMA testing if symptoms and signs or have more guidance around when, again this requires specialist knowledge. GPs would have to look these indeterminate reference ranges up every time; it should be stipulated that labs should ensure both normal, indeterminate and low reference ranges are included and state the guidance for patients in both low and the indeterminate range e.g. patients that continue to have symptoms should have MMA or if patients from black family backgrounds, these should be treated as having low B12 levels.	Thank you for your comment. The committee thought carefully before making the recommendations and took cost effectiveness into account. Economic modelling showed that MMA is likely to be cost effective for people with a B12 measurement in the indeterminate range. Implementing these recommendations will require some reallocation of resources, including investment in pathology services, so that MMA testing can become more widely available in primary care. A resource impact report and tool will be published alongside this guideline. The thresholds have been put in a table to make them easier to read. A recommendation has been added to advise using the laboratory's reference ranges to interpret serum MMA test results when deciding if vitamin B12 deficiency is likely.
124	British Medical Association	Guideline	011	001	How much higher reference range for 1 serum vitamin B12 concentrations?	Thank you for your comment. The findings in the study suggested cut-off for deficiency as 225 ng/L (166 pmol/L). This has been added to the evidence report. However, the committee were aware that this is one study and the result may need to be validated in other populations. Therefore they did not include it in the guideline recommendations.
125	British Medical Association	Guideline	012	019	This is specialist work and is not for GPs to decide which test especially as some require referral a recommendation should be made about referral to specialist instead.	Thank you for your comment. The committee decided that most of these tests can be ordered in primary care. There may be some variation in availability of tests which is why the committee have not tried to give a hierarchy. However, in the

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						absence of evidence the committee wanted to make it clear that there are further investigations available for consideration to help aid diagnosis. The main exception is for gastroscopy where the recommendation has been updated to make it clear this will need to be carried out by a specialist. The section on 'How recommendations might affect practice' has been updated to make it clear that these investigations are used in some cases depending on the availability of tests. However, the recommendation may raise awareness of these tests and lead to more tests being ordered.
126	British Medical Association	Guideline	019	011 & 016	Surely patient choice would say they can switch to oral in these cases if the patient wishes? (If they would have been offered initially?)	Thank you for your comment. The committee agreed it is important to continue treatment. No evidence was identified for switching from intramuscular injections to oral vitamin B12 replacement. Most people on intramuscular injections will be on them because they are considered the most effective form of vitamin B12 replacement. Should they request to switch to oral replacement, the committee agreed the clinician would take this into consideration. However, the committee agreed continuing with intramuscular injections was the better option.
127	British Society for Haematology	Guideline	006	006 - 007	The requirement that there need to be identifiable risk factor before offering testing for B12 deficiency may lead to under-recognition as the risk factors are frequently either not obvious (e.g. isolated	Thank you for your comment. No evidence was identified to make a strong recommendation that people with one of the symptoms or signs without a risk factor, or one of the risk factors without a symptom or sign, should be tested. The committee agreed that the symptoms and signs associated with vitamin B12 deficiency vary and can also be indicative of

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					autoimmune gastritis) or non-specific (e.g. metformin treatment) Suggest change "and" to "especially if they have"	other conditions. Without the evidence, making a recommendation to test people with just one of the symptoms or signs or risk factor would hugely increase resource impact without any evidence of benefit. The committee recognise that there may be people in whom there is a suggestion of vitamin B12 deficiency without a risk factor, however this would vary and need to be assessed on a case-by-case basis. Consequently, they recommended that clinical judgement would need to be used to decide if a person should be tested in these circumstances.
128	British Society for Haematology	Guideline	007		Box 1 Skin manifestations are not included Include skin manifestations e.g. pigmentary changes, vitiligo	Thank you for your comment. Only the most common symptoms and signs were included in the guideline review therefore the recommendations have been restricted to these. The recommendations and box have been updated to make it clear that these are common symptoms and signs.
129	British Society for Haematology	Guideline	009 013	003 – 004, 008 – 009 & 001	Recommendation for using holotranscobalamine for the audience mentioned in page 1 is likely to have significant: 1) Cost implications. 2) Practical implications: sample requirement (e.g. fresh blood sample is required which is not accessible for the community), and availability of the test (only in few centres) Rise awareness regarding the possibility of B12 deficiency despite normal serum or	Thank you for your comment. The committee agreed that using active B12 (holotranscobalamin) would not require a significant change in practice for GP surgeries because it can be carried out on the same serum sample as for total B12. They agreed that in their experience, while active B12 is more costly than total B12, it is also a more accurate test. However, they recommended either total or active B12 to reflect the lack of evidence demonstrating this and the lack of availability of active B12 at some laboratories. Following stakeholder comments the recommendations on who to test were revised. Age as a risk factor and symptoms of mental health problems have been removed from the

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					plasma B12 levels, but reserve specialised testing to secondary care (gastroenterologists, neurologists and haematologists) Page 31, lines 7 – 21 is acknowledged	respective boxes. This means there is no longer a suggestion to test people if they have these features. Therefore there are likely to be significantly fewer people being tested than recommended in the consultation version of the guideline. The committee agreed that most of these tests are available to order from primary care. The bullet point related to gastroscopy has been updated to make it clear it would need to be carried out by a specialist. The committee agreed that if required the GP would seek advice from a specialist to discuss any results.
130	British Society for Haematology	Guideline	011	004 - 005	Why is the recommendation for a trial of B12 therapy limited to people of black family background? Was this recommendation intended to be for all people meeting criteria of 1.3.10, or only for black people meeting this criterion? Is it not possible to include such people under 1.3.12 and 1.3.13? or are they considered to be especially at a higher risk? Page 30, lines 14 – 22 is acknowledged	Thank you for your comment. The recommendation related to Black ethnicity has been updated so that it only highlights the higher threshold for people with Black ethnicity and no longer recommends considering treatment without waiting for an MMA test result. This is in response to your comment and because the guideline does not define the threshold for vitamin B12 deficiency in people with Black ethnicity. The findings in the study suggested cut-off for deficiency as 225 ng/L (166 pmol/L). This has been added to the evidence report. However, the committee were aware that this is one study and the result may need to be validated in other populations. Therefore they did not include it in the guideline recommendations.
131	British Society for Haematology	Guideline	011	026	There are reports of B12 deficiency in people with levels higher than 350 ng/L.	Thank you for your comment. Several stakeholders commented on the thresholds. Some thought they were too

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					Those people for example may have high titre anti-IF antibody interering with the test. This pitfall is largely overcome by holotranscobalamine testing. Recommendation 1.3.15 is acknowledged, but there is however a risk of irreversible neurological damage during this 6 months period and hence it will be safer to still offer B12 trial of therapy to patients with symptoms, signs and risk factors for B12 deficiency even if B12 is > 350 ng/L Suggest remove line 26	low, others thought they were too high and there was also some support that they are about right. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not. Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests. The committee also recommend considering MMA as a further test for people with an indeterminate active or total B12 test result. This is to capture people who may have a vitamin B12 deficiency when their test result doesn't meet the criteria for deficiency. An indeterminate result covers an active B12 of between 25 and 70 pmol per litre, and a total B12 of between 180 and 350 nanograms (133 and 258 pmol) per litre. The committee has also added a recommendation to use the laboratory's reference ranges to decide if vitamin B12 deficiency is likely when interpreting serum MMA and plasma homocysteine test results. The committee noted that there is no universal international threshold with which to define deficiency; it will vary

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						according to how deficiency is diagnosed, the population studied and assay used for each country. Active B12 (holotranscobalamin) is an option as an initial test should healthcare professionals decide to use it. A trial of vitamin B12 deficiency for people whose test results suggest they don't have a deficiency was not included as part of the guideline review. Therefore, no recommendations have been made advising healthcare professionals whether or not to trial vitamin B12 replacement in this scenario. 1.3.15 has been updated (and is now 1.3.16) to advise investigating other causes as well as considering a repeat of the initial test if they are still experiencing symptoms or signs 3 to 6 months later. It is anticipated this would be for anyone with symptoms regardless of their severity.
132	British Society for Haematology	Guideline	012	022	Recommendation for gastrin level testing is likely to have significant: 3) Cost implications. 4) Practical implications: sample requirement (e.g. fresh blood sample is required which is not accessible for the community), and availability of the test (only in few centres) Rise awareness regarding the possibility of B12 deficiency despite normal serum or plasma B12 levels, but reserve specialised	Thank you for your comment. The committee agree that most of these tests can be ordered by primary care although the person may need to go to the hospital for the test. There may be some variation in availability of tests which is why the committee have not tried to give a hierarchy. However, in the absence of evidence the committee wanted to make it clear that there are further investigations available for consideration to help aid diagnosis. The main exception is for gastroscopy where the recommendation has been updated to make it clear this will need to be carried out by a specialist.

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					testing to secondary care (gastroenterologists, neurologists and haematologists). Potential impact on increased secondary care referrals is acknowledged Page 31, lines 7 – 21 is acknowledged	The section on 'How recommendations might affect practice' has been updated to make it clear that these investigations are used in some cases depending on the availability of tests. However, the recommendation may raise awareness of these tests and lead to more tests being ordered.
133	British Society for Haematology	Guideline	025	013 - 014	This indicates the guidelines are unlikely to have an impact on resources as it validates current practice. To my knowledge, the current level of awareness and use of specialised testing (holotranscombalamine, MMA, homocystiene, gastrin level, CobaSorb) is very limited. Given the target audience for this guidelines identified in page 1, the guidelines would have an impact on resources given the limited awareness (to my knowledge) on specialised testing. When the awareness is improved by this guidelines and a recommendation for testing is made, this is likely to impact on resources. Compare the impact on resources between:	Thank you for your comment. This statement relates to the recommendations on providing people with suspected or confirmed vitamin B12 deficiency with information about their condition. The committee agreed that providing information is current practice and therefore there would not be a resource impact. The statement has been updated to make it clear that it is providing information and support that will not lead to a resource impact. The resource impact of the tests you mention are discussed in those rationale sections.

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					1) Reommendations for specialised testing 2) Offering a trial of B12 replacement to patients with symptoms, signs and risk factors but normal B12levels 3) Appropriate secondary care referral for patients with symptoms, signs and risk factors but normal B12levels Page 29, lines 25 – 28 is acknowledged Page 31, lines 7 – 21 is acknowledged	
134	British Society for Haematology	Guideline	036	030	This is first and only reference to subcutaneous route for parenteral administration. There is a significant cohort of patients who are at higher risk of bleeding due to various reasons e.g. anticoagulation for various indications, thrombocytopenia, congenital bleeding disorders. Has the impact of the guidelines on patients at higher risk of bleeding been considered? Produce recommendation under a separate subheading for parenteral administration of B12 in people with higher bleeding risk	Thank you for your comment. People at a higher risk of bleeding were not considered as a specific group in the guideline and therefore no recommendations have been made in this area.

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135	Cardiff Metropolitan University	Guideline	General	003 - 005	Within the guideline the condition of PA is linked to autoimmune gastritis (AG) The phrasing of these statements suggest to the reader that PA and AG can be interchanged as diagnostic terms. The current evidence base does not suggest that PA and AG are synonymous; it is possible for AG to occur with or without PA. AG can also be present in the absence of a B12 deficiency Rustgi, S. D., Bijlani, P., & Shah, S. C. (2021). Autoimmune gastritis, with or without pernicious anemia: epidemiology, risk factors, and clinical management. *Therapeutic advances in gastroenterology*, *14*, 17562848211038771. https://doi.org/10.1177/17562848211038771 Asides from issues with accuracy only referring to clinical causes of B12 deficiency as AG within the guideline is problematic as NICE guidelines are not a suitable place to be change a frequently used diagnostic label. Most patients in the UK would refer to their condition (even if it originates from AG) as PA; PA is also the term that	Thank you for your comment. The guideline has been updated to acknowledge the difference between autoimmune gastritis and pernicious anaemia and provide a more detailed reason as to why the term 'pernicious anaemia' has not been used. This explains that autoimmune gastritis is sometimes referred to as pernicious anaemia which is a separate condition that can be a consequence of chronic, severe vitamin B12 deficiency, including deficiency caused by autoimmune gastritis. However, pernicious anaemia in its true sense (that is 'a life-threatening anaemia') is now extremely rare because of developments in testing and treatment for, and greater awareness of, vitamin B12 deficiency. For this reason, and to prevent any confusion with autoimmune gastritis, we have not used the term 'pernicious anaemia' in the recommendations.

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					healthcare professionals use within day to day practice. The use of PA in addition to AG would ensure effective signposting to the guideline and use language that is meaningful to the patient group and their healthcare providers.	
136	Cardiff Metropolitan University	Guideline	General	General	The term Pernicious Anaemia (PA) has been removed from title of this guideline. In the UK PA is the most frequent non-diet related cause of B12 deficiency including this is term within the title of the guideline will improve accessibility and help signpost the reader to the advice.	Thank you for your comment. The guideline has been updated to acknowledge the difference between autoimmune gastritis and pernicious anaemia and provide a more detailed reason as to why the term 'pernicious anaemia' has not been used. This explains that autoimmune gastritis is sometimes referred to as pernicious anaemia which is a separate condition that can be a consequence of chronic, severe vitamin B12 deficiency, including deficiency caused by autoimmune gastritis. However, pernicious anaemia in its true sense (that is 'a life-threatening anaemia') is now extremely rare because of developments in testing and treatment for, and greater awareness of, vitamin B12 deficiency. For this reason, and to prevent any confusion with autoimmune gastritis, we have not used the term 'pernicious anaemia' in the recommendations.
137	Cardiff Metropolitan University	Guideline	005	016	**"Some causes of vitamin B12 deficiency will need (and receive) lifelong treatment, such as deficiency caused by autoimmune gastritis"** In this recommendation it is important to list all the conditions that would require lifelong treatment. For example, PA would be a	Thank you for your comment. The recommendation has been updated to change 'lifelong treatment' to 'lifelong vitamin B12 replacement' to make it clear the committee are not talking about treatment of other conditions. The committee agreed that they wanted to emphasise autoimmune gastritis only in this point as an example of someone who is likely to need lifelong vitamin B12 replacement. The term pernicious anaemia is not used in the

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					type of B12 deficiency that would need lifelong treatment as the condition is not curable and cannot be reversed. A recent paper by Seage and Semedo (2021) highlights gaps in knowledge around the need for lifelong treatment in PA. During the Covid-19 pandemic many UK based patients with PA had their treatment stopped and/or were asked to have their B12 levels monitored to remain on treatment pathways. Seage, C. H., & Semedo, L. (2021). How Do Patients Receiving Prescribed B_{12} 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. https://doi.org/10.1177/2374373521998842	recommendations and a further description as to why is in the section on Terms used in this guideline. This also includes a description of the difference between autoimmune gastritis and pernicious anaemia.
138	Cardiff Metropolitan University	Guideline	005	018	**Explain to pregnant women and pregnant people who are receiving 19 vitamin B12 replacement that using nitrous oxide with air (gas and air) 20 during labour is unlikely to make their vitamin B12 deficiency worse**. **er** This statement appears to be based on an expert's opinion rather than published	Thank you for your comment. Several stakeholders commented on this suggesting that without evidence to support this the statement should not be made. The committee agreed and the recommendation relating to this has been removed from the guideline. Recommendations related to pregnant patients on gas and air are covered by MHRA guidance on Nitrous oxide: neurological and haematological toxic effects.

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					evidence. Given that there is very limited research in this area, and some which already indicates that nitrous oxide can be a risk factor for infant B12 deficiency NICE should be cautious with recommendations around this until more conclusive evidence is found. Ljungblad UW, Lindberg M, Eklund EA, Saeves I, Bjørke-Monsen AL, Tangeraas T. Nitrous oxide in labour predicted newborn screening total homocysteine and is a potential risk factor for infant vitamin B12 deficiency. Acta Paediatr. 2022 Dec;111(12):2315-2321. doi: 10.1111/apa.16530. Epub 2022 Sep 9. PMID: 36029294; PMCID: PMC9825840.	
139	cluB-12 UK	Guideline	General	General	There is a missing section from this guideline that speaks on the discontinuation of treatment. We are aware that treatment can be stopped within primary care but it's important for ongoing patient monitoring and symptom assessment should this decision be made. However, it's important to highlight that individuals with irreversible	Thank you for your comment. The recommendations for follow up and ongoing care have made reference to discontinuing treatment where symptoms are resolved. These have been edited to make them clearer.

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					malabsorption should never have their treatment discontinued. Here is a drafted guidelines from Club-12: **1.6 Discontinuation of pharmacological treatment with B12** 1.6.1 Discontinuation of treatment with high dose B12 oral (sublingual, nasal) or B12 injections if: • The original diagnosis of B12 deficiency is likely to be unwarranted. • The reason for an impaired uptake of B12 is discontinued. 1.6.2 Discontinuation should be followed for at least 2 years since recurrence of symptoms and alterations in biomarkers occur slowly. • The patient should be instructed to seek the doctor if symptoms reoccur. • Blood test for B12 deficiency should be performed every 6 months for at least two years. • If patient's symptoms and/or blood tests indicate recurrent B12 deficiency the patients should return to treatment with B12.	

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					• If no alteration in symptoms and no change in blood tests indicating reoccurrence of B12 deficiency, the patient can continue without further B12 treatment	
140	cluB-12 UK	Guideline	General	General	**Missing Self-injection guidance** There is a missing section in the guidelines regarding patient self-injection of vitamin B12, with or without healthcare professional authorisation. Many patients self-administer B12 injections or express they would like to. Therefore, if a patient is wanting to self-inject they should be taught to and be empowered to do so. This approach not only benefits the patients directly but also contributes to alleviating the burden on the healthcare system and economic savings. Some patients are concerned about informing their GP regarding their self-injection practices, as they fear it might lead to a discontinuation of their current treatment in the NHS. Patients should be encouraged to communicate openly with their GPs about self-injection practices and GPs they should support and provide advice on this. It's important that patients feel comfortable openly discussing their	Thank you for your comment. Self-injection was considered as part of the review on management. However, no evidence was identified so the committee made a key research recommendation in this area.

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					self-injection practices with their healthcare professionals. GPs should be a support offering guidance and advice for safe self-injection practices. As the reality is that patients often require self-injection to enhance their quality of life, with or without formal healthcare professional authorisation. Therefore, there is a need for guidance to assist practitioners in supporting patients self-injecting effectively.	
141	cluB-12 UK	Guideline	General	General	**There is an absence of reference to pernicious anaemia within the guidelines** The document makes only a passing reference to pernicious anaemia linking it to autoimmune gastritis (AIG). However, many **Challenges arise from this approach including:** • PA and AIG aren't synonymous. AIG can occur with and without PA. • Unawareness of PA-AIG Link: Healthcare practitioners might remain unaware of the connection between AIG and PA. including what is on the patient record	Thank you for your comment. The guideline has been updated to acknowledge the difference between autoimmune gastritis and pernicious anaemia and provide a more detailed reason as to why the term 'pernicious anaemia' has not been used. This explains that autoimmune gastritis is sometimes referred to as pernicious anaemia which is a separate condition that can be a consequence of chronic, severe vitamin B12 deficiency, including deficiency caused by autoimmune gastritis. However, pernicious anaemia in its true sense (that is 'a life-threatening anaemia') is now extremely rare because of developments in testing and treatment for, and greater awareness of, vitamin B12 deficiency. For this reason, and to prevent any confusion with autoimmune gastritis, we have not used the term 'pernicious anaemia' in the recommendations.

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					• Patient Confusion: Patients who are accustomed to the term "Pernicious anaemia" might find the shift to "AIG" confusing and unsettling. **Recommendation:** Use "autoimmune gastritis including pernicious anaemia" consistently throughout the guidelines	
142	cluB-12 UK	Guideline	General	General	**Recommendations for research** In addition to the important cost analysis highlighted for further research there is also a need to highlight a cost analysis of missed or misdiagnosis of vitamin B12 deficiency. This would be a crucial economic costing to calculate. The expenses associated with such analysis would be expected to be high involving not only financial aspects but also accounting for human, clinical, and social factors. Need to think about the countless appointments to the GP from persistent symptoms, as well as referrals to other services like psychologists and attempts of different interventions including trials of antidepressants. Furthermore, the many different tests that are explored for other diagnoses. The economic and societal	Thank you for your comment. The committee agreed that there needs to be more research into the diagnostic tests and have made a research recommendation in this area. We agree that the cost of a missed diagnosis is a crucial part of an evaluation of diagnostic tests. However, there are many challenges to doing research specifically in this area. Firstly, by definition, it would have to be retrospective to be ethical. Investigators would have to define as objectively as possible whether/when a diagnosis had been missed and controlling for co-morbidities and other confounding factors. NICE's preference is that the impact on patients is measured in terms of health-related quality of life instruments, in particular the EQ-5D, rather than through time off work. See Developing NICE guidelines.

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					costs from patients requiring government assistance, such as disability benefits, housing allowances, and caregiver, further increase the financial burden. Additionally, the economic impact of patients being unable to work. The non-financial costs of quality of personal and family lives should also be subjectively assessed. It can take patients many years to get a diagnosis and to then start treatment. This needs to be compared to a case where an array of different makers for vitamin B12 deficiency were tested, vitamin B12 treatment trialled, and clinical outcomes of the patient monitored. Moreover, a separate cost analysis should be conducted to explore the financial consequences of patients diagnosed with B12 deficiency who do not receive the optimal treatment regimen tailored to their specific needs. Comparing these costs to the resources required for providing the suitable treatment assessing the importance of tailored care. Overall, there needs to be broader cost analyses including these suggestions.	

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					Large numbers of experiences need to be documented to know what proportion of patients respond to standard treatment.	
143	cluB-12 UK	Guideline	General	General	Throughout the guidelines it needs to be clear that using biomarkers to look for deficiency when someone is already using vitamin B12 treatment should not be done.	Thank you for your comment. A recommendation has been made about using caution when interpreting test results in people already taking oral supplements. The recommendation to repeat the initial test at the first follow-up meeting for people taking oral B12 replacement has now been removed from the guideline. There is also a recommendation to not test people receiving intramuscular injections.
144	cluB-12 UK	Guideline	General	General	There should be markers of iron, folate and B6 that should be monitored as if these aren't within the optimal range then vitamin B12 cannot be adequately metabolised. Once these cofactors are considered patients report feeling better and better symptom improvement is seen. There should be a list of vitamins that should be looked at for vitamin B12 deficiency treatment to optimise treating all deficiencies, improving B12 metabolism and improving symptomology.	Thank you for your comment. Investigating and managing complications related to vitamin B12 deficiency and cofactors were not included as part of the scope of the guideline. Therefore they were not included as part of the guideline reviews and no recommendations have been made related to this.
145	cluB-12 UK	Guideline	004	003 - 006	Recommendations This could be rephrased to emphasise that autoimmune gastritis and pernicious anaemia (PA) are not synonymous.	Thank you for your comment. The guideline has been updated to acknowledge the difference between autoimmune gastritis and pernicious anaemia and provide a more detailed reason as to why the term 'pernicious anaemia' has not been

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					Autoimmune gastritis (AIG) can manifest with or without PA, typically progressing to the PA stage in its advanced phases. When referring to the stage of AIG resulting in vitamin B12 deficiency, this essentially refers to PA as this would be at the point of severe parietal cell destruction and intrinsic factor deficiency. A more precise formulation would be: "The consequence of this is vitamin B12 deficiency. B12 deficiency caused by autoimmune gastritis has historically been covered by the term pernicious anaemia."	used. This explains that autoimmune gastritis is sometimes referred to as pernicious anaemia which is a separate condition that can be a consequence of chronic, severe vitamin B12 deficiency, including deficiency caused by autoimmune gastritis. However, pernicious anaemia in its true sense (that is 'a life-threatening anaemia') is now extremely rare because of developments in testing and treatment for, and greater awareness of, vitamin B12 deficiency. For this reason, and to prevent any confusion with autoimmune gastritis, we have not used the term 'pernicious anaemia' in the recommendations.
146	cluB-12 UK	Guideline	005	003	Rec 1.1.2 - Suggest a rephrasing: "most people only need 1 blood test to **support** the diagnosis of vitamin B12 deficiency..."	Thank you for your comment. This has been updated to state 'a single blood test can be enough to support a diagnosis of vitamin B12 deficiency but some people may need further tests to diagnose the condition'.
147	cluB-12 UK	Guideline	005	018 - 020	Rec 1.1.4 – We are concerned that this recommendation is misleading. While it presents a forceful assertion, the available evidence to support the stated claim remains somewhat insufficient. There should be a change of tone of the statement.	Thank you for your comment. Several stakeholders commented on this suggesting that without evidence to support this the statement should not be made. The committee agreed and the recommendation relating to this has been removed from the guideline. Recommendations related to pregnant patients on gas and air are covered by MHRA guidance on Nitrous oxide: neurological and haematological toxic effects.
148	cluB-12 UK	Guideline	010	018	Rec 1.3.10 – Additional statement to include … Reference intervals and cut off	Thank you for your comment. Several stakeholders commented on the thresholds. Some thought they were too

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					limits are method dependent, thus locale values should be employed. This statement should also be repeated in sections 1.3.14 and 1.3.15.	low, others thought they were too high and there was also some support that they are about right. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not. Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests. The committee also recommend considering MMA as a further test for people with an indeterminate active or total B12 test result. This is to capture people who may have a vitamin B12 deficiency when their test result doesn't meet the criteria for deficiency. An indeterminate result covers an active B12 of between 25 and 70 pmol per litre, and a total B12 of between 180 and 350 nanograms (133 and 258 pmol) per litre. The committee has also added a recommendation to use the laboratory's reference ranges to decide if vitamin B12 deficiency is likely when interpreting serum MMA and plasma homocysteine test results.

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149	cluB-12 UK	Guideline	010	018	Rec 1.3.10 - Consider MMA urine testing as blood tests for MMA are not readily available in many areas.	Thank you for your comment. Evidence for urine MMA was not identified and the committee agreed that this is not a relevant marker for testing in vitamin B12 deficiency. Therefore, the committee have made it clear throughout the guideline that it is serum MMA that is recommended. Economic modelling showed that serum MMA is likely to be cost effective for people with a B12 measurement in the indeterminate range. Implementing these recommendations will require some reallocation of resources, including investment in pathology services, so that testing can become more widely available. A resource impact report and tool will be published alongside this guideline.
150	cluB-12 UK	Guideline	011	016 - 018	Rec 1.3.12 – Suggestion to change the recommendation to - "they have had surgery that is likely to lead to irreversible vitamin B12 malabsorption ….." vitamin B12 deficiency is reversible if you provide the vitamin, but the malabsorption is not reversible.	Thank you for your comment. We have updated the recommendation to state 'they have had surgery that can cause vitamin B12 deficiency (such as a gastrectomy, terminal ileal resection or some types of bariatric surgery).
151	cluB-12 UK	Guideline	011	024 - 028	Rec 1.3.14 – This recommendation remains unclear whether people meant to be in this category have or do not have clinical signs and symptoms. It is not possible to explain to someone that they have no deficiency if the blood values are normal, but they have	Thank you for your comment. This could apply to people with or without symptoms. The recommendation following this has been updated to advise investigating other causes if the person's test result suggests a deficiency is unlikely. It also advises considering a repeat of the initial test if the person is still experiencing symptoms or signs 3 to 6 months later.

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					symptoms. It would be necessary to evaluate causes of the symptoms other than B12 deficiency.	
152	cluB-12 UK	Guideline	012	001 - 005	Rec 1.3.15 - If the person has normal B12 and active B12 (higher than the suggested cut off values), but have clinical symptoms suggestive of B12 deficiency, plasma MMA concentrations should be measured earlier than 3-6 months. And alternative causes of the symptoms should be explored.	Thank you for your comment. The recommendation has been updated to advise investigating other causes as well as considering a repeat of the initial test if they are still experiencing symptoms or signs 3 to 6 months later. MMA has been removed because the committee agreed that most laboratories would not allow for an MMA without testing total or active B12 first.
153	cluB-12 UK	Guideline	012	001 - 005	Rec 1.3.15 - Blood sampling for MMA and homocysteine testing should not be used as a diagnostic tool but may support a metabolic / neurologic diagnosis. Blood sampling for MMA and homocysteine testing should not be used as an exclusionary tool as results within the normal ranges do not preclude metabolic / neurologic causes.	Thank you for your comment. The recommendation has been updated to advise investigating other causes as well as considering a repeat of the initial test if they are still experiencing symptoms or signs 3 to 6 months later. MMA has been removed because the committee agreed that most laboratories would not allow for an MMA without testing total or active B12 first.
154	cluB-12 UK	Guideline	012	002 - 005	Rec 1.3.15 - If the patient has normal B12 and holoTC (higher than the suggested cut off values), but have clinical symptoms suggestive of B12 deficiency, plasma MMA concentrations should be measured earlier	Thank you for your comment. The recommendation has been updated to advise investigating other causes as well as

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					than 3-6 months. And alternative causes of the symptoms should be explored.	considering a repeat of the initial test if they are still experiencing symptoms or signs 3 to 6 months later. MMA has been removed because the committee agreed that most laboratories would not allow for an MMA without testing total or active B12 first.
155	cluB-12 UK	Guideline	012	006	Suggested sentence to be included prior to 1.4.1 "The anamnesis may suffice to determine whether the deficiency is caused by a decreased intake of B12, an impaired uptake or utilisation. In addition, some tests may be helpful."	Thank you for your comment. It is anticipated that healthcare professionals will take a person's description of their symptoms into account when determining a diagnosis. The recommendations in this section are to advise which tests to use and when.
156	cluB-12 UK	Guideline	012	007	Rec 1.4.1 - Please check nomenclature for autoantibodies against intrinsic factor. Strictly speaking anti-intrinsic factor-antibody would indicate antibodies towards antibodies against intrinsic factor.	Thank you for your comment. The committee checked and decided that 'anti-intrinsic factor antibody test' is a widely accepted term to use and is also used in the British Society for Haematology guidelines.
157	cluB-12 UK	Guideline	012	009	Rec 1.4.1 - A statement on addressing the interpretation on the intrinsic factor and parietal cell antibody tests should be included, given the variable sensitivity and specificity. The intrinsic factor antibody assay used in the UK identifies fewer people than compared to the assays used in other areas of Europe. Additionally, an individuals could test positive with one assay whilst testing negative for the other.	Thank you for your comment. The committee agreed it was not possible to provide reference ranges for these tests and the laboratories will advise on this with the test results. The rationale in the guideline does state that the evidence 'showed that, while a positive anti-intrinsic factor antibody test strongly suggests autoimmune gastritis, a negative test is less reliable so cannot be used to rule out the condition.' This is why the committee recommended further tests. The committee also recommend that lifelong intramuscular

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					Therefore, a negative intrinsic factor antibody test does not prove the patient does not have pernicious anaemia including autoimmune gastritis.	vitamin B12 replacement is offered to people if autoimmune gastritis is the suspected cause. This is the same as the recommendation for those with a confirmed diagnosis to take account of the lack of certainty in the outcome of a negative test result.
158	cluB-12 UK	Guideline	012	009	Rec 1.4.1 - Suggest an additional bullet stating: "a positive test for autoantibodies against intrinsic factor underscores the diagnosis of autoimmune gastritis, while a negative result does not imply the absence of autoimmune gastritis."	Thank you for your comment. The rationale in the guideline does state that the evidence 'showed that, while a positive anti-intrinsic factor antibody test strongly suggests autoimmune gastritis, a negative test is less reliable so cannot be used to rule out the condition.' This is why the committee recommended further tests. The committee also recommend lifelong intramuscular vitamin B12 replacement is offered to people if autoimmune gastritis is the suspected cause. This is the same as the recommendation for those with a confirmed diagnosis to take account of the lack of certainty in the outcome of a negative test result.
159	cluB-12 UK	Guideline	012	013 - 014	Red 1.4.2 - There's no necessity to distinguish the identification of the cause for vitamin B12 deficiency during pregnancy and breastfeeding from other population groups, since the process of identifying the cause is the same.	Thank you for your comment. The aim of this recommendation is to highlight that treatment should be started without waiting for a test result. While a positive anti-intrinsic factor antibody test strongly suggests autoimmune gastritis, a negative test is less reliable so cannot be used to rule out the condition. Starting treatment without waiting for the test result if autoimmune gastritis is suspected could help ensure the person's health and that of their baby does not deteriorate.
160	cluB-12 UK	Guideline	012 - 013	0019 - 002	Rec 1.4.3 - Suggestion for changes to be made to the last two bullet points of this recommendation to include interpretation:	Thank you for your comment. The bullet points in the recommendation have been updated to state 'a CobaSorb test to measure whether vitamin B12 can be absorbed' and

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					• "a CobaSorb test to clarify whether the patient has lost the capacity for an active uptake of B12 or not. • "Gastroscopy with gastric body biopsy. A finding of an atrophic gastritis strongly supports an impaired capacity for active uptake of B12"	'gastroscopy with gastric body biopsy (to be carried out by a specialist)'.
161	cluB-12 UK	Guideline	013	001 - 002	Rec 1.4.3- It should also be highlighted that the CobaSorb test is not able to answer the question of causes of B12 malabsorption, especially those related to food cobalamin malabsorption (e.g. in the elderly). Its important to note that the Cobasorb test is done in people already on therapy, after stopping therapy for 3 months, so a selected population	Thank you for your comment. The bullet points in the recommendation have been updated to state 'a CobaSorb test to measure whether vitamin B12 can be absorbed'. Further detail has been added to the committee discussion of the evidence report.
162	cluB-12 UK	Guideline	013	Gener al	Section 1.5 – 1.7 is difficult to read. It could be merged, simplified, and improved along the following lines: 1.5 Preventing and managing B12 deficiency. 1.5.1Prevention of B12 deficiency should be considered when: • A person changes to a diet with an insufficient content of B12 (e.g. vegans). - A daily vitamin pill with at least 2.4 (2.6	Thank you for your comment. Prevention of vitamin B12 deficiency was not part of the scope and therefore no recommendations have been made relating to this. Evidence was not identified to suggest that intramuscular vitamin B12 replacement should be used for all causes of vitamin B12 deficiency. Therefore the committee made the recommendations based on their experience and expertise according to the cause of treatment. The recommendations have been updated. Intramuscular injections are offered to people with autoimmune gastritis or who have had a total

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					/2.8during pregnancy/lactation) microgram of B12 taken with food should be advised • A person undergoes a procedure that will decline/inhibit active uptake of B12 (e.g. bariatric surgery). -supplement with high dose (0.5-1 mg B12/day) oral (sublingual, nasal) should be advised from immediately after the procedure. • A person receiving medication that may interfere with the uptake of B12 (e.g. proton pump inhibitors) - supplement with vitamin B12 may be advisable. 1.5.2. Initial treatment of patients with vitamin B12 related symptoms and with a diagnosed B12 deficiency. • ALL patients should initially be treated with i.m. injections of the vitamin to restore the body content of B12. That also goes for vegans and persons using nitrous oxide. • In most patients it is recommended to administer 5 injections of 1 mg hydroxo-B12 over 10 days • If neurological symptoms remain continue with frequent injections until no further improvement. • Follow treatment response in anaemic patients by measuring haematological parameters including iron and folate weekly	gastrectomy or complete terminal ileal resection. For all other people with vitamin B12 deficiency because of malabsorption intramuscular injections are considered over oral replacement. The follow up recommendations have been updated following stakeholder comments to make it clearer when to optimise, change, continue or stop vitamin B12 replacement.

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					for the first three weeks and supplement with iron and/or folate if needed. 1.5.3. Initial treatment of patients with limited or no B12 related symptoms diagnosed with B12 deficiency based on borderline biochemistry. • Treatment should prevent symptomatic B12 deficiency, for treatment, see 5.1.1 1.5.4 Continued treatment and follow up in patients initially treated with injections. • Patients capable of absorbing B12 should be advised to change diet or to take a daily vitamin pill with at least 2.4 (2.6 /2.8 during pregnancy/lactation) microgram of B12 together with a meal. • Patients on nitrous oxide should be advised to stop immediately, and to ensure a sufficient intake of B12. • Long term replacement of intramuscular Hydroxocobalamin until all symptoms have disappeared (may take serval months to years) • Patients with a lasting decreased or absent capacity for uptake of B12 should receive a lifelong treatment. • Some of those patients may benefit from a daily oral (sublingual, nasal) dose of 0.5-1	

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					mg B12 others will need injections with 1 mg of B12 at intervals most often of 3 months, but sometimes with intervals of days to weeks. • Adjustment of treatment should be done based on relief of patient's symptoms and cannot be guided by measurement of plasma B12. • The patient should be scheduled for visits at least every 3rd month until the treatment scheme has been adjusted, and thereafter at biyearly interval. • The patients should be instructed to return if symptoms reoccur. • In patients with gastric atrophy, gastroscopy may be warranted at regular intervals, see: recommendations on upper gastrointestinal tract cancers in 10 NICE's guideline on suspected cancer.	
163	cluB-12 UK	Guideline	013 - 016	General	Rec - 1.5 Managing vitamin B12 deficiency While the guideline frequently emphasises patient preference in terms of oral supplementation or intramuscular injections (IM) injections, it's essential that treatment decisions should prioritise what is most effective first. While many patients may prefer IM injections, it's important to note that these injections see better outcomes	Thank you for your comment. Where recommendations have been made for intramuscular or oral vitamin B12 replacement based on the person's preference this is because no evidence was identified to suggest one option was better than the other. Therefore the committee agreed that the person should be given the choice.

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					than alternatives regarding symptom improvement. The GP should guide patients towards the most suitable treatment based on the specific cause of their vitamin B12 deficiency. In cases where patients are against the recommended treatment, their personal choice should be respected, and an alternative they agree upon should be administered. Remember that switching from IM to oral may lead to neurologic symptoms, which may not develop directly, but which may be permanent and persist after resumption of i.m. therapy.. However, patient choice should influence the frequency of treatment in relation to the occurrence of symptoms. Stressing the variation in treatment frequency is crucial for patients and clinicians to understand. It's advisable to present a suggested range of treatment frequencies, encompassing options from weekly to two monthly injections. This range provides a starting point for decision-making, but it's vital to emphasise that treatment plans must be tailored to each individual's needs.	The committee note your point on switching from intramuscular to oral replacement and have not made recommendations relating to this. No evidence was identified for the frequency of treatment and the committee have made a research recommendation in this area. Following your comment the recommendation for management of vitamin B12 deficiency caused by recreational nitrous oxide use has been updated to mirror the recommendation for medicine induced deficiency. It now makes it clear that the decision needs to be 'based on clinical judgement and the person's preference'.

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					These options should be highlighted as examples that can be adjusted based on the patient's response, medical assessment, and preferences. The goal from this would be to empower both patients and clinicians with a framework to determine the most appropriate treatment frequency, ensuring individualised care and optimal outcomes.	
164	cluB-12 UK	Guideline	015	008 - 012	Rec 1.5.11, this sentence does not belong to the chapter of management of B12. It is rather related to finding the cause of B12 deficiency.	Thank you for your comment. This recommendation is here because it relates to conversations when management starts or has started. The committee agreed that a person may have been assessed to have a dietary deficiency however it may become apparent that another or additional cause is the reason for their symptoms. The guideline does cross refer to the section on identifying the cause of vitamin B12 deficiency.
165	cluB-12 UK	Guideline	015	012 - 020	Rec 1.5.12 – It is unclear what is meant by over-the counter supplements. In many countries you can find 1 mg B12 as a drug and as over the counter supplements as well or as a multivitamin.	Thank you for your comment. The terms 'over-the-counter supplements' is defined in the section 'Terms used in this guideline'. The definition states 'Vitamin B12 supplements, or supplements containing vitamin B12 like multivitamins, that can be obtained without a prescription (for example, in a pharmacy, supermarket or online). These can include vitamin B12 tablets (including sublingual tablets), injections and transdermal patches.'
166	cluB-12 UK	Guideline	015	012 - 020	Rec 1.5.12 - Please provide a dose range for clarity regarding the	Thank you for your comment. A review of the effectiveness of over-the-counter (OTC) supplements was not included as

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					present recommendations and include information on how best to take – i.e. with food.	part of the scope of the guideline and therefore no recommendations have been made on whether to suggest them and what dosage to use. The recommendation relating to OTC oral supplements is to highlight which supplements are appropriate. This is because some oral supplements that are labelled as containing vitamin B12 do not contain a form that is appropriate to use as vitamin B12 replacement.
167	cluB-12 UK	Guideline	015	012 - 020	Rec 1.5.12 – Please specify that supplements should be GMP certified and regulated with MHRA approval	Thank you for your comment. Over-the-counter vitamins, as included in this recommendation are food supplements, which are required to comply with food legislation in terms of their composition, manufacturer and control. It is outside the remit of NICE to cover such legislative issues in recommendations.
168	cluB-12 UK	Guideline	015	015 - 020	Rec 1.5.12 - Hydroxycobalamin as an oral supplement is unstable and might not be effectively absorbed [Greibe et al. (2018). Increase in circulating holotranscobalamin after oral administration of cyanocobalamin or hydroxocobalamin in healthy adults with low and normal cobalamin status. Eur J Nutr 57:2847-2855.]. Preference to restrict this statement to the two most used forms of B12 in oral supplements (cyano and methyl). For IM use the use of hydroxyl and adenosyl at therapeutic dose could be equivalent to that of cyano and methylcobalamin.	Thank you for your comment. Mention of hydroxocobalamin as an oral supplement has been removed from the guideline.

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169	cluB-12 UK	Guideline	017 - 018	General	Rec - 1.6 Follow-up appointments for people taking oral replacement. It is essential to establish a well-defined time interval for the purpose of re-investigation or revising the diagnosis. However, it's important to acknowledge that a universally defined time frame for reinvestigation might not be suitable. The reason for this is that the rate of symptom improvement can vary among individuals and certain symptoms might take longer to show improvement. This variability in response to treatment should be taken into account. When considering individuals who are undergoing vitamin B12 supplementation, it's crucial to recognise that retesting will not produce reliable results. Serum vitamin B12 levels do not necessarily reflect the progression of symptoms related to vitamin B12 deficiency when supplementation is ongoing. Therefore, for someone supplementing you shouldn't monitor serum B12 but you should monitor symptoms.	Thank you for your comment. The follow up recommendations have been updated to 'at 3 months after they started treatment, or earlier depending on severity of symptoms'. The recommendation to follow up at 1 month during pregnancy has stayed the same. Following stakeholder comments the recommendation for repeating the initial test for people on oral vitamin B12 replacement has been removed from the guideline. The ongoing care and follow up recommendations have also been updated to make it clearer that response to treatment should be made by assessing symptoms.

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170	cluB-12 UK	Guideline	019	006 - 010	Rec - 1.6 Follow-up appointments for people receiving intramuscular replacement Where there is neurological-only B12 deficiencies frequency of administration should take priority over dose as it may be cell absorption is restricted to 'free' unbound B12. Higher 'excess' levels of B12 will become bound to proteins such as haptocorrin or transcobalamin and therefore effectively useless for cell absorption in these instances. Bound B12 is unable to permeate the cell membrane by passive diffusion due to its relatively large size. By conventional routes, where there is no 'free' unbound B12 in the bloodstream, the normal situation, B12 can only enter cells once the B12 binds to transcobalamin ("TC-Cbl") and is, in turn, bound to the cell surface receptor CD320. Where there is a defect in the TC-Cbl molecule or in the cell surface receptor CD320 then B12 will either not enter the cell or will be severely inhibited in doing so, depending on the defect involved. Passive diffusion of 'free' B12 occurs by means of the process of hydrophobicity. The relatively large size of B12 molecules is nugatory in the process.	Thank you for your comment. The recommendation has been updated so it only refers to the frequency of injections and not the dose.

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171	cluB-12 UK	Guideline	020	006 - 010	Rec - 1.7 monitoring for gastric cancer in people with autoimmune gastritis Individuals with pernicious anaemia and autoimmune gastritis are at an elevated risk of developing gastric cancer. In the presence of upper gastrointestinal symptoms, it's important to prioritise a prompt endoscopy rather than considering it as an option. Given the challenges in diagnosing these conditions, it's advisable to extend monitoring to individuals with malabsorption issues. Anyone displaying indications suggestive of pernicious anaemia or autoimmune gastritis should undergo endoscopic investigation. If atrophic gastritis is detected, routine monitoring is essential. The management of pernicious anaemia and vitamin B12 deficiency remains a prominent concern within primary care. Currently, General Practitioners (GPs) may not routinely engage in monitoring unless it's explicitly emphasised as a necessity. The guidelines are lacking in specific guidance for GPs. It's vital to address this gap and outline the essential steps for GPs to take. They should inform patients about	Thank you for your comment. We did not have the evidence to make a strong recommendation that all people should be referred for gastrointestinal endoscopy. Therefore, the strength of the recommendation in this guideline matches the strength of the recommendations on upper gastrointestinal tract cancers in NICE's guideline on suspected cancer.

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					their heightened risk of gastric cancer and educate them about potential warning signs to watch for. However, it's important to recognise that symptoms often manifest in the advanced stages of gastric cancer, leading to palliative care rather than curative care. Early diagnosis of stomach cancer is challenging however difficulty increases when there is no routine monitoring done for those individuals at an increased risk. This results in a poor 20% survival rate in the UK. However, when detected early, the five-year survival rate increases considerably to 65%. But at stage 3, the survival rate drops to 25%, and beyond stage 4, a five-year survival is not seen. This emphasises the importance of closely monitoring individuals at high risk.	
172	cluB-12 UK	Guideline	022	006	Recommendation for research 3 Self- administration - Two further non-medical outcomes should also be considered. The first of those is the cost of the patient being prescribed B12 set against the cost of treating the same patient on the NHS on an on-going basis without B12 supplementation. The second cost is	Thank you for your comment. The research recommendations here are written as broad questions giving an indication of what area and interventions are considered for further research. More detail is provided in the appendix of the evidence report linked to just below the research recommendation. The outcomes in the research protocol include quality of life and patient reported outcomes.

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					the economic and societal cost of the patient no longer requiring government financial support e.g. disability benefits, housing benefits, carer's allowances and so on, if the patient can return to the workforce. The non-financial costs of quality of personal and family lives should be subjectively assessed.	
173	cluB-12 UK	Guideline	025	006	The primary concern is not that patients are afraid of total withdrawal, but rather the prevalence of the current mindset among primary healthcare clinicians that often leads to refusals. Guidance dictates maintenance doses of 1mg/ml every 2-3 months. For many patients that is completely inadequate. Greater freedom must be given in the guidance to encourage physicians to optimize the frequency of parietal B12 supplementation. The author personally knows considerable numbers of patients who feel let down by current guidelines. These patients purchase additional B12 for self-administration from potentially unreliable sources but do not share the information with healthcare providers in case NHS support is withdrawn. Many of those requiring B12 supplementation require intramuscular or subcutaneous injections to be administered	Thank you for your comment. The recommendations in the ongoing care and follow up section advise optimising treatment if symptoms do not improve or they have new symptoms.

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					at least weekly and sometimes daily. The cohort members involved are likely to require maintenance from 'free' unbound B12 which can only derive from frequent injections.	
174	cluB-12 UK	Guideline	025	General	Rational and impact A concern with these guidelines is the often-limited awareness among GPs about vitamin B12 deficiency and conditions like pernicious anaemia. While giving information about vitamin B12 deficiency is very important for patients, it raises the question of who should be responsible for this education and what level of training GPs have received to deliver accurate information and answer the questions patients have. While healthcare professionals are the most appropriate to do the job, it's important consider how would they obtain the knowledge to explain this when they get near to no training in this area. This presents an opportunity to direct patients to official charities specialising supporting people with vitamin B12 deficiency. These charitable organisations have great knowledge and can collaborate	Thank you for your comment. The committee hope this guideline will raise awareness of vitamin B12 deficiency among healthcare professionals. The section on 'Information for the public' on this guideline's web page also provides links to other organisations' websites which provide more detailed advice directly written for people with suspected or confirmed vitamin B12 deficiency. The committee have made recommendations based on the best available evidence. Several recommendations have been updated based on stakeholder comments with the aim of making practice clearer.

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					with patients and GPs to enhance the quality of care. There is a clear gap within the current guidelines regarding personalised medicine and shared decision making process between clinicians and patients. It's important that treatment must be tailored to the unique symptoms of each patient. By aligning treatment plans with patient symptoms, the guidelines can drive enhanced patient outcomes and experiences. This principle should be very clearly communicated. Although stated within the rationale this is not done.	
175	cluB-12 UK	Guideline	026	021	Oral administration of B12 will be ineffective even at megadose levels in instances of neurological-only B12 deficiencies as the cubam availability will be relatively constant. Ample oral supplementation will provide no additional benefit to the patient and will be excreted without absorption.	Thank you for your comment. This section is on risk factors rather than treatment. As well as recommending oral treatment the committee has recommended switching to intramuscular injections should this not work.
176	cluB-12 UK	Guideline	033	013-016	**Managing vitamin B12 deficiency** **Time frame for symptom improvement** There haven't been have been enough studies to establish an estimated timeframe for symptom improvement. This could risk clinicians deciding a time frame is sufficient,	Thank you for your comment. This recommendation has been updated to give more specific information on what to advise people starting vitamin B12 replacement.

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					then when symptoms return, the patient is assumed to have something else instead. I don't think a correct time-frame for treatment of neurological involvement is usually acted on in practice (ie. it should be an injection e.o.d until no further improvement), that is typically reduced to a set number of injections, potentially without further assessment.	
177	De Montford University	Guideline	001	005	Title of guideline: It is noted that Pernicious Anaemia has been excluded from the title. Previous versions were titled Vitamin B12 deficiency, including Pernicious Anaemia. We are concerned that removing Pernicious Anaemia from the title may potentially cause confusion to clinicians and patients who may not consider that the guideline includes the diagnosis and management of people with Pernicious Anaemia. It is unclear why this was removed.	Thank you for your comment. The guideline has been updated to acknowledge the difference between autoimmune gastritis and pernicious anaemia and provide a more detailed reason as to why the term 'pernicious anaemia' has not been used. This explains that autoimmune gastritis is sometimes referred to as pernicious anaemia which is a separate condition that can be a consequence of chronic, severe vitamin B12 deficiency, including deficiency caused by autoimmune gastritis. However, pernicious anaemia in its true sense (that is 'a life-threatening anaemia') is now extremely rare because of developments in testing and treatment for, and greater awareness of, vitamin B12 deficiency. For this reason, and to prevent any confusion with autoimmune gastritis, we have not used the term 'pernicious anaemia' in the recommendations.
178	De Montford University	Guideline	001	008 and general	It is noted that the term "autoimmune gastritis" is used within the introductory text box and throughout this document instead of Pernicious Anaemia. Whilst it is noted	Thank you for your comment. The guideline has been updated to acknowledge the difference between autoimmune gastritis and pernicious anaemia and provide a more detailed reason as to why the term 'pernicious anaemia' has not been

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					that there is an ongoing debate regarding the most appropriate terminology to use to describe Pernicious Anaemia, we would question whether using this terminology without further explanation in this introductory text box may result in confusion; especially in primary care where healthcare practitioners may not be familiar with this.	used. This explains that autoimmune gastritis is sometimes referred to as pernicious anaemia which is a separate condition that can be a consequence of chronic, severe vitamin B12 deficiency, including deficiency caused by autoimmune gastritis. However, pernicious anaemia in its true sense (that is 'a life-threatening anaemia') is now extremely rare because of developments in testing and treatment for, and greater awareness of, vitamin B12 deficiency. For this reason, and to prevent any confusion with autoimmune gastritis, we have not used the term 'pernicious anaemia' in the recommendations.
179	De Montford University	Guideline	004	020	It states that "signs and symptoms are linked to many other conditions". It is unclear whether the intention is to imply that there is overlap with the signs and symptoms of a vitamin B12 deficiency with other conditions or whether a vitamin B12 deficiency can cause other conditions. This would benefit from clarification.	Thank you for your comment. The intention is to highlight that there is overlap between the symptoms of vitamin B12 deficiency and other conditions. The recommendation has been updated to 'symptoms and signs of vitamin B12 deficiency may also be associated with many other conditions.'
180	De Montford University	Guideline	006	018	It is noted that it is stated that symptoms can vary between individuals and a list of symptoms and signs are provided in box 1, however, the spectrum of symptoms is known to be diverse and many other symptoms are experienced by patients but not listed in the box. It would be beneficial to state that other symptoms can be associated with a deficiency, and patients	Thank you for your comment. The committee have highlighted the common symptoms and signs and have updated the recommendations and table to reflect this. Evidence was not identified to recommend testing in people with other symptoms.

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					with any other unexplained symptoms should also be tested.	
181	De Montford University	Guideline	009	041	The guideline recommends that clinicians should ask patients what dosage of over-the-counter supplement they are taking. It would be beneficial to specify to confirm the amount of vitamin B12 contained in the supplement and the form of vitamin B12 (cyanocobalamin, methylcobalamin etc). It should also be noted that some energy drinks and meal-replacement shakes also contain vitamin B12, and patients may not mention these if asked specifically about supplements.	Thank you for your comment. This recommendation is just to highlight that oral vitamin B12 supplements may affect test results. It has been updated to include all forms of vitamin B12 supplementation including vitamin B12 tablets, injections or transdermal patches. Assessing the person's dietary intake is included as part of the risk factors in the section on 'When to recognise vitamin B12 deficiency'. This includes by the section on recognising vitamin B12 deficiency and has been updated to include food or drinks fortified with vitamin B12.
182	De Montford University	Guideline	010	015	The guideline states that clinical judgement should be used in interpreting homocysteine levels. Most primary care practitioners will not be familiar with this test or its interpretation, so further guidance here would be advisable.	Thank you for your comment. We have updated this to make it more specific. The recommendation now states 'Use laboratory reference ranges to interpret plasma homocysteine test results when deciding if vitamin B12 deficiency is likely, but take into account additional factors that may increase plasma homocysteine levels (such as folate deficiency).'
183	De Montford University	Guideline	012	019	The guideline states that other tests should be considered if a negative anti-intrinsic factor antibody test is obtained. However, it is widely acknowledged how inaccurate this test is- but this is not stated here. This is a common cause of patients being informed by healthcare practitioners that they do not have Pernicious Anaemia and subsequently	Thank you for your comment. The rationale in the guideline does state that the evidence 'showed that, while a positive anti-intrinsic factor antibody test strongly suggests autoimmune gastritis, a negative test is less reliable so cannot be used to rule out the condition.' This is why the committee recommended further tests. The committee also recommend lifelong intramuscular vitamin B12 replacement is offered to people if autoimmune gastritis is the suspected

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					having their treatment stopped. It would be important to highlight the issues with this test in the guideline and to state that people should not have their treatment stopped if a negative result is obtained.	cause. This is the same as the recommendation for those with a confirmed diagnosis to take account of the lack of certainty in the outcome of a negative test result.
184	De Montford University	Guideline	014	004	The guideline states that patients should be offered oral or intramuscular treatment based on their preference. Whilst shared decision making is essential, it should be stated that patients should be provided with information regarding the absorption and efficacy of these formulations to enable them to make an informed choice.	Thank you for your comment. There was no evidence identified in the evidence reviews that would enable healthcare professionals to provide useful information on the efficacy of treatment.
185	De Montford University	Guideline	014	008	The guideline states that patients with nitrous oxide-induced vitamin B12 deficiency should be offered oral or intramuscular treatment based on their preference. If patients have any neurological symptoms oral treatment is unlikely to be sufficient to effectively manage these. It would be recommended to add a statement regarding this.	Thank you for your comment. There is no clear evidence to distinguish which out of oral or intramuscular vitamin B12 replacement was more clinically or cost effective for medicine induced vitamin B12 deficiency. Therefore the committee agreed to recommend either oral or intramuscular vitamin B12 replacement.
186	De Montford University	Guideline	015	013	The guideline states that it should be explained that supplements contain varying amounts and types of vitamin B12. No recommendations are given regarding an optimal dosage of vitamin B12, and no statement is made regarding the variable quality of supplements available. Further	Thank you for your comment. A review of the effectiveness of over-the-counter (OTC) supplements was not included as part of the scope of the guideline and therefore no recommendations have been made on whether to suggest them and what dosage to use. The recommendation relating to OTC oral supplements is to highlight which supplements are appropriate. This is because some oral supplements that

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					clarity is needed to ensure that patients are taking a sufficient dosage of a reliable product.	are labelled as containing vitamin B12 do not contain a form that is appropriate to use as vitamin B12 replacement.
187	De Montford University	Guideline	016	001	The guideline states that a dosage of "at least 1000micrograms day" should be considered. Further clarity is needed here to advise whether a licensed product should be prescribed or the patient is expected to purchase their own supplement, which may be of variable quality. The statement "at least" is ambiguous, and practitioners less-familiar with treating deficiency may be unclear exactly what doses are advised.	Thank you for your comment. Where the guideline recommends 'vitamin B12 replacement' it is assumed to be prescribed. The terms 'over-the-counter supplements' and 'vitamin B12 replacement' are defined in the section 'Terms used in this guideline'. Over-the-counter supplements are described as supplements 'that can be obtained without a prescription'. Vitamin B12 replacement is described as 'where a deficiency is treated with prescribed doses of the vitamin'.
188	De Montford University	Guideline	017	008	The guideline states that people should be asked if they are taking "oral" replacement. It should be noted that patients may take additional supplementation to that which has been prescribed via a variety of routes including subcutaneous injections, sublingual and transdermal patches- so it should be clarified that clinicians should ask about additional supplementation via any route of administration.	Thank you for your comment. This recommendation relates to treatment the person may have been prescribed to check they are taking the tablets. Subcutaneous injections, sublingual and transdermal patches are not licenced medications and would not be prescribed.
189	De Montford University	Guideline	019	008	The guideline states that the dose and frequency of treatment should be optimised. This is ambiguous as no further guidance is provided regarding how. We are unaware of any evidence to support increasing the dose of 1000micrograms, but are aware	Thank you for your comment. The recommendation has been updated to recommend increasing the frequency of injections if needed, in line with the summary of product characteristics.

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					there is widespread experience of the benefits for many patients from having their dose more frequently than every 2-3 months.	The guideline did look for clinical evidence relating to the frequency of intramuscular injections however no evidence was identified and the committee made a research recommendation. Loading doses are covered in the BNF and therefore not included in the guideline. NICE does not generally include dosages in recommendations where they are available in the BNF or SPC. A dosage may be included if this information is not available, or the committee agrees that there needs to be a change to current recommended dosages, for example because of new evidence.
190	De Montford University	Guideline	019	021	The guideline states that treatment could be stopped. However, for many patients the cause of their deficiency is never known- predominantly due to the inaccuracies of diagnostic testing. Many patients would be at risk of having their treatment unnecessarily stopped if this statement is included without further qualification.	Thank you for your comment. The committee would interpret this to be a cause that has not been addressed but understand that is not clear in the consultation version of the recommendation. Therefore, the preceding recommendation has been updated to include unknown causes of vitamin B12 deficiency to take into account this point. The two recommendations are: 1.6.13 If the person's symptoms have improved, or are no longer present, and they have either a reversible cause of vitamin B12 deficiency that has not been addressed, or the cause is unknown: • continue with intramuscular injections and • agree a date for their next follow-up. 1.6.14 If the cause, or suspected cause, of vitamin B12 deficiency has been resolved and the person's symptoms have improved, or are no longer present: • think about stopping or reducing the frequency of the intramuscular injections and

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						• advise them to come back if their symptoms get worse, reappear, or they get new symptoms.
191	De Montford University	Guideline	034	009	It is stated that there is no evidence that oral treatment is ineffective in these groups. However, it should be noted that neither is there evidence that oral treatment is effective in these groups, so this should be highlighted.	Thank you for your comment. We have updated the rationale to make this clear.
192	De Montford University	Guideline	035	025	Linked with comment 10 above. It is stated here that wide variation in supplements is noted, and the committee agreed to list the types of vitamin B12 people should look out for. The list of forms of cobalamin stated in the main guideline does not provide sufficient guidance for people wishing to purchase a quality supplement.	Thank you for your comment. A review of the effectiveness of over-the-counter (OTC) supplements was not included as part of the scope of the guideline and therefore no recommendations have been made on whether to suggest them and what dosage to use. The recommendation relating to OTC oral supplements is to highlight which supplements are appropriate should a person wish to buy them. This is because some oral supplements that are labelled as containing vitamin B12 do not contain a form that is appropriate to use as vitamin B12 replacement.
193	De Montford University	Evidence review E	058	030	It is stated that the British Society for Haematology (BSH) published a recommendation during the pandemic, that people should not be switched to self-administration, and this appears to have been cited as one source of evidence against self-administration. The statement by the BSH that "…patients who are already self-administering IM hydroxocobalamin should continue to do so	Thank you for your comment. This sentence has now been removed.

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					but we do not recommend a patient switching to self-administration during the COVID-19 pandemic since instruction is likely to be difficult" was made in the context of the pandemic. Such barriers to effective training are no longer relevant.	
194	De Montford University	Equality impact assessment	General	General	It is noted that gender was not considered as a potential source of inequalities relating to diagnosis and treatment. Current data indicates that vitamin B12 deficiency, including Pernicious Anaemia is more common in women. The experiences of women seeking a diagnosis for their symptoms reported in papers such as that by Seage et al (2020) illustrates frequent dismissal of symptoms such as fatigue by healthcare professionals, and instead attribution to lifestyle and womens' health issues, such as menopause. Similar experiences are noted when ineffective symptom control is reported.	Thank you for your comment. Autoimmune conditions as a risk factor were included under sex in the equality impact assessment, however no mention of vitamin B12 deficiency as a risk factor was noted. This has been added to the updated version of the equality impact assessment. The information and support evidence review includes a study by Seage detailing individuals' experiences of receiving a diagnosis of pernicious anaemia. It is hoped that this guideline will improve diagnosis and management of vitamin B12 deficiency and lead to more appropriate participant inclusion in future studies where research is lacking.
195	Diabetes UK	Guideline	006	002 - 011	We welcome the inclusion of the use of metformin as a risk factor for B12 deficiency. 1 in 10 people treated with metformin develop B12 deficiency and the risk increases as the dose and duration of treatment with metformin increases so it is an important risk factor to consider whether or not symptoms of deficiency are present.	Thank you for your support of this recommendation.

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					Metformin is licensed for the treatment and prevention of type 2 diabetes mellitus. There are over 5 million people living with the diabetes, around 90% of which have type 2 diabetes. It has been predicted that approximately one million people with type 2 diabetes have yet to be diagnosed. As such, the use of metformin is widespread and presents a risk to a significant number of people. Metformin can also be used off-label for women with PCOS, increasing the number of people at risk of B12 deficiency associated with metformin use.	
196	Diabetes UK	Guideline	015		The guidance should consider a recommendation to refer an individual to a registered dietitian if suspected dietary deficiency. This would allow for a detailed nutritional assessment to take place in order to ascertain the individual's nutritional status where initial questions around their diet do not provide adequate explanation for deficiency. The individual can then be provided with individualised advice and may not require long-term oral supplementation.	Thank you for your comment. Referral to a dietitian was not considered as part of the review and therefore has not been mentioned.
197	Health Food Manufacturers Association	Evidence Review A	General	General	**Literature References** Adaikalakoteswari A, Rabbani N, Waspadji S, Tjokroprawiro A, Kariadi SH, Adam JM, Thornalley PJ. 2012.	Thank you for providing the list of references. These have been screened for eligibility against our review protocols to ensure we have not missed any evidence. No extra studies have been included in the guideline. Studies were generally

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					Disturbance of B-vitamin status in people with type 2 diabetes in Indonesia--link to renal status, glycemic control and vascular inflammation. Diabetes Res Clin Pract 95 (3): 415-424. Andrès E, Perrin A-E, Demangeat C, Kurtz J-E, Vinzio S, Grunenberger F, Goichot B, Schlienger J-L. 2003. The syndrome of food-cobalamin malabsorption revisited in a department of internal medicine. A monocentric cohort study of 80 patients. European Journal of Internal Medicine 14: 221-226. Andrès E, Zulfiqar AA, Serraj K, Vogel T, Kaltenbach G. 2018. Systematic Review and Pragmatic Clinical Approach to Oral and Nasal Vitamin B12 (Cobalamin) Treatment in Patients with Vitamin B12 Deficiency Related to Gastrointestinal Disorders. J Clin Med. Sep 26;7(10):304. doi: 10.3390/jcm7100304. Andrès, E., Zulfiqar, A. A., Vogel, T. 2020. State of the art review: oral and nasal vitamin B12 therapy in the	excluded from the evidence reviews because: the populations or interventions did not meet the protocol criteria (for example, they included people who were not vitamin B12 deficient); they included an unlicenced form or preparation of vitamin B12 replacement (such as nasal or sublingual treatments) or the study design did not meet the protocol criteria.

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					elderly. Qjm, 113(1), 5-15. doi:10.1093/qjmed/hcz046 Bolaman Z, Kadikoylu G, Yukselen V, Yavasoglu I, Barutca S, Senturk T. 2003. Oral versus intramuscular cobalamin treatment in megaloblastic anemia: a single-center, prospective, randomized, open-label study. Clin Ther 25 (12): 3124-3134. Carmel R. 2012. Subclinical cobalamin deficiency. Curr Opin Gastroenterol 28 (2): 151-158. de Groot-Kamphuis DM, van Dijk PR, Groenier KH, Houweling ST, Bilo HJ, Kleefstra N. 2013. Vitamin B12 deficiency and the lack of its consequences in type 2 diabetes patients using metformin. The Netherlands journal of medicine 71 (7): 386-390. Castelli MC, Friedman K, Sherry J, Brazzillo K, Genoble L, Bhargava P, Riley MG. 2011. Comparing the efficacy and tolerability of a new daily oral vitamin B12 formulation and intermittent intramuscular vitamin B12 in normalizing low cobalamin	

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					levels: a randomized, open-label, parallel-group study. Clin Ther 33 (3): 358-371 e352. Damiao CP, Rodrigues AO, Pinheiro MF, Cruz RAF, Cardoso GP, Taboada GF, Lima GA. 2016. Prevalence of vitamin B12 deficiency in type 2 diabetic patients using metformin: a cross-sectional study. Sao Paulo medical journal = Revista paulista de medicina 134 (6): 473-479. Devalia V, Hamilton MS, Molloy AM. 2014. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. Br J Haematol 166 (4): 496-513. Didangelos T, Karlafti E, Kotzakioulafi E, Margariti E, Giannoulaki P, Batanis G, Tesfaye S, Kantartzis K. 2021. Vitamin B12 Supplementation in Diabetic Neuropathy: A 1-Year, Randomized, Double-Blind, Placebo-Controlled Trial. Nutrients;13(2):395. https://doi.org/10.3390/nu13020395 Dullemeijer C, Souverein OW, Doets EL, van der Voet H, van Wijngaarden JP, de Boer WJ, Plada M,	

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					Dhonukshe-Rutten RA, In 't Veld PH, Cavelaars AE, de Groot LC, van 't Veer P. 2013. Systematic review with dose-response meta-analyses between vitamin B-12 intake and European Micronutrient Recommendations Aligned's prioritized biomarkers of vitamin B-12 including randomized controlled trials and observational studies in adults and elderly persons. Am J Clin Nutr 97 (2): 390-402. EFSA. 2015. (European Food Safety Authority). (Draft) Scientific Opinion on Dietary Reference Values for cobalamin (vitamin B12). Panel on Dietetic Products, Nutrition, and Allergies (NDA). Available online: www.efsa.europa.eu/efsajournal. Eussen SJ, de Groot LC, Clarke R, Schneede J, Ueland PM, Hoefnagels WH, van Staveren WA. 2005. Oral cyanocobalamin supplementation in older people with vitamin B12 deficiency: a dose-finding trial. Arch Intern Med 165 (10): 1167-1172.	

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					Arvizu RA, Eckfeldt JH, Green R, Gregory JF, III, Hoofnagle AN, Jacobsen DW, Jacques PF, Lacher DA, Molloy AM, Massaro J, Mills JL, Nexo E, Rader JI, Selhub J, Sempos C, Shane B, Stabler S, Stover P, Tamura T, Tedstone A, Thorpe SJ, Coates PM, CL Johnson, and Picciano MC 2011. Biomarkers of vitamin B-12 status in NHANES: a roundtable summary. Am J Clin Nutr. 2011, 94(1):313S-321S	
198	Health Food Manufacturers Association	Evidence review B	General	General	With reference to section **1.2 Recognizing vitamin B12 deficiency: Risk factors** Due to a high medical need and growing prevalence of diabetes, we suggest adding the following health conditions as a common risk factor for vitamin B12 deficiency: - Diabetes mellitus Scientific justification:	Thank you for your comment. Diabetes as a risk factor was not included as part of the review protocol and therefore has not been included. However, metformin as a risk factor is included which is commonly used in people with type 2 diabetes.

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					Vitamin B12 deficiency in Diabetes mellitus **The number of people with diabetes, especially with type 2 diabetes, is growing rapidly worldwide. This rise is associated with ageing populations, economic development, increasing urbanisation, less healthy diets and reduced physical activity (IDF, 2021). According to the International Diabetes Federation (IDF), an estimated 537 million adults aged 20–79 years worldwide (10.5% of all adults in this age group) have diabetes (Table 1). By 2030, 643 million, and by 2045, 783 million adults aged 20–79 years are projected to be living with diabetes (Table 1). In the UK, 1 in 12 adults aged 20–79 years (8.2% of all adults in this age group) has diabetes.**	

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					Table 1 **[Data supplied]** **Estimated total number of adults (20–79 years) with diabetes and prevalence in the years 2021, 2030 and 2045** *i Prevalence is standardized to each national population for the respective year* *ii Health expenditure for people with diabetes is assumed to be on average two-fold higher than people without diabetes* *Source: (IDF, 2021)* **Diabetes estimates for 2021 show increasing prevalence of diabetes by age. Similar trends are predicted for 2045. The aging of the world's population will produce an increasing proportion of those with diabetes being over the age of 60 years. Prevalence is lowest among adults aged 20–24 years (2.2% in 2021). Among adults aged 75–79 years diabetes prevalence is estimated to be 24.0% in 2021 and**	

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					predicted to rise to 24.7% in 2045 (Figure 1). **Figure 1 Number of people with diabetes in adults (20–79 years) by age group in 2021 (columns) and estimated prevalence across age groups in 2045 (black line)** **[Data supplied]** *Source: (IDF, 2021)* **Deficiency in vitamin B12 has been observed in diabetes patients. Generally, diabetes patients tend to have lower vitamin B12 serum levels and a higher risk for deficiency (e.g. (Solomon, 2011; de Groot-Kamphuis et al., 2013; Khan et al., 2017).** **In a study with 115 diabetes patients compared to healthy controls, diabetes patients demonstrated cytosolic metabolic resistance to vitamin B12 by elevated cobalamin and**	

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					holotranscobalamin levels (Adaikalakoteswari et al., 2012). **In a cross-sectional study of 203 outpatient type 2 diabetic patients, 22% of diabetic patients had metabolically confirmed B12 deficiency (Pflipsen et al., 2009). Of note, prevalence of B12 deficiency was lower in patients taking multivitamin supplements.** **Vitamin B12 status in diabetes patients was investigated in more detail by Obeid et al. (Obeid et al., 2013). These authors compared extracellular (serum) B12 status with intracellular (red blood cell [RBC]) status. Concentrations of total vitamin B12 and holotranscobalamin (holoTC) did not differ significantly between the groups, but plasma methylmalonic acid (MMA) concentrations were significantly higher in diabetics. RBC-vitamin B12 was lower in diabetics compared to controls. The authors conclude that patients with type 2 diabetes had a lower vitamin status characterized by a normal extracellular vitamin B12 level but disturbed intracellular B12-dependent biochemical reactions.**	

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					Indeed, Solomon found that MMA values are probably a more reliable biomarker for vitamin B12 status in diabetes than serum vitamin B12 levels (Solomon, 2011). In this study, MMA values in nondiabetic subjects (n= 369), varied directly with age and inversely with serum vitamin B12. In diabetic subjects (n= 57), MMA values also increased with age but did not fall as vitamin B12 levels increased, especially > 400pg/ml. Thus, mean MMA values and the incidence of functional vitamin B12 deficiency were both significantly greater in elderly diabetic subjects (at least 70 years old) than in elderly nondiabetic subjects. Of note, intake of multivitamins reduced the risk of vitamin B12 deficiency measured as vitamin B12 serum levels (Kancherla et al., 2016; Khan et al., 2017) and intake of vitamin B12 at pharmacological doses improved MMA values and neuropathy in diabetic patients (Solomon, 2011). Different factors can increase the risk to develop a B12 deficiency such as unbalanced dietary habits or certain medications such as metformin (see also Draft for Consultation Box 2 *Common risk factors for vitamin B12*	

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					deficiency: medicines**). Metformin is the preferred initial pharmacologic agent for treatment of type 2 diabetes mellitus (T2DM) and the most used pharmacotherapy of T2DM worldwide. In UK primary care, approximately 90% of newly diagnosed T2DM patients are prescribed metformin to initiate treatment and approximately 80% of all T2DM patients are prescribed metformin (Sharma et al., 2016). Once initiated, metformin treatment should be maintained on long-term (as long as tolerated and not contraindicated).** Figure 2 Prevalence of prescribing of different antidiabetic medications used to initiate treatment in newly diagnosed patients with T2DM. **[Data supplied]** ***Other=Sum of prevalence of Insulins, Thiazolidinediones, Gliptins, Acarbose, GLP-1 analogues, Meglitinides and SGLT-2 inhibitors.*** Figure 3 Prevalence of prescribing of different antidiabetic medications among all patients with T2DM on treatment.	

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					[Data supplied] ***Other=Sum of prevalence of Acarbose, GLP-1 analogues, Meglitinides and SGLT-2 inhibitors.*** **Metformin was found to be associated with low serum vitamin B12 levels or even vitamin B12 deficiency in several recent large epidemiological studies (de Groot-Kamphuis et al., 2013; Damiao et al., 2016; Kancherla et al., 2016; Russo et al., 2016; Gupta et al., 2017; Kancherla et al., 2017; Khan et al., 2017; Raizada et al., 2017). Depending on cohort and definition of vitamin B12 deficiency based on serum levels, up to 30% of patients receiving long-term metformin treatment experienced malabsorption of vitamin B12, with a decrease in serum vitamin B12 concentration of 14% to 30% (Liu et al., 2014; Holmes, 2016). While one study showed a positive correlation between the duration of metformin therapy and peripheral neuropathy (r=0.40) (Gupta et al., 2017), two other studies did not find a correlation between metformin treatment, serum vitamin B12 and diabetic neuropathy (Russo et al., 2016;**	

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					Raizada et al., 2017) and in one study, metformin users had less neuropathy than non-metformin users (p=0.35), (de Groot-Kamphuis et al., 2013) indicating that the association between metformin, vitamin B12 and neuropathy in diabetes may be more complex.	
199	Health Food Manufacturers Association	Evidence review C	General	General	**1.3 Diagnosing vitamin B12 deficiency** To improve sensitivity when screening risk populations for B12 deficiency, we suggest adding measurement of a second marker for vitamin B12 deficiency as an initial test. Scientific justification: **There is no "gold standard" for laboratory chemistry confirmation of a clinically relevant vitamin B12 deficiency since all markers have some advantages and disadvantages and the cut-off levels for vitamin B12 deficiency and subclinical deficiency are still a matter of debate (Andrès et al., 2003; Carmel, 2012; Devalia et al., 2014; Wong, 2015).**	Thank you for your comment. Combinations of tests were considered as part of the review protocol however no evidence was identified in this area. Therefore the committee made a research recommendation. Further testing with MMA is included for people if they have an indeterminate test result.

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					In practice, diagnosis of B12 deficiency is usually made in the presence of typical neurological symptoms, hematological abnormalities, and serum vitamin B12 levels (serum cobalamin level). However, serum vitamin B12 is a test with limited specificity and sensitivity (Obeid et al., 2013). The normal serum levels are 200–1000ng/L. Levels <200ng/L (<150pmol/L) are sure signs of a B12 deficiency. However, a significant proportion of patients may have serum levels within normal range (especially under 450ng/L) but present with a functional B12 deficiency and already manifest clinical signs (Rizzo et al., 2016). Furthermore, both false negative and false positive values are common (occurring in up to 50% of tests) with the use of the laboratory-reported lower limit of the normal range as a cutoff point for deficiency (Hvas and Nexo, 2006; Stabler, 2013). Measurement of the serum metabolites MMA and homocysteine (Hcy) can improve the sensitivity significantly in patients with low normal range of B12 (Stein, 2021; EFSA, 2015; Campos, 2020). In the large-scale US National	

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					Health and Nutritional Examination Survey also a combination of vitamin B12 and one functional marker, such as MMA or Hcy was suggested to diagnose B12 deficiency (Yetley, 2011). **If measurement of MMA and Hcy is not available in clinical practice, treatment should be considered in people with a risk factor and symptoms or signs of vitamin B12 deficiency even when test results of total B12 (serum cobalamin) are indeterminate.**	
200	Health Food Manufacturers Association	Evidence review D	General	General	**1.5 Managing vitamin B12 deficiency** A clear definition of the daily dose is critical to ensure sufficient treatment outcomes. Therefore, we suggest adding guidance on the daily dose of vitamin B12 needed to correct B12 blood levels. Scientific justification: **Vitamin B12 is a relatively large molecule. Absorption of vitamin B12 takes place by saturable active absorption and by passive diffusion. While the active mechanism is more important for low physiological amounts**	Thank you for your comment. NICE does not include dosage in recommendations where they are available in the BNF or SPC. A dosage may be included if this information is not available, or the committee agrees that there needs to be a change to current recommended dosages, for example because of new evidence. The guideline has been updated to recommend at least 1mg a day when oral vitamin B12 replacement is prescribed in cases of malabsorption. This is because all comparisons for oral with intramuscular vitamin B12 replacement used 1mg of oral replacement. The committee also agreed that there was no evidence to suggest a lower dose would be effective in this group and that using this dose is likely to be current practice for this group. The dosage is stated to ensure that these patients receive the appropriate treatment.

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					of vitamin B12, the passive diffusion plays a role for uptake of pharmacological doses. **Several studies investigated the optimal dose needed to correct B12 levels based on a dose-dependent effect of vitamin B12.** **Eussen et al. (Eussen et al., 2005) conducted a randomized, double-blind dose-response study in 120 otherwise healthy elderly (≥70 years) with mild vitamin B12 deficiency (serum vitamin B12 concentration was between 100 and 300pmol/L, MMA concentration was 0.26 µmol/L or greater) to find the lowest dose of cyanocobalamin that is required for a maximal reduction in MMA concentrations. MMA was chosen as marker since it is specific for vitamin B12 and always associated with deficiency. Subjects received daily oral doses of 2.5, 100, 250, 500, and 1000µg of cyanocobalamin for 16 weeks. As expected, on average, the absolute decreases in plasma MMA and Hcy concentrations and the absolute increases in plasma vitamin B12 and holoTC concentrations increased with increasing doses of cyanocobalamin.**	There wasn't evidence to recommend a 1mg dose for people with medicine or nitrous oxide induced deficiency. Oral vitamin B12 replacement can be prescribed at lower doses for a dietary deficiency.

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					The reductions in MMA concentrations in all cyanocobalamin treated groups were significant during the first 8 weeks of treatment and remained stable during the second 8 weeks of treatment. The lowest daily oral dose of cyanocobalamin that resulted in 80% to 90% of the maximum reduction in MMA concentrations varied from 647 to 1032µg. On average, such doses of cyanocobalamin reduced plasma MMA concentrations by approximately 33%. Comparable proportional increases in concentrations of serum vitamin B12 and plasma holoTC were observed in response to the different doses of cyanocobalamin. The dose-finding curve for holoTC demonstrated that daily oral doses of 527 to 759µg of cyanocobalamin resulted in 80% to 90% of the estimated maximum increase in holoTC concentrations. The curve for Hcy did not show such a behavior, however, Hcy is not specific for vitamin B12, but also influenced by vitamin B6 and folate. **Figure 4 Proportional effects of different doses of cyanocobalamin on mean methylmalonic acid (MMA) (A), total**	

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					homocysteine (tHcy) (B), holotranscobalamin (holoTC) (C), and vitamin B12 (D) concentrations after 16 weeks of supplementation. **[Data supplied]** **In a recent placebo-controlled, observer-blinded RCT, oral vitamin B12 1000µg/daily for 4 weeks in patients with mild vitamin B12 deficiency (vitamin B12 serum levels 125-200pmol/L) led to a significant decrease in MMA serum levels and significant increase in serum vitamin B12 levels compared to a placebo group (Favrat et al., 2011). However, 3 months after discontinuation of treatment, at 4 months, while there was still a significant change observed for the B12 serum levels, there was no significant differences in MMA levels detected anymore at one and 4 months without continued treatment. No effects were seen on hematocrit and Hcy. Thus, it seemed that in this population, 1000µg daily was effective in significantly changing surrogate parameters during treatment but was not enough to obtain**	

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					a longer hematological effect indicating the need for long term treatment. Evidence that an oral dose of 500µg/day might be not sufficient to treat vitamin B12 deficiency comes from a double-blind, placebo-controlled RCT in elderly with moderate to poor vitamin B12 status (plasma vitamin B12 <250pmol/L and a urinary MMA ratio >1.5mmol MMA/mmol creatinine) (Hill et al., 2013). A total of 100 subjects were randomized to receive placebo, 10, 100 or 500µg vitamin B12 daily for 8 weeks. All biomarkers had a dose response to supplemental vitamin B12. The response in urinary MMA was comparable with plasma MMA. Improvements in plasma vitamin B12 and serum holoTC were achieved at cobalamin supplements of 10 µg/d. However even 500µg/d for 8 weeks did not normalize plasma vitamin B12 in 8% and serum holoTC in 12% of subjects. With respect to MMA, 15–25% of people still showed evidence of metabolic deficiency (plasma MMA>0.35 mmol/L and a urinary MMA ratio> 2.0) after 500µg/d cobalamin for 8 weeks. Plasma Hcy levels decreased in all groups.	

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					In a recent meta-analysis on the association between vitamin B12 intake and biomarkers in RCTs and observational studies, the pooled dose-response relation of all studies between vitamin B12 intake and status indicated that a doubling of the vitamin B12 intake increased vitamin B12 concentrations by 11% (95% CI: 9.4%, 12.5%) (Dullemeijer et al., 2013). These statements were based on studies with participants without severe deficiencies and, therefore, were valid when vitamin B12 intake was ≥1.3µg/d. This increase was larger for studies in elderly persons (13%) than in studies in other adults (8%). A large heterogeneity of studies was observed. **Figure 5 Serum or plasma vitamin B12 concentration (pmol/L) as a function of dietary vitamin B12 intake (µg/ day) estimated by using random-effects meta-analyses of observational studies and RCTs** **[Data supplied]** **Solid line; $\log^e(y) = 0.15\ 3\ \log^e(x) + 5.50$], RCTs only [dashed line; loge(y) = 0.17 3**	

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					$\log^e(x)$ + 5.47], and observational studies only [dotted line; $\log^e(y)$ = 0.10 3 $\log^e(x)$ + 5.57]. RCTs, randomized controlled trials. **A systematic review on the efficacy of oral and nasal vitamin B12 in the treatment of patients with vitamin B12 deficiency related to gastrointestinal disorders concluded that oral vitamin B12 at a daily dose of 1000µg, was adequate to normalize serum vitamin B12 levels and cure main clinical manifestations related to vitamin B12 deficiency in GI disorders and is therefore an effective alternative to i.m. vitamin B12 (Andrès et al. 2018). A review on vitamin B12 treatment in elderly also concluded that oral vitamin B12 replacement at 1000µg daily proved adequate to cure vitamin B12 deficiency, with a good safety profile (Andrès et al., 2020).** **A prospective, double-blind, placebo-controlled trial in patients with diabetic neuropathy and low vitamin B12 levels at baseline showed that treatment with 1 mg of oral vitamin B12 (as methylcobalamin) for twelve months increased vitamin B12 levels and**	

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					improved all neurophysiological parameters, sudomotor function, pain score, and QoL (Didangelos et al. 2021). A dose of oral 1000µg vitamin B12 daily has also been shown to be effective in improving clinical symptoms of peripheral neuropathy, e.g. neuropathic pain and other neurological symptoms as well as hematological symptoms associated with vitamin B12 deficiency (Bolaman et al., 2003). A recent Cochrane review found that high oral doses of vitamin B12 (1000 and 2000µg) were as effective as intramuscular administration in achieving hematological and neurological responses (Vidal-Alaball et al., 2005). This is in agreement with a recent RCT showing similar changes of parameters after 1000µg i.m. or oral vitamin B12 for 3 months (Castelli et al., 2011) and a case series by (Nyholm et al., 2003). In summary, 1000µg oral vitamin B12 daily is assumed to be optimal to treat or prevent vitamin B12 deficiency in most cases of mild to moderate deficiency. Severe deficiency cases might require higher oral doses (2 mg daily) or an initial i.v. or i.m. application.	

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201	Hull University Teaching Hospital NHS Trust	Guideline	General	General	As an Immunologist, I have significant concerns regarding the decision to use the tests in identifying the cause of vitamin B12 deficiency as they will have significant impact on the laboratories My concerns are with 1.4.1 where anti-intrinsic factor antibody tests is being considered as 1st line and 1.4.3 suggests to use GPC as confirmatory test It is well-recognised that GPC antibody has sensitivity >90% with low specificity while anti-intrinsic factor antibody has specificity >98% So these tests should be used the other way around, as is routinely done in all Immunology laboratories Hence, the reasons behind these recommendations remain unclear We have new data from our laboratory using a total of 14997 samples tested (between 2019-2021) that continues to show very low level IFA positivity in-spite of GPC positivity A response will be much appreciated	Thank you for your comment. Evidence was not identified to suggest that anti-gastric parietal cell antibody test should be used first therefore it is only considered as a second-line test. The evidence identified reported a 90% sensitivity and 56% specificity, whereas the evidence for GPC reported an 83% sensitivity and 0% specificity. Based on this and that anti-intrinsic factor antibody tests are widely available the committee agreed that anti-intrinsic factor is the best first-line test to use. More detail can be found in Evidence review D on Identifying the cause. We will flag to the surveillance team the possibility that new data may be published in this area.

Vitamin B12 deficiency in over 16s: diagnosis and management

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11/07/2023 – 22/08/2023

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202	Institute of Biomedical Science	Guideline	General	General	The blood film morphology features of megaloblastic anaemia should be listed rather than the vague notions of anaemia and macrocytosis. These include **hypersegmented neutrophils** and macrocytes, particularly **oval macrocytes**. The neutrophil shown has six lobes and is therefore classified as hypersegmented, with florid examples showing blastic features, including nucleated erythrocytes and even blasts. **Full Blood Count and Film** should be defined explicitly as an initial screening.	Thank you for your comment. The committee agreed that any abnormal findings on a blood count may be a sign of vitamin B12 deficiency and therefore the recommendation has not changed. Anaemia and macrocytosis were given as examples of this.
203	Institute of Biomedical Science	Guideline	009	010 – 014	Homocysteine is a very unstable analyte (samples need collecting on ice) and received in the lab within an hour or so of collection (so unfeasible for most GPs). A much better analyte is methylmalonic acid which has no particular sample requirements and can be analysed in serum or urine. From local experience, secondary care has not been happy when asked to do a homocysteine.	Thank you for your comment. Following stakeholder comments the committee have recommended using either homocysteine or serum MMA when testing for vitamin B12 deficiency suspected to be caused by recreational nitrous oxide use. The recommendation has also been updated to state that if homocysteine is the chosen test then the person should be referred to phlebotomy services in secondary care.

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204	Institute of Biomedical Science	Guideline	029	014 - 020	Guidance could also describe that between methodology B12 testing demonstrates a high degree of variability. Although this is a clinical guide, this technicality is an equally important factor that can impact test result. It is recommended that the guidance alerts clinicians to this source of variation and urge caution/contact lab if questions arise.	Thank you for your comment. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not. Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests. It is anticipated that healthcare professionals would contact the laboratory if they have any queries about test results.
205	Leeds Teaching Hospitals NHS Trust	Guideline	007		Unexplained fatigue will result in a high number of B12 tests being undertaken	Thank you for your comment. The committee discussed this. The risk factors box has been updated so that increasing age has been removed. The committee agreed that this would greatly reduce the number of tests. They also agreed that anyone with one of the remaining risk factors and unexplained fatigue would indicate an increased likelihood that vitamin B12 was the cause of their fatigue.
206	Leeds Teaching Hospitals NHS Trust	Guideline	010		There is no acknowledgment regarding the issues of B12 assay variability, reproducibility and variable NEQAS test results. This needs to be taken into consideration when the assay is being undertaken.	Thank you for your comment. Several stakeholders commented on the thresholds. Some thought they were too low, others thought they were too high and there was also some support that they are about right. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those

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						recommended in the guideline, however 1 does not. Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests. The committee also recommend considering MMA as a further test for people with an indeterminate active or total B12 test result. This is to capture people who may have a vitamin B12 deficiency when their test result doesn't meet the criteria for deficiency. An indeterminate result covers an active B12 of between 25 and 70 pmol per litre, and a total B12 of between 180 and 350 nanograms (133 and 258 pmol) per litre. The committee has also added a recommendation to use the laboratory's reference ranges to decide if vitamin B12 deficiency is likely when interpreting serum MMA and plasma homocysteine test results.
207	Leeds Teaching Hospitals NHS Trust	Guideline	010		MMA testing is not easily available in a lot of centres	Thank you for your comment. The committee thought carefully before making the recommendations and took cost effectiveness into account. Economic modelling showed that MMA is likely to be cost effective for people with a B12 measurement in the indeterminate range. Implementing these recommendations will require some reallocation of resources, including investment in pathology

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						services, so that testing can become more widely available. A resource impact report and tool will be published alongside this guideline.
208	Leeds Teaching Hospitals NHS Trust	Guideline	011		Black family background – some parameters regarding an adjusted reference range would be useful eg % higher than current normal range as lab normal ranges will vary	Thank you for your comment. The findings in the study suggested cut-off for deficiency as 225 ng/L (166 pmol/L). This has been added to the evidence report. However, the committee were aware that this is one study and the result may need to be validated in other populations. Therefore they did not include it in the guideline recommendations.
209	Leeds Teaching Hospitals NHS Trust	Guideline	011	024	This range is well above the normal range for most labs (350ng/l), which will make it difficult for clinicians to reassure patients with a B12 within normal range for the lab, but below 350ng/l that replacement is not required. A lot of patients get a B12 tested for vague reasons and a B12 within a lab normal range and a normal FBC does not require replacement	Thank you for your comment. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not. Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests.
210	Leeds Teaching Hospitals NHS Trust	Guideline	019		1.6.12 Adjusting the dosing of IM B12 is very difficult for GPs. There are some patients who request to take treatment alternate days, weekly, monthly. Written in this way would suggest this is permissible and effective to resolve symptoms. Would suggest the terminology/sentence is amended to provide some increased guidance for GPs	Thank you for your comment. The recommendation has been updated so it only refers to the frequency of injections and not the dose. The guideline did look for clinical evidence relating to the frequency of intramuscular injections however no evidence was identified and the committee made a research recommendation. Loading doses are covered in the BNF and therefore not included in the guideline. NICE does not generally include dosages in recommendations where they

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						are available in the BNF or SPC. A dosage may be included if this information is not available, or the committee agrees that there needs to be a change to current recommended dosages, for example because of new evidence.
211	Leeds Teaching Hospitals NHS Trust	Guideline	019		1.6.15 Guidance as to follow-up testing for patients stopping IM B12 would be useful. A service improvement project undertaken by primary and secondary care to stop IM B12 in a group of patients was undertaken within the trust in 2017, with a programme for post cessation testing of B12. 157 patients had their B12 indications reviewed and B12 stopped. 33% (52) were male. Review of blood results prior to B12 commencement revealed a mean Hb on starting B12 was 127g/dl, with a median of 128 g/dl. The majority of patients (103/157) were normocytic, with 39 patients having a high MCV, 9 had no data and 8 had a low MCV. 6 having classical macrocytic anaemia 133 of 157 completed the 2 years of monitoring or longer (84.7%). 9 (5.7%) did not attend follow-up blood tests despite repeated invites. 4 left the GP practice during the project, 17 died during the service development. 2 had borderline low B12 who declined intervention with medication.	Thank you for your comment. There wasn't the evidence for the committee to provide more detailed guidance on stopping intramuscular medications. The committee agreed that if it looks like the cause of the deficiency has been resolved because they no longer have symptoms then stopping or decreasing the frequency of injections should be thought about. Treating healthcare professionals would need to use their clinical judgement in discussion with the person to decide the best way forward.

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					20 restarted B12, mean time from stopping to restarting B12 of 22.5 months (range 17-36 months). Median % drop in patients restarted was 9% (range 1%-38%) mean 12.3% below normal. The median level of B12 below normal prior to the 20 patients commencing B12 originally was 22%. 11 patients had an oral course of B12, 5 patents started IM and 4 had oral then IM due to repeated oral courses. The option to restart oral or IM replacement was patient and physician choice. 2 patients had borderline B12 and decided to amend their diet, declined IM or oral B12. Reference: https://www.postersessiononline.eu/173580348_eu/congresos/BSH2020/aula/-PO_52_BSH2020.pdf	
212	Leeds Teaching Hospitals NHS Trust	Guideline	037	012	There are resource implications for a nursing appointment for administration	Thank you for your comment. We have changed this section to acknowledge the increase in nursing appointments.
213	NHS Birmingham and Solihull ICB	Guideline	General	General	The guideline does not include any guidance on whether there is a need to treat if a low vit B12 level is picked up incidentally in the absence of any	Thank you for your comment. The treatment recommendations apply to anyone who has been diagnosed with a vitamin B12 deficiency including those identified on incidental findings. No evidence was identified to suggest not

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					symptoms. We understand that the guideline says only test if the patient has symptoms, but the reality is that there are a lot of patients (especially those over 65) with low B12 levels but no symptoms, and we are seeing that B12 is now often added to routine bloods e.g. for patients with diabetes. A recommendation on low B12 levels where the patient is not symptomatic would be helpful and/or a DO NOT DO recommendation for routine testing to be explicitly clear.	treating people with a diagnosed deficiency and no symptoms. This guideline doesn't make a statement on screening or routine testing of vitamin B12 concentrations because this was excluded from the guideline scope. Regarding routine testing, the MHRA advice is to consider periodic vitamin B12 monitoring in patients with risk factors for vitamin B12 deficiency. Metformin is included as a risk for vitamin B12 deficiency in this guideline and it is also recommended as a treatment in the NICE guidelines for type I and type II diabetes.
214	NHS Birmingham and Solihull ICB	Guideline	013	021	Lifelong oral therapy will significantly increase costs compared to lifelong IM therapy as shown in Evidence Review 5 Table 19. This increase in cost will be even greater than stated in Evidence Review 5 Table 19 if the 50 microgramme tablet is prescribed. Without clear information in the guideline about which oral product to prescribe it is likely that this strength will be prescribed as reflected in current prescribing data (from ePACT). Where either oral or IM therapy is an option, clinicians in primary care may opt to prescribe oral therapy due to current workforce pressures.	Thank you for your comment. The committee agree that lifelong treatment with oral vitamin B12 replacement is currently more costly and may not be cost-effective compared to intramuscular treatment. However, without evidence to demonstrate that intramuscular vitamin B12 replacement is more effective than oral B12 and given the workforce pressures the committee have made a weaker 'consider' recommendation for intramuscular instead of oral. The recommendations have been updated. Intramuscular injections are offered to people with autoimmune gastritis or who have had a total gastrectomy or complete terminal ileal resection. For all other people with vitamin B12 deficiency because of malabsorption intramuscular injections are considered over oral replacement.

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					While the guideline states there was no evidence to suggest that oral replacement was ineffective in these groups (post surgery – Guideline page 34 lines 8-10), there is no explanation showing that that the increased cost of lifelong oral therapy was cost-effective to justify including this option.	
215	NHS Birmingham and Solihull ICB	Guideline	013 - 015		There is no recommendation of dose of cyanocobalomin to be prescribed for oral therapy, despite the Evidence Review E stating (page 58 line 38 to page 59 line 21): ***Oral cyanocobalamin*** *In the BNF there are predominantly two strengths of cyanocobalamin tablets. These are the 50mcg and 1000mcg. There is a Drug Tariff price for each strength but, the one for the 1000mcg tablet is lower than the one for the 50mcg tablet. Therefore, it was considered preferable to use the 1000mcg cyanocobalamin assuming that it would be at least as effective as the lower strength tablet as well as cyanocobalamin being generally well tolerated and unlikely to cause harm. Although there are cheaper 1000mcg cyanocobalamin preparations in*	Thank you for your comment. NICE does not include dosages in recommendations where they are available in the BNF or SPC. A dosage may be included if this information is not available, or the committee agrees that there needs to be a change to current recommended dosages, for example because of new evidence. The guideline has been updated to recommend at least 1mg a day when oral vitamin B12 replacement is prescribed in cases of malabsorption. This is because all comparisons for oral with intramuscular vitamin B12 replacement used 1mg of oral replacement. The committee also agreed that there was no evidence to suggest a lower dose would be effective in this group and that using this dose is likely to be current practice for this group. The dosage is stated to ensure that these patients receive the appropriate treatment. There wasn't evidence to recommend a 1mg dose for people with medicine or nitrous oxide induced deficiency. Oral

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					the BNF, only Orobalin 1000mcg is licensed. Where there is a licensed preparation, alternative preparations should not be prescribed. The reimbursement to pharmacy contractors who dispense any standard release preparation of cyanocobalamin 1000mcg will be the same, therefore the Drug Tariff price was used in the cost analysis. For the licensing of Orobalin, the initial dose is 4000mcg daily until remission. However, there is uncertainty about how long the time taken to remission is and how to assess remission which may be evaluated by further B12 tests or assessment of a person's symptoms. The experience of the committee is that for newly diagnosed people with B12 deficiency, when cyanocobalamin 1000mcg tablets are prescribed, the starting dose is one tablet a day rather than four tablets a day. This was the assumption within the cost comparison for people who have B12 deficiency. For people with suspected dietary deficiency whose test results indicate they are B12 deficient, it was recommended that dietary advice be provided. Weaker ('consider') recommendations were made for oral vitamin B12 replacement for people who	vitamin B12 replacement can be prescribed at lower doses for a dietary deficiency.

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					have a confirmed dietary deficiency. If treatment was offered to all people with a confirmed dietary deficiency of vitamin B12, this would have a significant resource impact because this does not reflect usual clinical practice. For vitamin B12 deficiency (and not pernicious anaemia) the BNF recommended dose is 50mcg to 150mcg daily. By switching patients from 100mcg (costs £0.86 per daily dose) or 150mcg (costs £1.29 per daily dose) to one 1000mcg tablet (costs £0.33 per daily dose) this would be cost saving – this would save approximately £75 - £173 annually per patient. The committee members did not think that there would be any adverse effects from the increase in dose and the savings may be significant due to many people on these doses. These assumptions are not reflected in the guideline (initial dose or strength of oral therapy recommended in cost-effective analysis). Without clarity, the 50mg strength may be prescribed; this is reflected in current practice and increases costs as described in Evidence review E above.	

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					While there would be a saving in switching people from 100mcg or 150mcg (using 50mcg tabs) to 1mg tablets, the new guideline will result in an increase in the number of patients who are prescribed B12 so has the potential to significantly increase net spend from prescribing B12 in primary care.	
216	NHS Birmingham and Solihull ICB	Guideline	014	003 - 004	Lifelong oral therapy will significantly increase costs compared to lifelong IM therapy as shown in Evidence Review 5 Table 19. This increase in cost will be even greater than stated in Evidence Review 5 Table 19 if the 50 microgramme tablet is prescribed. Without clear information in the guideline about which oral product to prescribe it is likely that this strength will be prescribed as reflected in current prescribing data (from ePACT). Where either oral or IM therapy is an option, clinicians in primary care may opt to prescribe oral therapy due to current workforce pressures. It is not clear in this statement (1.5.5) that therapy may not need to be lifelong. The omission of a duration for this cohort at this stage in the guideline may result in	Thank you for your comment. Following stakeholder comments the recommendations have been updated. Intramuscular injections are offered to people with autoimmune gastritis or who have had a total gastrectomy or complete terminal ileal resection. For all other people with vitamin B12 deficiency because of malabsorption intramuscular injections are considered over oral replacement. It is written in the rationale that treatment in this group may not be lifelong. The management recommendations and rationales have been updated so that they will appear together by cause of deficiency in the final guideline. Therefore the recommendations for managing vitamin B12 deficiency caused by malabsorption will be immediately followed by its rationale. This will make it easier to see rationales than in the consultation version of the guideline

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					prescribers assuming therapy is lifelong, especially as this is stated in 1.5.3 and 1.5.4.	where there was one section of recommendations and one rationale for all management. The ongoing care and follow up recommendations have been updated to make it clearer when vitamin B12 replacement should be changed, continued or stopped.
217	NHS Birmingham and Solihull ICB	Guideline	014 - 015	026 021	For dietary and unknown causes of B12 deficiency there are no recommendations on duration of therapy within this section whereas other causes include duration (lifelong) at this point in the guideline. This may result in prescribers assuming therapy is lifelong.	Thank you for your comment. The ongoing care and follow up recommendations of medications advise assessing the person's symptoms to determine the response to treatment. Depending on this response the committee have also recommended that treatment may need to be changed, continued or stopped. These recommendations apply to all causes of vitamin B12 deficiency.
218	NHS Birmingham and Solihull ICB	Guideline	015	026 - 027	Evidence Review E states (page 59, lines 10-15): ***Oral cyanocobalamin*** *For people with suspected dietary deficiency whose test results indicate they are B12 deficient, it was recommended that dietary advice be provided. Weaker ('consider') recommendations were made for oral vitamin B12 replacement for people who have a confirmed dietary deficiency. If treatment was offered to all people with a confirmed dietary deficiency of vitamin B12, this would have a significant resource impact because this does not reflect usual clinical practice.*	Thank you for your comment. The committee agreed that if people have a confirmed deficiency then that deficiency is likely to need to be treated with oral vitamin B12 replacement. The committee agreed that in their experience where people have a confirmed deficiency it would be current practice to consider oral supplementation. The committee were aware of the NHSE guidance and their understanding is that while it is recommended that vitamins are not routinely prescribed a 'Course of treatment for medically diagnosed deficiency' is an exception to the rule. 'Consider' recommendations are written when the committee agree that one intervention is likely to be more clinically and

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					A 'consider' recommendation for oral cyanocobalamin for dietary deficiency still has the potential to significantly increase current prescribing of oral cyanocobalamin. While it does not represent usual clinical practice currently, having a positive 'consider' recommendation is likely to be translated into usual clinical practice and hence create a significant resource impact as described. A 'consider' recommendation may create inequalities, where some patients are prescribed therapy and others are not. This does not align with national guidance (NHSE) on prescribing of vitamins (and local policy) where maintenance therapy would not be provided on the NHS once deficiency has been treated.	cost effective than another however there is a lack of evidence to definitively state this. The implication is that while the committee agree the recommended intervention is likely to be the best option that may not always be the case. In this guideline they apply to all populations and are not thought to create an inequality to one group.
219	NHS Birmingham and Solihull ICB	Guideline	018	008 - 010	The recommendation to '*stop treatment if cause or suspected cause has been addressed (for example, if the person is following advice on improving their dietary intake of vitamin B12)'* allows for continued prescribing where there is no 'medical' reason for deficiency but the patient hasn't	Thank you for your comment. It is beyond the remit of NICE to recommend people buying their own supplements.

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					taken on any self care responsibility e.g. improving diet. A stronger self care message is encouraged, once deficiency has been corrected, where pateints are able to address the cause e.g. dietary deficiency; this would align with national policy guidance (NHSE) and local policy (Over the counter medicines) on prescribing of vitamins where maintenance therapy would not routinely be provided on the NHS once deficiency has been treated in this cohort of patients.	
220	NHS Birmingham and Solihull ICB	Guideline	019	021 - 024	The recommendation to 'think about stopping' therapy *if* cause or suspected cause has been resolved and symptoms are no longer present allows for continued prescribing where there is no 'medical' reason for deficiency. A stronger self care message is encouraged, once deficiency has been corrected, where patients are able to address the cause e.g. dietary deficiency; this would align with national guidance (NHSE) on prescribing of vitamins (and local policy) where maintenance therapy would not be provided on the NHS once deficiency has been treated.	Thank you for your comment. This recommendation relates to intramuscular injections and these currently need to be administered by a healthcare professional. There was no evidence for switching from intramuscular injections to oral vitamin B12 replacement. The committee agreed that it would not be possible to describe all scenarios in the recommendation where it would be better to stop or reduce injections. For some people reducing the frequency of injections would be safer than just stopping.

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221	NHS England	Guideline	General	General	The NHSE Patient Safety Team had previously identified patient safety concerns with the management of vitamin b 12 deficiency and worked with Mamta Garg (Cons Haematologist / Chair BSH General Haem Task Force) to try and address the identified issues. It is therefore good to see that the draft NICE guidance provides clarity around our concerns including when to offer/ consider oral or IM treatment, how to monitor and when to review this treatment. Excellent work.	Thank you for your comment.
222	NHS England	Guideline	General	General	Many of our cohort will be more at risk of vitamin B12 deficiency because: 1.they may have a restricted diet (due to sensory issues, eating disorder more common in people who are autistic,) 2. some anti-epileptic meds (epilepsy more common in people who have learning disability	Thank you for your comment. These factors are all listed in the risk factor box in the guideline.

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					3. thyroid disease (more common in Down's)	
223	NHS England	Guideline	General	General	Blood tests are needed to diagnose vitamin B12 deficiency which may be a problem to do, and there may be issues with treatment as some people need injections of vitamin B12 so a problem for those with sensory issues.	Thank you for your comment. The committee agree that injections can be a problem for people with sensory issues. This has not been addressed in this guideline as it is a wider issue than vitamin B12 deficiency. The NICE guideline on Shared decision making covers recommendations on ways for healthcare professionals and people using services to work together. Both are linked to in this guideline. The NICE guideline on Patient experience in adult NHS services recommends listening to and discussing any fears or concerns the patient has.
224	NHS England	Guideline	General	General	We strongly suggest reference to making reasonable adjustments: This is a legal requirement as stated in the Equality Act 2010 and is important to help you make the right diagnostic and treatment decisions for an individual. You can ask the person and their carer or family member what reasonable adjustments should be made. Adjustments aim to remove barriers, do things in a different way, or to provide something additional to enable a person to receive the assessment and treatment they need. Possible examples include; allocating a clinician by gender, taking blood samples by thumb prick rather than needle,	Thank you for your comment. Making reasonable adjustments as required by the Equality Act is a statutory requirement and this requirement would not be repeated in each individual NICE guideline. This guideline cross refers to the NICE guideline on Patient experience in adult NHS services which mentions the requirements of the Equalities Act.

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					providing a quiet space to see the patient away from excess noise and activity.	
225	NHS England	Guideline	General	General	We recommend including reference to the importance of Communication: Communicate with and try to understand the person you are caring for. Check with the person themselves, their family member or carer or their hospital or communication passport for the best way to achieve this. Use simple, clear language, avoiding medical terms and 'jargon' wherever possible. Some people may be non-verbal and unable to tell you how they feel. Pictures may be a useful way of communicating with some people, but not all.	Thank you for your comment. This guideline cross refers to the NICE guideline on Patient experience in adult NHS services which covers recommendations on communicating with the patient. This includes avoiding the use of 'jargon' and establishing the most effective way of communicating with each patient. Using pictures is given as an example of a way of improving communication.
226	NHS England	Guideline	General	General	A person with a learning disability and some autistic people may not be able to articulate their response to pain in the expected way: for example, they may say that they have a pain in their stomach when the pain is not there; may say the pain is less acute than you would anticipate; or not say they are in pain when they are. Some may feel pain in a different way or respond to it differently: for example, by displaying challenging behaviour; laughing or crying; trying to hurt themselves; or equally may become withdrawn or quiet. People who	Thank you for your comment. Recommendations to help healthcare professionals and the people using services manage in these situations are covered in other NICE guidance including the NICE guidelines on Patient experience in adult NHS services, Shared decision making and Decision-making and mental capacity. This guideline cross refers to those guidelines.

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					use a wheelchair may have chronic pain. Understanding what is 'normal' for that person by talking to	
227	NHS England	Guideline	General	General	Be aware of diagnostic overshadowing: This occurs when the symptoms of physical ill health are mistakenly either attributed to a mental health or behavioural problem or considered inherent to the person's learning disability or autism diagnosis. People with a learning disability or autism have the same illnesses as everyone else, but the way they respond to or communicate their symptoms may be different and not obvious. Their presentation with COVID-19 may be different from that for people without a learning disability or autism	Thank you for your comment. Recommendations to help healthcare professionals and the people using services manage in these situations are covered in other NICE guidance including the NICE guidelines on Patient experience in adult NHS services, Shared decision making and Decision-making and mental capacity. This guideline cross refers to those guidelines. There is also a NICE guideline on Learning disabilities and behaviour that challenges that provides recommendations on communication needs.
228	NHS England	Guideline	General	General	Pay attention to healthcare passports: Some people with a learning disability and some autistic people may have a healthcare passport giving information about the person and their health needs, preferred method of communication and other preferences. Ask the person or their accompanying carer if they have one of these.	Thank you for your comment. Recommendations to help healthcare professionals and the people using services manage in these situations are covered in other NICE guidance including the NICE guidelines on Patient experience in adult NHS services, Shared decision making and Decision-making and mental capacity. This guideline does not cover recommendations related to healthcare passports.
229	NHS England	Guideline	General	General	The recommendations in this guidance for b12 deficiency will not have any material impact on primary care services as the	Thank you for your comment.

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					testing and treatment is already well established.	
230	NHS England	Guideline	009	003	1.3.1 Could they clarify in 1.3.1 whether interpreting total B12 is absolutely contradicted in pregnancy i.e. if a woman happens to have had 1 total B12 (regularly happens in practice) should the result should be ignored and an active B12 taken (and is this any or just a low result?)	Thank you for your comment. The committee recommend using active B12 because it is the better test to use during pregnancy. However, they did not have the evidence to state not to use total B12. They made a research recommendation on the best test to use for diagnosing a vitamin B12 deficiency. This included suggesting the tests be examined separately during pregnancy.
231	NHS England	Guideline	010 010 011	009, 018, 024	1.3.8 1.3.10 1.3.14 Re the first bullets related to total B12 1.3.8, 1.3.10 and 1.3.14. Do these thresholds also apply to pregnant women if they happen to have had a total rather than active B12? Could this be clarified, or mitigated by more explanation in 1.3.1?	Thank you for your comment. Following stakeholder comments the committee agree that there is no need for a higher threshold during pregnancy and have removed the recommendation from the guideline.
232	NHS Gloucestershire Integrated Care Board	Guideline	010	015	Could 'clinical judgement' lead to inaccuracies when interpreting results? Could this be more specific?	Thank you for your comment. We have updated this to make it more specific. The recommendation now states 'Use laboratory reference ranges to interpret plasma homocysteine test results when deciding if vitamin B12 deficiency is likely, but take into account additional factors that may increase plasma homocysteine levels (such as folate deficiency).'

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233	NHS Gloucestershire Integrated Care Board	Guideline	010	027	What is the higher reference range referred to in this part of the guidance? Can this be more specific to avoid misinterpretation?	Thank you for your comment. The findings in the study suggested cut-off for deficiency as 225 ng/L (166 pmol/L). This has been added to the evidence report. However, the committee were aware that this is one study and the result may need to be validated in other populations. Therefore they did not include it in the guideline recommendations.
234	NHS Gloucestershire Integrated Care Board	Guideline	014 014 014 034 034 034 035	004 009 021 019 019 024 006	At multiple points in the guideline (see page and line numbers detailed to the left), it states that treatment should be patient preference between tablets and intramuscular. We don't agree with patient preference being a factor in the treatment decision making process if the tablets are considered as clinically effective as the intramuscular treatment. If patients choose to have intramuscular treatment when tablet treatment would have offered the same outcome this will lead to significant unnecessary costs to the NHS, including taking up limited clinical staff time and patient appointments for unnecessary injection administration.	Thank you for your comment. The committee agreed that where there is no evidence that one form of vitamin B12 replacement is more effective or cost-effective than the other then the options should be offered on an equal basis. That would involve a discussion with the person and including them in the decision. Following stakeholder comments patient preference has been removed from the recommendation on vitamin B12 deficiency because of malabsorption that is not caused by autoimmune gastritis or surgery. The recommendation now states to offer vitamin B12 replacement and consider intramuscular instead of oral vitamin B12 replacement. There is no clear evidence to distinguish which out of oral or intramuscular vitamin B12 replacement was more clinically or cost effective for vitamin B12 deficiency caused by medicine or recreational nitrous oxide use. Therefore the committee agreed to recommend either oral or intramuscular vitamin B12 replacement. In both these causes the recommendation states the decision should be based on clinical judgement and patient preference.

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						The guideline's economic modelling indicated that oral vitamin B12 is more costly than injections based on the drug tariff prices and including staff time for injections. Therefore, it is unlikely that tablets are more cost effective. However, given the workforce problems, we have left oral as an option for some indications.
235	NHS Gloucestershire Integrated Care Board	Guideline	014	009	If tablets would be as effective as intramuscular then on the basis that tablets are more cost effective for the NHS, we believe that tablets should be the treatment option promoted.	Thank you for your comment. There is no clear evidence to distinguish which out of oral or intramuscular vitamin B12 replacement was more clinically or cost effective for medicine induced vitamin B12 deficiency. Therefore the committee agreed to recommend either oral or intramuscular vitamin B12 replacement is recommended. The guideline's economic modelling indicated that tablets are more costly than injections based on the drug tariff prices and including staff time for injections. Therefore, it is unlikely that tablets are more cost effective.
236	NHS Gloucestershire Integrated Care Board	Guideline	014	019	Patient preference regarding treatment method should not be prioritised when a patient's vitamin B12 deficiency has been self-inflicted by recreational nitrous oxide use. We feel that tablets should be the recommended treatment on the basis that it is more cost effective for the NHS and will achieve the same outcome when treating the B12 deficiency.	Thank you for your comment. There is no clear evidence to distinguish which out of oral or intramuscular vitamin B12 replacement was more clinically or cost effective for vitamin B12 deficiency caused by recreational nitrous oxide use. Therefore the committee agreed to recommend either oral or intramuscular vitamin B12 replacement.
237	NHS Gloucestersh	Guideline	018	004	We believe that once B12 deficiency has been corrected the maintenance doses should be purchased by the patient over the	Thank you for your comment. It is beyond the remit of NICE to recommend people buying their own supplements.

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	ire Integrated Care Board				counter. This should be specified in the NICE guideline otherwise patients will expect B12 tablets to be prescribed indefinitely which is both unsustainable and an unnecessary use of NHS money when tablets can be purchased relatively cheaply over the counter. The OTC purchase of vitamins after correction of deficiency is also an NHS England recommendation which the NICE guidance should align with: https://www.england.nhs.uk/medicines-2/conditions-for-which-over-the-counter-items-should-not-routinely-be-prescribed/	
238	NHS Gloucestershire Integrated Care Board	Guideline	018	010	Should there be another bullet point advising that if prescribed treatment has corrected the vitamin B12 deficiency and the patient no longer has symptoms but is unable to improve their vitamin B12 intake through diet alone (e.g., due to strict vegan diet) recommend over the counter vitamin B12 supplements for maintenance purposes?	Thank you for your comment. It is beyond the remit of NICE to recommend people buying their own supplements.
239	NHS Gloucestershire Integrated Care Board	Guideline	018	016	We believe that increasing the oral dose should be trialled before intramuscular treatment is considered here. If increased oral dose leads to improvement in symptoms this will prevent unnecessary costs associated with intramuscular treatment.	Thank you for your comment. Evidence was not available to suggest which was more effective and some people may have already been started on a high dose of oral vitamin B12 replacement. Therefore the committee agreed that both should be options.

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240	NHS Gloucestershire Integrated Care Board	Guideline	027	017	Could the specific anti-seizure medicines be listed where evidence is strong?	Thank you for your comment. The antiseizure medicines are listed in the risk factor box. This rationale appears directly under the recommendations so they have not been repeated in the rationale. The antiseizure medicines included as risk factors are phenobarbital, pregabalin, primidone and topiramate.
241	NHS Gloucestershire Integrated Care Board	Guideline	036	013	We think there are 2 ways of looking at this. Another view is that if a patient is not adhering to taking tablets that are available to them within their own home, why would a patient be more likely to attend a GP practice appointment to obtain an intramuscular injection? Or if the intramuscular injections are going to be delivered by home visits, then we feel that needs to be clarified as this will lead to increased costs of NHS staff time due to travel time, travel costs, the injection itself.	Thank you for your comment. The committee agreed that older people who have recently been in hospital are likely to be having health care visits because they were hospitalised. These would not be additional health care visits just for vitamin B12 replacement. Therefore there would be someone to give them the injections. They also agreed it is one less pill to take. For people with delirium or cognitive impairment injections may ensure they receive the vitamin B12 replacement and their symptoms do not deteriorate. Homeless people may not be able to store medicines safely therefore there may be concern that people may not be adherent to treatment. It would be more practical for people to attend one appointment to receive parenteral treatment every two to three months than to be responsible for ordering medicine on a regular basis and keeping the medicine safe and taking the medicine daily. This recommendation hopes to address any potential health inequality.
242	NHS Gloucestersh	Guideline	037	013	Has this statement factored in the cost of employing NHS staff to arrange and	Thank you for this comment. NHS staff time was included in the health economic analysis. We have now added an additional analysis to account for home visits. 10% of

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	ire Integrated Care Board				administer the B12 injections? (Including travel time and fuel costs for home visits).	patients (same proportion as the included study by Houle 2014) were administered their intramuscular treatment at home (assuming 50 minutes of nurse time). In this analysis, parenteral treatment was cost saving by 12 months for those with vitamin B12 deficiency and by 6 months for those with pernicious anaemia.
243	NHS Surrey Heartlands ICB	Guideline	General	General	Throughout the guideline "over-the-counter" is used to described purchased supplements. This is defined on page 21 "Over-the-counter supplements- Vitamin B12 or multivitamin tablets that contain vitamin B12, obtained without a prescription." Most purchased supplements are truly not "over-the -counter" requiring purchased from a pharmacy with pharmacist supervision. "Purchased supplements" may be a better term to indicate this refers to all purchased micronutrient or dietary supplements, including those purchased online, which is a major route for purchase of dietary supplements.	Thank you for your comment. We have kept the term 'over-the-counter' because this has been used in other NICE guidelines. The definition has been updated to state 'Vitamin B12 supplements, or supplements containing vitamin B12 like multivitamins, that can be obtained without a prescription (for example, in a pharmacy, supermarket or online). These can include vitamin B12 tablets (including sublingual tablets), injections and transdermal patches.'
244	NHS Surrey Heartlands ICB	Guideline	014 - 015	027	**1.5.10** Dietary vitamin b12 deficiency - "ask them about their diet" does not refer what needs to be asked about to identify whether the individuals diet includes good sources of B12, for example meat, milk and dairy	Thank you for your comment. The recommendation has been updated to state 'ask what they eat or drink including any foods or drinks that contain vitamin B12'. The rationale has also been updated in relation to this to state that 'as well as meat, fish and dairy products sources of vitamin B12

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					products, salmon and cod, marmite, nutritional yeast and other yeast extract products, fortified soy products and fortified breakfast cereals. It would be helpful to include these sources of b12 in the guidelines.	include yeast extract and foods fortified with vitamin B12 such as some breakfast cereals.'
245	NHS Surrey Heartlands ICB	Guideline	015	012	**1.5.12** Advise them to pick an oral supplement that contains 1 of the following types of vitamin b12 (4 listed). Some supplements contain more than one form, e.g. methylcobalamin and adenosylcobalamin, so suggest alternative wording of "at least 1 of the following types of vitamin b12"	Thank you for your comment. The recommendation has been updated to state 'at least 1 of the following types of vitamin B12' as suggested.
246	NHS Surrey Heartlands ICB	Guideline	015	012	**1.5.12** This describes if a person is taking or plans to take purchased supplements, then 1.5.13 goes on to recommend consideration of oral vitamin B12 replacement (unclear if this is purchased or prescribed). It would be helpful for the guidance to be clearer when prescriptions should be initiated versus encouraging individuals to purchase supplements.	Thank you for your comment. The terms 'over-the-counter supplements' and 'vitamin B12 replacement' are defined in the section 'Terms used in this guideline'. Over-the-counter supplements are described as supplements 'that can be obtained without a prescription'. Vitamin B12 replacement is described as 'where a deficiency is treated with prescribed doses of the vitamin'.
247	NHSE Getting It Right First Time (GIRFT)	Guideline	General	General	These comments have been compiled by the NHSE Pathology Getting it Right First Time (GIRFT) Clinical team: Dr Martin Myers, Dr Tom Lewis, Dr Marion Wood. A GIRFT led Vitamin B12 Task Force was set	Thank you for your comment and offer of sharing the audit.

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					up to gather data and undertake a National Audit of UK Pathology Laboratories. This was a recent Audit and is currently not published, but we would be happy to share our results.	
248	NHSE Getting It Right First Time (GIRFT)	Guideline	General	General	We found variation in units of measurement. 82% of laboratories use ng/L, 10% use pmol/L and 8% use pg/L. We suggest that all laboratories should use a single Unit of Measurement and that this should be ng/L	Thank you for your comment. The committee provided both measurements for total B12 as they were aware that some laboratories use pmol/L. It is beyond the remit of this guideline to advise laboratories on what unit to use.
249	NHSE Getting It Right First Time (GIRFT)	Guideline	General	General	Patients on Dialysis are at risk of vitamin B12 deficiency. Yet we found that laboratories did not have guidance on this. We suggest that you include a section on patients on dialysis to assess vitamin B12 status	Thank you for your comment. The guideline didn't include a review of dialysis as a risk factor and therefore it was not included as part of the recommendations. Should a person develop a deficiency then they would be covered by the guideline recommendations.
250	NHSE Getting It Right First Time (GIRFT)	Guideline	General	General	GIRFT Pathology found that local guidelines relating to vitamin B12 assessment were not available in most hospitals for 1. pregnant patients on gas and air. 2. Acute patients presenting with symptoms after nitrous oxide abuse. 3. Patients on Dialysis. We would suggest that Pathways are developed for these and we would be able to help support developing these.	Thank you for your comment. Recommendations related to pregnant patients on gas and air were not covered in this guideline as they are covered in MHRA guidance on Nitrous oxide: neurological and haematological toxic effects.

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251	NHSE Getting It Right First Time (GIRFT)	Guideline	General	General	We found that only 62% of laboratories added comments to low TB12 results and most of these were LIMS generated and not patient-focussed. We suggest that laboratories should develop informative interpretive comments based on the new NICE guidelines on deficiency and intermediate levels. GIRFT found that Vitamin B12 is mostly analysed in Clinical Biochemistry Departments. In the past Vitamin B12 was seen as a Haematology test. There is a risk that co-ownership may result in less optimal service. We would suggest that Pathology should ensure that the service is co-delivered to ensure appropriate testing and interpretation.	Thank you for your comment. The committee hope that laboratories will provide informative comments in their reports on test results. How or who deliver the tests is beyond the remit of this guideline.
252	NHSE Getting It Right First Time (GIRFT)	Guideline	005	018 - 020	**Rec 1.1.4 –** This recommendation assumes that the pregnant women who are receiving vitamin B12 replacement have adequate vitamin B12. This cannot be assumed as it depends on the level of deficiency and the type, and amount, of vitamin B12 replacement. We suggest that you add a phrase such as "and the measured total or active B12 is adequate"	Thank you for your comment. Several stakeholders commented on this suggesting that without evidence to support this the statement should not be made. The committee agreed and the recommendation relating to this has been removed from the guideline. Recommendations related to pregnant patients on gas and air are covered by MHRA guidance on Nitrous oxide: neurological and haematological toxic effects.
253	NHSE Getting It Right First	Guideline	009	003 - 007	**Rec 1.3.1** – This recommendation is confusing. Suggest simply say "*Use either total B12 (serum cobalamin) or active B12 (serum holotranscobalamin) as the initial*	Thank you for your comment. The recommendation is written this way to make it clear that this recommendation does not apply during pregnancy or with recreational nitrous oxide use. The following recommendations then advise what

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	Time (GIRFT)				*tests for suspected vitamin B12 deficiency*" as recommendations on pregnancy and breastfeeding, and comments on nitrous oxide use are covered in later recommendations.	should be used for pregnancy and recreational nitrous oxide use.
254	NHSE Getting It Right First Time (GIRFT)	Guideline	009	008 – 009	**Rec 1.3.2 -** Suggest re-word this guideline to "*Use active B12 as the initial test for suspected vitamin B12 deficiency during pregnancy and breastfeeding,* ***especially in women whose diet is primarily plant based***." This recommendation requires greater clarity. Is the recommendation that all pregnant women should have vitamin B12 status assessed early in pregnancy or is the recommendation that all pregnant women with risk factors (see Box 2) should have vitamin B12 status assessed in early pregnancy? An Audit led by NHSE GIRFT showed that very active B12 tests occur in the UK and very few laboratories measure active B12 in their laboratory. 54% of laboratories do provide this service (either locally or by sending it to other laboratories) and 40% send it away (albeit very low numbers). The increased requesting of active B12 put financial pressure on the Pathology laboratories and this needs to be taken into	Thank you for your comment. Active B12 is recommended for everyone during pregnancy regardless of their diet therefore we have not added the text 'especially in women whose diet is primarily plant based'. The recommendation only applies when vitamin B12 deficiency is suspected, we are not suggesting screening should be conducted during pregnancy. Implementing these recommendations will require some reallocation of resources, including investment in pathology services, so that testing can become more widely available. A resource impact report and tool will be published alongside this guideline. The guideline initially provided reference intervals specifically for active B12 during pregnancy. However, following stakeholder comments the committee agreed to update this so that the same reference ranges are recommended whether a person is pregnant or not.

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					account. For Pathology Laboratories to support this recommendation, extra finances would need to be available. We are concerned that lack of finances in Pathology may hinder the support to this guideline. GIRFT has shown that 97% of pathology laboratories do not provide reference intervals during pregnancy. This needs to be addressed with advice that reference intervals for both Total B12 and active B12 should be added to the result.	
255	NHSE Getting It Right First Time (GIRFT)	Guideline	009	010 - 014	**Rec 1.3.3 –** We would suggest that this should be re-worded to emphasise that total B12 should not be used in assessing B12 status in patients using recreational nitrous oxide, especially in acute presentations as the Total B12 is often within the reference interval in these cases. We suggest that total and active B12, plus serum methylmalonic acid and Homocysteine be measured in the assessment of vitamin B12 in patients with recreational nitrous oxide use. However these tests are not available in over 90% of Pathology Laboratories and would need to be sent away; hence the risk that in the acute setting, physicians may	Thank you for your comment. The committee discussed using combinations of tests for diagnosing vitamin B12 deficiency. However, in the absence of clinical and cost effectiveness evidence they recommended serum MMA or plasma homocysteine should be used. Recommendation 1.3.1 does state to use total or active B12 unless recreational nitrous oxide is the suspected cause of deficiency. It is also stated in the rationale that total and active B12 are not suitable tests for people who use nitrous oxide recreationally. This is because the substance inactivates the B12 molecule, so the person's active or total B12 concentrations would appear to be normal even when they have a deficiency.

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					rely on the rapid local total B12 which would be misleading and may alter treatment.	
256	NHSE Getting It Right First Time (GIRFT)	Guideline	009	017 - 019	**Rec 1.3.5 –** Suggest adding "*acute presentation of nitrous oxide recreational use*" to the clinical use case where B12 replacement should not be delayed while waiting for the test results.	Thank you for your comment. The committee has not made recommendations relating to the acute management of vitamin B12 deficiency caused by recreational nitrous oxide use because they agreed this would be handled by the emergency department. In this situation factors other than vitamin B12 deficiency are likely to be considered first and any vitamin B12 replacement would need to be considered within this context. Other guidance such as the Royal College of Emergency Medicine's best practice guidelines on Suspected nitrous oxide toxicity in Emergency Departments and guidance from the National Poisons Information Service covers this aspect of care.
257	NHSE Getting It Right First Time (GIRFT)	Guideline	010	002 - 006	**Rec 1.3.7 –** Suggest adding *"acute presentation after recreational use of nitrous oxide*" to the list where caution is required when interpreting test results.	Thank you for your comment. The recommendation has been updated to relate to testing active or total B12 test results only. Testing related to recreational nitrous oxide use has not been added to this list because the committee recommend using serum MMA or plasma homocysteine for this situation.
258	NHSE Getting It Right First Time (GIRFT)	Guideline	010	009 - 014	**Rec 1.3.8 –** NHSE GIRFT Pathology found significant unwarranted variation of total B12 reference intervals between manufacturers and between laboratories using the same method. This data is readily available from UKNEQAS. For example, our GIRFT Audit found that the	Thank you for your comment. Several stakeholders commented on the thresholds. Some thought they were too low, others thought they were too high and there was also some support that they are about right. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted

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					lower reference interval for adult white males spanned 110 to 250 ng/L between different laboratories; 72% of laboratories claim that the provenance of the reference interval is from the Kit insert and 25% use local reference intervals. In addition there are difference in the bias of different methods that are not reflected by logical changes in reference intervals. This has been published by UKNEQAS. https://www.sciencedirect.com/science/article/pii/S0006497119382795 This unwarranted variation and bias needs to be taken into account when producing guidelines based on single cut-offs. Hence we would suggest a comment like "*In the UK, for all commonly used total B12 assays, a level above 350ng/L makes B12 deficiency unlikely. Levels below 350ng/L will require interpretation according to the performance of the specific assay.*" However we would agree that vitamin B12 deficiency is present with total B12 of less than 180 ng/L and support the recommendation that intermediate results between 180-350 ng/L require further investigation.	that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not. Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests. The committee also recommend considering MMA as a further test for people with an indeterminate active or total B12 test result. This is to capture people who may have a vitamin B12 deficiency when their test result doesn't meet the criteria for deficiency. An indeterminate result covers an active B12 of between 25 and 70 pmol per litre, and a total B12 of between 180 and 350 nanograms (133 and 258 pmol) per litre. The committee has also added a recommendation to use the laboratory's reference ranges to decide if vitamin B12 deficiency is likely when interpreting serum MMA and plasma homocysteine test results. Following stakeholder comments the committee agree that there is no need for a higher threshold during pregnancy or breastfeeding and have removed the recommendation from the guideline.

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					There is also variation in active B12 reference intervals. For example Roche state that their assay has a lower reference interval of 38 pmol/L. Therefore, patients with vitamin B12 deficiency would be missed if active B12 was measured on a Roche platform and 25 pmol/L was used as a threshold to diagnose deficiency. Suggest that cut-offs for specific assays should be used for active B12. We are unclear of the rationale of having a higher threshold of active B12 in people who are pregnant or breastfeeding. Total serum B12 decreases in the third trimester, but no evidence has been given to support using different cut-offs for active B12 in pregnant women.	
259	NHSE Getting It Right First Time (GIRFT)	Guideline	010	015 - 016	**Rec 1.3.9 –** We would suggest that as Manufacturers have provenance in the reference intervals (accepting that there is still variation) local reference intervals are used for homocysteine and that clinical judgement alone should not be used. However homocysteine can be elevated in conditions other than vitamin B12 deficiency.	Thank you for your comment. We have updated this to make it more specific. The recommendation now states 'Use laboratory reference ranges to interpret plasma homocysteine test results when deciding if vitamin B12 deficiency is likely, but take into account additional factors that may increase plasma homocysteine levels (such as folate deficiency).'
260	NHSE Getting It	Guideline	010	018 - 026	**Rec 1.3.10** - We welcome the guidance on recommending that intermediate results in	Thank you for your support of the recommendations for thresholds.

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	Right First Time (GIRFT)				vitamin B12 require further testing. This may overcome the concern that unwarranted variation, difference in reference intervals and bias between laboratories may risk missing vitamin B12 deficiency when relying on a single test with known significant variation in result obtained between laboratories. We would agree that total vitamin B12 results between 180 and 350 ng/L may include patients that are vitamin B12 deficient and would need secondary tests to assess vitamin B12 deficiency. We are unclear what the evidence is for different cut-offs for pregnant and non-pregnant women for active B12. We suggest that the sample type for methylmalonic acid (MMA) is specified as MMA can be measured in both serum and urine. We support the second line test of MMA but an Audit performed by GIRFT showed that very little cascading to MMA is occurring at present in the UK and this recommendation will increase the cost to Pathology laboratories and more laboratories would	Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not. Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests. Following stakeholder comments the committee agree that there is no need for a higher threshold during pregnancy and have removed the recommendation from the guideline. Economic modelling showed that serum MMA is likely to be cost effective for people with a B12 measurement in the indeterminate range. Implementing these recommendations will require some reallocation of resources, including investment in pathology services, so that testing can become more widely available. A resource impact report and tool will be published alongside this guideline.

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					need to offer this test. At present 81% of Pathology Laboratories do not add a cascade test to an abnormal total B12 result from primary care. Very few laboratories offer MMA (either in serum or urine) and finances are not available to pay for the service. We found that 90% of MMA acid requests and 78% of homocysteine are send to a reference laboratory; the cost of these referral tests would be significant as the total cost will be charged, not the direct reagent costs.	
261	NHSE Getting It Right First Time (GIRFT)	Guideline	010 and 011	027 001 005	**Rec 1.3.11** - An audit performed by NHSE GIRFT Pathology indicated that Pathology Laboratories in England do not provide different reference intervals for people from a Black family background. We welcome this guidance from NICE but suggest that this guidance should be firmer. Kit inserts do not include reference intervals for people from a Black family background. Therefore, tentative guidance on cut-offs from NICE would be required.	Thank you for your comment. The findings in the study suggested cut-off for deficiency as 225 ng/L (166 pmol/L). This has been added to the evidence report. However, the committee were aware that this is one study and the result may need to be validated in other populations. Therefore they did not include it in the guideline recommendations.
262	NHSE Getting It Right First Time (GIRFT)	Guideline	011	024 - 028	**Rec 1.3.14** – we would support this guideline.	Thank you for your comment.

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263	NHSE Getting It Right First Time (GIRFT)	Guideline	012	001 - 005	**Rec 1.3.15** – if the person's initial test result suggested that vitamin B12 deficiency was unlikely but still had symptoms, we would recommend repeat testing and MMA within 3 months. However it should be noted that MMA and homocysteine can be elevated in other metabolic conditions and on their own are not diagnostic of Vitamin B12 deficiency.	Thank you for your comment. The recommendation has been updated to advise investigating other causes as well as considering a repeat of the initial test if they are still experiencing symptoms or signs 3 to 6 months later. MMA has been removed because the committee agreed that most laboratories would not allow for an MMA without testing total or active B12 first.
264	NHSE Getting It Right First Time (GIRFT)	Guideline	012	019 - 020	**Rec 1.4.3 -** NHS GIRFT Pathology found that there are methodological issues with Intrinsic factor antibody testing. There are methodological differences in assays in the detection of Type 1 and Type 2 antibodies. We would suggest that laboratories indicate what their test is identifying, adding appropriate comments as necessary. A positive intrinsic factor antibody result would indicate autoimmune mechanisms, but a negative result may miss autoimmunity depending on the method used. Guidance may be needed to recommend which antibodies would need to be picked up in an Intrinsic factor Antibody assay	Thank you for your comment. A recommendation has been added stating 'Laboratories should provide information on what their anti-intrinsic factor antibody assay detects and how to interpret results'.
265	NHSE Getting It Right First	Guideline	014	019 - 023	**Rec 1.5.8 -** We would recommend that further guidance should be given on vitamin B12 replacement for patients presenting	Thank you for your comment. The committee has not made recommendations relating to the acute management of vitamin B12 deficiency caused by recreational nitrous oxide use because they agreed this would be handled by the

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	Time (GIRFT)				acutely to ED departments, where significant neurological risk is present.	emergency department. In this situation factors other than vitamin B12 deficiency are likely to be considered first and any vitamin B12 replacement would need to be considered within this context. Other guidance such as the Royal College of Emergency Medicine's best practice guidelines on Suspected nitrous oxide toxicity in Emergency Departments and guidance from the National Poisons Information Service (https://www.npis.org/) covers this aspect of care.
266	NHSE Getting It Right First Time (GIRFT)	Guideline	017	017 - 018	**Rec 1.6.3** – GIRFT pathology are working with UKNEQAS to identify whether methods used in Pathology Laboratories in the UK can pick up the different analogues of oral Vitamin B12.	Thank you for your comment. Following stakeholder comments the recommendation for repeating the initial test for people on oral vitamin B12 replacement has been removed from the guideline.
267	NHSE Getting It Right First Time (GIRFT)	Guideline	018	019 - 022	**Rec 1.6.8 –** we support this recommendation for the use of MMA in monitoring symptomatic patients with normal vitamin B12. However, we need to raise state that the use of MMA for diagnosing and monitoring will be a cost burden to the Pathology laboratory. We are concerned that the Pathology laboratories would not be able to support this recommendation due to financial pressures.	Thank you for your comment. The committee made the recommendations because they agreed it was important to be sure that the correct diagnosis is obtained. In light of stakeholder comments the committee agreed to update the recommendation so that plasma homocysteine is also an option where serum MMA is not available. The use of MMA testing after an indeterminate total B12 test was shown to be likely to be cost effective. Implementing these recommendations will require some reallocation of resources, including investment in pathology services, so that testing can become more widely available. A resource impact report and tool will be published alongside this guideline.

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268	NHSE Getting It Right First Time (GIRFT)	Guideline	023	004	We would suggest research is required on Nitrous oxide use in labour on patients with plant based diets	Thank you for your comment. The guideline did not include a review on the use of nitrous oxide during pregnancy and therefore no research recommendations have been made relating to this.
269	NHSE Getting It Right First Time (GIRFT)	Guideline	023	004	We suggest that research is required on vitamin B12 status, monitoring and replacement in patients on Dialysis	Thank you for your comment. The guideline did not include a review on patients on dialysis and therefore no research recommendations have been made relating to this.
270	NHSE Getting It Right First Time (GIRFT)	Guideline	023	007	We suggest that the research on diet includes communities with plant based diets to assess vitamin B12 status to identify the scale of vitamin B12 deficiency in these communities	Thank you for your comment. The research recommendations here are written as broad questions giving an indication of what area and interventions are considered for further research. More detail is provided in the appendix of the evidence report linked to just below the research recommendation. Veganism as a risk factor is included as part of the research protocol.
271	NHSE Getting It Right First Time (GIRFT)	Guideline	025	013 - 014	**How the recommendations might affect practice:** We do not agree with the statement that "the recommendations reflect current practice and are therefore unlikely to have a big resource impact". Whilst that may be true primary and secondary care clinical practice, this Guideline and the Recommendations contained therein will have a significant resource impact in Pathology with new diagnostic services required to be set up	Thank you for your comment. This statement relates to the recommendations on providing people with suspected or confirmed vitamin B12 deficiency with information about their condition. The committee agreed that providing information is current practice and therefore there would not be a resource impact. The statement has been updated to make it clear that it is providing information and support that will not lead to a resource impact. The resource impact of testing is mentioned in the rationales related to recommendations that mention tests.

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					and the increased requesting that will occur.	
272	NHSE Getting It Right First Time (GIRFT)	Guideline	026	027 - 031	**Risk factors: -** We agree that people who have a plant based diet are at risk of vitamin B12 deficiency and we would support the call for research into assessing Vitamin B12 status in communities that have a plant based diet.	Thank you for your support for the research recommendation.
273	NHSE Getting It Right First Time (GIRFT)	Guideline	027	020 - 027	**Recreational nitrous oxide use-** we agree that recreational nitrous oxide can cause significant harm to people, and that this harm can occur due to inactivation of vitamin B12. We agree that this is a significant public health issue. We would support more research into this area in order to advise on the classification of this drug based on harm.	Thank you for your comment. The committee did not prioritise this as an area for research. They guideline focuses on how to diagnose and treat vitamin B12 deficiency and does not cover public health aspects.
274	NHSE Getting It Right First Time (GIRFT)	Guideline	031	006 - 016	**How the recommendations might affect practice:** GIRFT Pathology has shown that total B12 is the first line tests for almost all Pathology laboratories and 82% of laboratories do not add on further tests from primary care. Thus, all additional tests will cost money and given that the active vitamin B12 test is more expensive than the total B12 test, then "initial testing using total or active B12" will result in an increase in cost. The recommendations will significantly affect clinical practice and will result in a	Thank you for your comment. We acknowledge that implementing these recommendations will require some reallocation of resources. The committee agreed that while total B12 is cheaper and more commonly available active B12 is likely to be the better test because it measures the form of B12 that can be taken up and used by the body, whereas total B12 measures both active and inactive forms. Serum MMA and plasma homocysteine are only recommended where the committee agreed that total or active B12 would not be suitable.

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					significant increase in pathology testing for Total B12, Active B12, Methylmalonic acid and Homocysteine. This will result in a significant financial impact on pathology and there is a risk that Pathology could not support these recommendations without additional cost. We would not agree that the costs to Pathology would be offset by "*reducing the number of referrals to secondary care and unnecessary investigations*". In practice (and in our experience) Pathology is unlikely to be offered finance to support these recommendations based on potential reduction in costs to other stakeholders in patient care.	A resource impact report and tool will be published alongside this guideline. The committee still assert that some investigations and referrals will be avoided by providing more definitive test results sooner with these tests. The sentence has been updated to read 'However, increased use of serum MMA testing is also likely to lead to faster diagnosis and treatment, which, in some cases, could avoid unnecessary investigations or avoid a referral to secondary care.'
275	NHSE Getting It Right First Time (GIRFT)	Guideline	031	017 - 021	**How the recommendations might affect practice:** Whilst this guideline may result in cost saving compared to routine practice, it is largely based on the introduction of increased, new and expensive Pathology tests. Therefore for success we need to ensure that payment is made available for these tests. GIRFT Pathology would support working with NICE and the Accelerated Access Collaborative to identify how we can implement and adopt the diagnostics to support this guideline. We	Thank you for your comment and offer of support. As you note, implementing these recommendations will require some reallocation of resources, including investment in pathology services, so that testing can become more widely available. Please note that, the committee has updated the recommendation for testing when deficiency is suspected to be caused by recreational nitrous oxide use, either MMA or homocysteine are now recommended.

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					would also support the development of clinical diagnostic and monitoring pathways.	
276	NHSE Getting It Right First Time (GIRFT)	Evidence review C		045	**Units of Measurement:** We suggest that there is a requirement to standardise units of measurement. To quote both ng/L and pmol/L can cause diagnostic confusion. An Audit undertaken by NHSE GIRFT Pathology showed that 81% of laboratories used ng/L and we would recommend that only a single unit of measurement is used, and that should be the one that the majority of laboratories use- ng/L	Thank you for your comment. The committee agreed that standardising units of measurement would be beneficial. However, as different laboratories currently use different units, the committee considered it important to give values using both units of measurement for clarity.
277	NHSE Getting It Right First Time (GIRFT)	Evidence review C		045	GIRFT found significant unwarranted variation of Total B12 between manufacturers and between laboratories using the same method. This data is readily available from UKNEQAS. This bias needs to be taken into account. To take this into account there is a need to safety-net the results. Hence we would suggest a comment like "*In the UK, for all commonly used total B12 assays, a level above 350ng/l makes B12 deficiency unlikely. Levels below 350ng/l will require interpretation according to the performance of the specific assay."* Blood, Volume 132, Supplement 1, 2018, Page 2230	Thank you for your comment. The evidence report has been updated to state 'The committee noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not. In the UK, for all commonly used total B12 assays, a level above 350ng/l makes B12 deficiency unlikely. Levels below 350ng/l will require interpretation depending on the specific assay as mentioned above. Therefore, while the thresholds should be applicable to most tests, some laboratories have their own validated thresholds total B12 which would need to be used instead.

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					Laboratory Performance of Serum B12 Assay in the United Kingdom (UK) As Assessed By the UK National External Quality Assessment Scheme for Haematinics: Implications for Clinical Interpretation Finlay Mackenzie, Vinod Devalia DOI: 10.1182/blood-2018-99-110597. https://www.sciencedirect.com/science/article/pii/S0006497119382795	
278	NHSE Getting It Right First Time (GIRFT)	Evidence Review C		049	We are concerned that the costings used by NICE for total B12 and active B12 are wrong. The Evidence Review quotes a price of £2 for a total B12 assay and £18 for an active B12 assay. Whilst we accept the relative costs (active B12 is significantly more expensive that total B12) the costs would appear to be direct reagent costs only. The cost of a test is more than the reagent costs. This is a concern as, based on these assumed low costs, other conclusions about the cost of implementing NICE guideline significantly underestimates the cost of following the NICE recommendations.	Thank you for your comment. The unit costs were obtained by committee members from their Trusts. They have described these as the full cost, not just the reagent cost.
279	NHSE Getting It Right First	Evidence review C		050	**Resource impact:** We are concerned with the comments on Resource implication. The cost of introducing this guideline is	Thank you for this comment. The committee agreed that while total B12 is cheaper and more commonly available active B12 is likely to be the better test because it measures

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	Time (GIRFT)				significant. If clinicians followed this NICE guidance, there will be a significant increase in Total B12, Active B12, MMA and homocysteine measurements. Most laboratories in England do not measure Active B12, MMA and Homocysteine. A GIRFT Audit showed that the testing volume for active B12 is very low at present. Most laboratories do not offer active B12 testing. 54% of laboratories do not offer Active B12 locally and 41% send the sample away for analysis if thought that the test is required; for MMA 90% of laboratories send the sample away for analysis; for homocysteine 78% of laboratories send the sample away for analysis. When a laboratory sends samples away, the cost per test is not the direct reagent costs; the costs includes to full cost. Thus if laboratories followed this NICE Guideline, the cost to the Pathology service will be significant. We are concerned that this will result in laboratories not being able to support this Guidance. I would suggest that NICE discuss this with NHSE GIRFT to ensure that cost pressures will not lead to laboratories not providing a service to support this NICE Guideline.	the form of B12 that can be taken up and used by the body, whereas total B12 measures both active and inactive forms. Serum MMA and plasma homocysteine are only recommended where the committee agreed that total or active B12 would not be suitable. The costs of testing include staff time in addition to reagent cost. However, we note that significant investment will be required. Our implementation team are discussing this with NHS England.

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280	NHSE Getting It Right First Time (GIRFT)	Evidence review C		General	Methylmalonic Acid can be measured in both serum and urine. To avoid ambiguity we suggest that NICE specify which matrix they are referring to in both the Evidence and the guidance.	Thank you for your comment. We have now specified the matrix as you have requested. With regard to the guidance, it is serum MMA that we are recommending, not urine MMA.
281	NICE GP panel	Guideline	General	General	This is a topic of very great importance to primary care. We received 20 responses to this invitation despite the timing during the peak of the summer holiday period. This is more than double the average response rate. We have also incorporated views (in the general comments) expressed during the previous consultation in 2020 that are more relevant to the draft guidance than to scoping. In total, therefore, this response represents the views of 27 different GPs on the NICE GP panel.	Thank you for organising and collating the responses.
282	NICE GP panel	Guideline	General	General	Some respondents felt that the guidance was very helpful. In particular, they liked the clear thresholds for diagnostic tests, clarification on oral as well as IM treatment, and the standards on follow up and monitoring.	Thank you for letting us know where people agreed with recommendations.
283	NICE GP panel	Guideline	General	General	…However, this was a minority view, and very many concerns were raised. Recurrent themes centred around: 1) the recommendations to test people with vague symptoms, and common mental health problems,	Thank you for your comment. We have responded to each of those where they are raised as separate comments. A brief summary to your points here is: 1. Mental health problems have been removed from the symptoms and signs box and age over 65 removed from the risk factors box. This also means there is no

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					2) the massive workload implications, including capacity issues, and cost in time and money to GP practices and the wider NHS as a result of screening a very large population cohort, overdiagnosis and false positive tests 3) the exclusion of co-existent folate abnormalities 4) the inclusion of tests that are unavailable in primary care 5) the need for precise guidance on monitoring B12 levels where patients are on medications that increase risk of deficiency. All of these major themes were highlighted by the GP panel during the scoping process.	longer a statement explicitly recommending testing in these groups. 2. The above 2 edits should greatly reduce the resource impact. 3. Investigating and managing complications related to vitamin B12 deficiency and cofactors were not included as part of the scope of the guideline. Therefore they were not included as part of the guideline reviews and no recommendations have been made related to this. The committee agreed that everyone will still test folate and vitamin B12 together despite there being no mention of folate in this guideline. It is also anticipated that Clinical Knowledge Summaries (CKS) will use this guideline to update their topic on 'Anaemia – B12 and folate deficiency' following publication of this guideline. Therefore it is likely to address co-existent folate abnormalities. 4. The committee agreed that most of the tests are available to primary care and where they aren't we have added that specialist input would be needed or that the person would need to go to phlebotomy in secondary care. We have provided more detail on your specific responses to this issue. 5. Unfortunately, no evidence was identified and the committee were unable to provide precise guidance on monitoring levels where people are on medications that increase the risk of vitamin B12 deficiency. The committee recommend that vitamin

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						B12 replacement is continued while the person is still taking the medicine and that this is reviewed if the person stops taking the medicine. They also recommend that symptoms are used to assess the need to adjust or change treatment. Because of the lack of evidence the committee made a research recommendation in this area.
284	NICE GP panel	Guideline	General	General	Three Quotes covering some of the themes in Row 3: "GPs will really struggle to manage this guidance-we will now be expected to send B12 levels [and not just screen with FBC] on patients with fatigue/anxiety/depression and over 65/on a PPI etc, this will be a huge proportion of the patients we see, many will have indeterminate results and end up on lifelong treatment, often this will be im B12. B12 injections are a big consumer of practice and district nursing appointments-have you looked at this?" "Deary me, it really is a poor guideline, it doesn't help primary care and just adds a complexity to a previously easy to manage condition with really little evidence." "Excessively detailed guidance for something that in its true form (autoimmune malabsorption) is rare."	Thank you for your comment. The committee were restricted in what they could recommend because of the lack of high-quality evidence. They only made recommendations where they agreed it would benefit people with suspected or confirmed vitamin B12 deficiency and it was likely to be cost-effective. The guideline recommendations have been updated in relation to symptoms, signs and risk factors. Mental health problems have been removed from the symptoms and signs box and age over 65 removed from the risk factors box. This also means there is no longer a statement explicitly recommending testing in these groups. This also means testing in these groups is not explicitly recommended. Intramuscular injections have only been recommended where they are thought to be necessary. The committee agreed that where recommended this does not represent a change in practice. The guideline has been updated in the hope of making recommendations clearer.

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285	NICE GP panel	Guideline	General	General	Please add a flow diagram to aid decision making and care pathways in primary care. The diagram should include assessment, investigations, and management based on the presentation and test results.	Thank you for your comment. A visual summary has been added for the ongoing care and follow up recommendations.
286	NICE GP panel	Guideline	General	General	Folate: The assessment and management of folate deficiency is intertwined in investigation and treatment. B12/ folate requests are commonly inseparable laboratory tests, and the management of the deficiencies should not be undertaken in isolation.	Thank you for your comment. Investigating and managing complications related to vitamin B12 deficiency and cofactors were not included as part of the scope of the guideline. Therefore they were not included as part of the guideline reviews and no recommendations have been made related to this. The committee agreed that everyone will still test folate and vitamin B12 together despite there being no mention of folate in this guideline. It is also anticipated that Clinical Knowledge Summaries (CKS) will use this guideline to update their topic on 'Anaemia – B12 and folate deficiency' following publication of this guideline. Therefore it is likely to address co-existent folate abnormalities.
287	NICE GP panel	Guideline	004	020	1.1.2 This is often an asymptomatic biochemical finding. Please reflect this in this recommendation.	Thank you for your comment. The committee agreed that this recommendation is for people suspected of vitamin B12 deficiency and therefore most people will probably have symptoms. They did not think this was an important factor to highlight in the recommendations.
288	NICE GP panel	Guideline	005	007	1.1.3 Please include the recognition that some will be asymptomatic	Thank you for your comment. The committee agreed to focus on key points in this section and how it might affect symptoms and the person's daily activities rather than provide a detailed description of vitamin B12 deficiency.
289	NICE GP panel	Guideline	005	014	1.1.3 contradicts line 16 – lifelong treatment	Thank you for your comment. The committee are not sure what the contradiction is. The first of the 2 bullet points to which you refer is to stress the importance of continuing with

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						any treatment or advice that has been offered to ensure symptoms do not return. The treatment could be oral or intramuscular vitamin B12 replacement and is offered regardless of the duration of treatment. This has been updated to state 'it is important to continue treatment as advised so that symptoms do not return or get worse'. The second point is to emphasise that some forms of vitamin B12 deficiency will need lifelong vitamin B12 replacement.
290	NICE GP panel	Guideline	005	016	1.1.3 Please add a) malabsorption syndromes (e.g. coeliac disease) and b) 'certain long-term medications' to 'autoimmune gastritis'.	Thank you for your comment. The recommendation has been updated to change 'lifelong treatment' to 'lifelong vitamin B12 replacement' to make it clear the committee are not talking about treatment of other conditions. The committee agreed that they wanted to emphasise autoimmune gastritis only in this point as an example of someone who is likely to need lifelong vitamin B12 replacement. They agreed that if the coeliac disease is adequately treated then the person will not need lifelong vitamin B12 replacement. Similarly, if the medicine is stopped then the person may not need vitamin B12 replacement.
291	NICE GP panel	Guideline	005	018	1.1.4 Thank you. This is useful information	Thank you for your support for the recommendation. However, several stakeholders commented on this suggesting that without evidence to support this the statement should not be made. The committee agreed and the recommendation relating to this has been removed from the guideline.

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						Recommendations related to pregnant patients on gas and air are covered by MHRA guidance on Nitrous oxide: neurological and haematological toxic effects.
292	NICE GP panel	Guideline	006	003	1.2.1 We see huge numbers of people with fatigue and mental health problems with at least one risk factor (some of which are also very common), but the likelihood of their symptoms being due to true B12 deficiency is low NB false positives will be much higher in such low prevalence populations.	Thank you for your comment. Following stakeholder comments mental health problems have been removed from the symptoms and signs box, and age over 65 removed from the risk factors box. This also means there is no longer a statement explicitly recommending testing in these groups. The committee agreed that unexplained fatigue is an important symptom in vitamin B12 deficiency and that this in combination with the risk factors did warrant people being tested for a vitamin B12 deficiency. They agreed that now that age has been removed as a risk factor this would greatly reduce the number of people being tested. The committee agreed that while there is little or no evidence for all of the other entries in the boxes they are commonly accepted as likely symptoms, signs and risk factors for vitamin B12 deficiency. The committee has been careful to only offer a test if the person has at least 1 symptom or sign and 1 risk factor.
293	NICE GP panel	Guideline	006	003	1.2.1 A systematic review (quoted in NICE CKS) found that mental health conditions are the most likely cause of fatigue, serious underlying conditions were rare and that 'excessive diagnostic testing will lead to considerable false-positive results that	Thank you for your comment. Following stakeholder comments mental health problems have been removed from the symptoms and signs box, and age over 65 removed from

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					rarely help to detect serious underlying disease if fatigue occurs as an isolated symptom.' https://bmcprimcare.biomedcentral.com/articles/10.1186/s12875-016-0545-5	the risk factors box. This also means there is no longer a statement explicitly recommending testing in these groups. The committee agreed that unexplained fatigue is an important symptom in vitamin B12 deficiency and that this in combination with the risk factors did warrant people being tested for a vitamin B12 deficiency. They agreed that now that age has been removed as a risk factor this would greatly reduce the number of people being tested. The committee agreed that while there is little or no evidence for all of the other entries in the boxes they are commonly accepted as likely symptoms, signs and risk factors for vitamin B12 deficiency. The committee has been careful to only offer a test if the person has at least 1 symptom or sign and 1 risk factor. Thank you for the citation. We checked the cited study for inclusion in our review. The study did not meet the inclusion criteria due to not specifically focussing on vitamin B12 deficiency as a cause of symptoms, so has not been included in the guideline.
294	NICE GP panel	Guideline	006	003	1.2.1 As there is little/no evidence base for these recommendations, we do not feel that you can usually justify the recommendation to 'OFFER' tests and should reword, where testing is reasonable, the recommendation to 'CONSIDER'	Thank you for your comment. Following stakeholder comments mental health problems have been removed from the symptoms and signs box, and age over 65 removed from

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						the risk factors box. This also means there is no longer a statement explicitly recommending testing in these groups. The committee agreed that unexplained fatigue is an important symptom in vitamin B12 deficiency and that this in combination with the risk factors did warrant people being tested for a vitamin B12 deficiency. They agreed that now that age has been removed as a risk factor this would greatly reduce the number of people being tested. The committee agreed that while there is little or no evidence for all of the other entries in the boxes they are commonly accepted as likely symptoms, signs and risk factors for vitamin B12 deficiency. The committee has been careful to only offer a test if the person has at least 1 symptom or sign and 1 risk factor.
295	NICE GP panel	Guideline	006	003	1.2.1 Please clarify when we should be looking for other (more likely) causes of non-specific presentations first before considering B12 testing.	Thank you for your comment. The guideline has not reviewed the evidence for when to look for other conditions for non-specific presentations and therefore has not made recommendations for this.
296	NICE GP panel	Guideline	006	011	1.2.3 The panel were sceptical about this assertion (which lacks evidence?)	Thank you for your comment. The committee agreed that there is a common misconception that you cannot have a deficiency without either, or both, of anaemia or macrocytosis being present. This is also supported by other stakeholder comments.
297	NICE GP panel	Guideline	006 – 8	001 - 002	1.2 general: We have very great concerns about the recommendations of who to test for B12 deficiency (see Row 3 above). Not only does this have workload implications	Thank you for your comment. Following stakeholder comments mental health problems have been removed from the symptoms and signs box, and age over 65 removed from

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					for primary care which do not appear to have been fully realised (despite the statement that that this 'could lead to more testing and treatment') It will result in a significant increase in B12 requests with resource implications for phlebotomy, lab capacity, nursing capacity for investigation and treatment, and GP/ nurse practitioner capacity to check results and start treatment.	the risk factors box. This also means there is no longer a statement explicitly recommending testing in these groups. The committee agreed that unexplained fatigue is an important symptom in vitamin B12 deficiency and that this in combination with the risk factors did warrant people being tested for a vitamin B12 deficiency. They agreed that now that age has been removed as a risk factor this would greatly reduce the number of people being tested. The committee agreed that while there is little or no evidence for all of the other entries in the boxes they are commonly accepted as likely symptoms, signs and risk factors for vitamin B12 deficiency. The committee has been careful to only offer a test if the person has at least 1 symptom or sign and 1 risk factor. With these changes to the recommendations, the committee think that there should no longer be such a large impact on general practice workload.
298	NICE GP panel	Guideline	007	001	1.2.5 Box 1: Please provide evidence and the biochemistry behind this recommendation or omit. Estimates of the prevalence of common mental health problems varied from 40% (from QoF depression +ONS anxiety – a likely underestimate) to 100% (a likely overestimate). Fatigue was considered equally unsuitable for inclusion as it is a very common and ill-defined symptom.	Thank you for your comment. Following stakeholder comments mental health problems have been removed from the symptoms and signs box, and age over 65 removed from the risk factors box. This also means there is no longer a statement explicitly recommending testing in these groups. The committee agreed that unexplained fatigue is an important symptom in vitamin B12 deficiency and that this in combination with the risk factors did warrant people being tested for a vitamin B12 deficiency. They agreed that now

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						that age has been removed as a risk factor this would greatly reduce the number of people being tested. The committee agreed that while there is little or no evidence for all of the other entries in the boxes they are commonly accepted as likely symptoms, signs and risk factors for vitamin B12 deficiency. The committee has been careful to only offer a test if the person has at least 1 symptom or sign and 1 risk factor.
299	NICE GP panel	Guideline	007	001	1.2.5: Box 1 Overall we felt that the symptom list in this Box was helpful, especially: The inclusion of optic neuropathy, peripheral neuropathy, glossitis and macrocytosis. Paraesthesia or dysthesia should be higher up the list of symptoms in box1 But echoing the thoughts in Row 18 a quote from one respondent: "This statement starts off well (anaemia, macrocytosis, eyesight) but descends into sublime farce!"	Thank you for your comment. Following stakeholder comments mental health problems have been removed from the symptoms and signs box, and age over 65 removed from the risk factors box. This also means there is no longer a statement explicitly recommending testing in these groups. The committee agreed that unexplained fatigue is an important symptom in vitamin B12 deficiency and that this in combination with the risk factors did warrant people being tested for a vitamin B12 deficiency. They agreed that now that age has been removed as a risk factor this would greatly reduce the number of people being tested. The committee agreed that while there is little or no evidence for all of the other entries in the boxes they are commonly accepted as likely symptoms, signs and risk factors for vitamin B12 deficiency. The committee has been careful to only offer a test if the person has at least 1 symptom or sign and 1 risk factor.

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300	NICE GP panel	Guideline	007	006	1.2.7 Is oral (rather than IM) B12 actually advocated after gastrectomy?	Thank you for your comment. The treatment recommendations are covered in section 1.5 on managing vitamin B12 deficiency. The committee agreed there was no evidence to suggest oral treatment would not work in this group. However following stakeholder comments the recommendation has been updated to state 'Consider intramuscular instead of oral vitamin B12 replacement'.
301	NICE GP panel	Guideline	007	006	1.27 Suggest link to BOMSS guidance on pre-and post-bariatric surgery B12 monitoring	Thank you for your comment. NICE guidelines do not generally link to other organisation guidelines or websites because these may change and NICE has no control over the content. The section on 'Information for the public' on this guideline's web page also provides links to other organisations' websites which provide more detailed advice directly written for people with suspected or confirmed vitamin B12 deficiency. This recommendation is just to highlight that certain types of bariatric surgery could be the likely cause of vitamin B12 deficiency in these patients.
302	NICE GP panel	Guideline	008	001	1.2.7 Box 2 We agree with the addition of age, diet and atrophic gastritis. Box 2 is clear and helpful	Thank you for your comment. Following stakeholder comments age as a risk factor has been removed from the box. This is because age combined with a symptom and sign would lead to a huge resource impact without evidence to demonstrate it would identify a significant number of people with vitamin B12 deficiency.

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303	NICE GP panel	Guideline	008	001	The list of medicines are very common in primary care and deficiency may be asymptomatic. Please clarify if active monitoring is suggested. Should >1 risk factor e.g. age >65 lead to annual testing?	Thank you for your comment. Screening for vitamin B12 deficiency in people with a risk factor was out of scope of the guideline. Following stakeholder comments age as a risk factor has been removed from the box. This is because age combined with a symptom and sign would lead to a huge resource impact without evidence to demonstrate it would identify a significant number of people with vitamin B12 deficiency.
304	NICE GP panel	Guideline	008	001	1.2.7: box 2 Please define the risk more precisely to support decision-making and monitoring – are these common or rare and over what time do the side-effects appear?	Thank you for your comment. Due to the lack of evidence the committee was unable to make more definitive statements in this area such as when side effects appear. The intention of the risk factors box is to highlight when to suspect a deficiency and to test if they occur in combination with a symptom or sign.
305	NICE GP panel	Guideline	008	001	1.2.7: box 2 Comments on specific medications: Colchicine is rarely used long-term (and the BNF does not list B12 deficiency as a side-effect) Pregabalin is most commonly used as a pain modifier	Thank you for your comment. The committee used their expertise and experience to make consensus recommendations. They were aware of evidence that colchicine and antiseizure medicines including pregabalin reduce the level of circulating vitamin B12. This evidence did not meet inclusion criteria for the evidence review as it is unclear whether the reduction in circulating vitamin B12 is reflective of true vitamin B12 deficiency. However, the committee agreed that awareness should still be raised.
306	NICE GP panel	Guideline	008	001	1.2.7: box 2 With regards to dietary causes of B12 deficiency, it would be helpful to list the foods containing B12 directly in that section. At a glance, it can be seen if a better diet is acceptable or which foods	Thank you for your comment. More detail has been added to the rationale for the recommendations on managing dietary vitamin B12 deficiency. There is also a link to an NHS web page from recommendation 1.5.14 that lists sources of food that are high in vitamin B12.

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					patients are missing. The food link is excellent, but long.	
307	NICE GP panel	Guideline	009	001	1.3 It would be more helpful to have guidance on when NOT to test for B12, given how commonly it is slightly under the reference range even though the patient is entirely well.	Thank you for your comment. We did not do a review on when not to test and therefore have not made recommendations in this area.
308	NICE GP panel	Guideline	009	001	1.3 We have previously said that BHS guidance and NICE CKS recommendations are too complex and rely on tests unavailable in primary care. There were many concerns expressed that NICE has also adopted this approach. Widespread availability in primary care: FBC, B12/folate; unknown availability (most GPs?): intrinsic factor and parietal cell antibodies; little or no availability: active B12, homocysteine, MMA.	Thank you for your comment. The committee thought carefully before making the recommendations. The committee agreed that using active B12 would not require a change in practice for GP surgeries because it can be carried out on the same serum sample as for total B12. They agreed that in their experience, active B12 is a more accurate test than total B12. However, they recommended either total or active B12 to reflect the lack of evidence demonstrating this and the lack of availability of active B12 at all laboratories. For homocysteine the committee has updated the recommendation to make it clear that if this is the chosen test then the person will need to be referred to hospital for testing. The committee has also updated the recommendations so that MMA is an option as well as homocysteine for nitrous oxide induced vitamin B12 deficiency. They made the change after agreeing with stakeholder comments that MMA is also a suitable test for these people. However, the

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						committee still agree that neither total nor active B12 are suitable tests for this cause because nitrous oxide inactivates the B12 molecule, so the person's active or total B12 concentrations would appear to be normal even when they have a deficiency. Economic modelling showed that MMA is likely to be cost effective for people with a B12 measurement in the indeterminate range. Implementing these recommendations will require some reallocation of resources, including investment in pathology services, so that testing can become more widely available. A resource impact report and tool will be published alongside this guideline.
309	NICE GP panel	Guideline	009	008	1.3.2 GPs have no control over B12 laboratory assessment and active B12 is not routinely available to most GPs	Thank you for your comment. The committee thought carefully before making the recommendations and took cost effectiveness into account. Both active and total B12 are options as tests. Active B12 is recommended over total B12 during pregnancy because the committee agreed that it is a more reliable test. Total B12 concentrations in the body fall during pregnancy even when there is no deficiency. Implementing these recommendations will require some reallocation of resources, including investment in pathology services, so that testing can become more widely available.

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						A resource impact report and tool will be published alongside this guideline.
310	NICE GP panel	Guideline	009	010	1.3.3 We would have thought it's more helpful to advise them to stop using nitrous oxide, than getting them a blood test for homocysteine!	Thank you for your comment. The committee also recommend advising the person to stop using nitrous oxide recreationally as part of the recommendations on management of vitamin B12 deficiency.
311	NICE GP panel	Guideline	010	006	1.3.7 Please be specific e.g oral contraception can falsely lower B12	Thank you for your comment. We have updated this recommendation to advise caution when interpreting the active or total B12 test results of people who are taking the combined oral contraceptive pill because this can lower total B12 concentrations without causing a deficiency (however, low total B12 concentrations may still mean the person has a deficiency).
312	NICE GP panel	Guideline	010	009	1.3.8 We note your comments on the thresholds (which are quite high) and may lead to a risk of false positives but that 'treatment is not expensive'. Oral treatment may not be expensive but the extra work for assessing, testing and following up for GPs and nurses/HCAs is costly (with significant opportunity costs). The committee does not seem to have fully appreciated or factored in the workload costs this guideline will generate in primary care.	Thank you for your comment. Several stakeholders commented on the thresholds. Some thought they were too low, others thought they were too high and there was also some support that they are about right. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not. Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests.

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						The committee also recommend considering MMA as a further test for people with an indeterminate active or total B12 test result. This is to capture people who may have a vitamin B12 deficiency when their test result doesn't meet the criteria for deficiency. An indeterminate result covers an active B12 of between 25 and 70 pmol per litre, and a total B12 of between 180 and 350 nanograms (133 and 258 pmol) per litre. The committee has also added a recommendation to use the laboratory's reference ranges to decide if vitamin B12 deficiency is likely when interpreting serum MMA and plasma homocysteine test results. The committee have considered primary care workload. In particular, they have recommended more accurate tests so that vitamin B12 deficiency can be detected more effectively and hence reducing the need for further appointments and investigations.
313	NICE GP panel	Guideline	010	009	1.3.8 2.5% of normal people will fall below the lower test distribution line of any test.	Thank you for your comment. Several stakeholders commented on the thresholds. Some thought they were too low, others thought they were too high and there was also some support that they are about right. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not.

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						Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests. The committee also recommend considering MMA as a further test for people with an indeterminate active or total B12 test result. This is to capture people who may have a vitamin B12 deficiency when their test result doesn't meet the criteria for deficiency. An indeterminate result covers an active B12 of between 25 and 70 pmol per litre, and a total B12 of between 180 and 350 nanograms (133 and 258 pmol) per litre. The committee has also added a recommendation to use the laboratory's reference ranges to decide if vitamin B12 deficiency is likely when interpreting serum MMA and plasma homocysteine test results. Thank you for your comment. Following stakeholder comments mental health problems have been removed from the symptoms and signs box, and age over 65 removed from the risk factors box. This also means there is no longer a statement explicitly recommending testing in these groups. The committee agreed that unexplained fatigue is an important symptom in vitamin B12 deficiency and that this in combination with the risk factors did warrant people being tested for a vitamin B12 deficiency. They agreed that now

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						that age has been removed as a risk factor this would greatly reduce the number of people being tested. The committee agreed that while there is little or no evidence for all of the other entries in the boxes they are commonly accepted as likely symptoms, signs and risk factors for vitamin B12 deficiency. The committee has been careful to only offer a test if the person has at least 1 symptom or sign and 1 risk factor.
314	NICE GP panel	Guideline	010	009	1.3.8 A quote "The 'indeterminate range' you quote as 180-350 ng/L [section 1.3.10] would include most of the B12 results we get back from our lab, our indeterminate range is 150-200 ng/l."	Thank you for your comment. Several stakeholders commented on the thresholds. Some thought they were too low, others thought they were too high and there was also some support that they are about right. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not. Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests. The committee also recommend considering MMA as a further test for people with an indeterminate active or total B12 test result. This is to capture people who may have a vitamin B12 deficiency when their test result doesn't meet

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						the criteria for deficiency. An indeterminate result covers an active B12 of between 25 and 70 pmol per litre, and a total B12 of between 180 and 350 nanograms (133 and 258 pmol) per litre. The committee has also added a recommendation to use the laboratory's reference ranges to decide if vitamin B12 deficiency is likely when interpreting serum MMA and plasma homocysteine test results. Thank you for your comment. Following stakeholder comments mental health problems have been removed from the symptoms and signs box, and age over 65 removed from the risk factors box. This also means there is no longer a statement explicitly recommending testing in these groups. The committee agreed that unexplained fatigue is an important symptom in vitamin B12 deficiency and that this in combination with the risk factors did warrant people being tested for a vitamin B12 deficiency. They agreed that now that age has been removed as a risk factor this would greatly reduce the number of people being tested. The committee agreed that while there is little or no evidence for all of the other entries in the boxes they are commonly accepted as likely symptoms, signs and risk factors for vitamin B12 deficiency. The committee has been careful to only offer a test if the person has at least 1 symptom or sign and 1 risk factor.

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315	NICE GP panel	Guideline	010	009	1.3.8 A couple of respondents commented that expert advice confirms that B12 assays vary around the country, so a one size fits all management strategy based on a single test appears unwise.	Thank you for your comment. Several stakeholders commented on the thresholds. Some thought they were too low, others thought they were too high and there was also some support that they are about right. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not. Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests. The committee also recommend considering MMA as a further test for people with an indeterminate active or total B12 test result. This is to capture people who may have a vitamin B12 deficiency when their test result doesn't meet the criteria for deficiency. An indeterminate result covers an active B12 of between 25 and 70 pmol per litre, and a total B12 of between 180 and 350 nanograms (133 and 258 pmol) per litre. The committee has also added a recommendation to use the laboratory's reference ranges to decide if vitamin B12 deficiency is likely when interpreting serum MMA and plasma homocysteine test results.

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316	NICE GP panel	Guideline	010	015	1.3.9 Please be more specific about the association between B12 and homocysteine. A quote from one respondent: 'use clinical judgment to determine what reference range to use' What on earth?!	Thank you for your comment. We have updated this to make it more specific. The recommendation now states 'Use laboratory reference ranges to interpret plasma homocysteine test results when deciding if vitamin B12 deficiency is likely, but take into account additional factors that may increase plasma homocysteine levels (such as folate deficiency).'
317	NICE GP panel	Guideline	010	018	1.3.10 There was very significant disquiet that this recommendation would drive investigation into secondary care (99% currently managed in GP) with consequent resource implications. MMA is not directly available to GPs – retest B12 instead?	Thank you for your comment. Economic modelling showed that serum MMA is likely to be cost effective for people with a B12 measurement in the indeterminate range. Implementing these recommendations will require some reallocation of resources, including investment in pathology services, so that testing can become more widely available in primary care. A resource impact report and tool will be published alongside this guideline.
318	NICE GP panel	Guideline	011	020	1.3.13 There appears to be reluctance in the guideline to agree that some people do not have B12 deficiency and do not need retesting. Is this intentional? Alternative or no diagnoses should be considered.	Thank you for your comment. This recommendation applies to people who had a total or active B12 test as part of routine testing rather than they were suspected of having a deficiency. In this case the committee agreed that because the test result was indeterminate it was not possible to say categorically that the person doesn't have a deficiency. The recommendation has been updated removing reference to repeat testing and advising people to seek medical help if they develop symptoms or signs of deficiency. Investigating alternative diagnoses has not been included for this recommendation because it applies to people with no symptoms or signs of vitamin B12 deficiency.

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319	NICE GP panel	Guideline	012	007	1.4.1 low B12 levels are common and autoimmune gastritis is rare – please provide information on when we should we suspect it. Can the need be determined by the results of initial tests?	Thank you for your comment. The committee agreed that unfortunately this is a difficult area to be more specific and the healthcare professional will need to use their clinical judgement.
320	NICE GP panel	Guideline	012	019	1.4.3 – we suggest that a hierarchy of testing is included to reflect the ability (in some areas) to investigate in primary care before referral.	Thank you for your comment. The committee agree that most of these tests can be ordered in primary care. There may be some variation in availability of tests which is why the committee have not tried to give a hierarchy. However, in the absence of evidence the committee wanted to make it clear that there are further investigations available for consideration to help aid diagnosis. The main exception is for gastroscopy where the recommendation has been updated to make it clear this will need to be carried out by a specialist. The section on 'How recommendations might affect practice' has been updated to make it clear that these investigations are used in some cases depending on the availability of tests. However, the recommendation may raise awareness of these tests and lead to more tests being ordered.
321	NICE GP panel	Guideline	013	001	1.4.3– please add a brief description of the CobaSorb test to aid appropriate referral	Thank you for your comment. The bullet points in the recommendation have been updated to state 'a CobaSorb test to measure whether vitamin B12 can be absorbed'.
322	NICE GP panel	Guideline	013	003	1.4.4 Include in initial testing? Repeated reviews and stepwise investigation are heavy on clinical costs	Thank you for your comment. The cross reference comes here because the person needs a confirmed vitamin B12 deficiency before being tested for Coeliac disease. The

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						recommendation in the Coeliac disease guideline is for 'unexplained vitamin B12 deficiency' therefore the committee agreed it would probably need to come after other tests have been conducted.
323	NICE GP panel	Guideline	013	007	1.5 Please clarify the dose of oral B12 – the current recommendations are confusing and the BNF treatment range is wide	Thank you for your comment. A recommendation has been added when oral replacement is offered to people with vitamin B12 deficiency caused, or suspected to be caused, by malabsorption which advises prescribing a dosage of at least 1 mg a day. This is because evidence that compared oral vitamin B12 replacement with intramuscular injections used a dosage of 1 mg a day. The committee agreed that usual practice is to offer intramuscular injections and without evidence that lower doses of oral vitamin B12 replacement are effective it was important to specify the dose used in the available evidence. However, for other causes of vitamin B12 deficiency the expectation is that the committee follow the BNF.
324	NICE GP panel	Guideline	013	007	1.5 During the COVID-19 pandemic some patients were successfully and sustainably changed to oral therapy. We agree with the option for oral treatment in most of the subsections to 1.5 as lifelong injections have significant implications and compliance issues but please summarise the evidence to aid decision-making conversations.	Thank you for your comment. Unfortunately, there isn't any evidence other than from studies that were based on blood test results and made little reference to quality of life or other patient-reported outcomes, such as an improvement in symptoms. Therefore, the committee made the recommendations based on their experience and expertise. This is explained in the rationale.
325	NICE GP panel	Guideline	013	007	1.5 Please produce recommendations for patients who maintain that early	Thank you for your comment. The guideline does not go into the detail of when to start treatment as the committee have

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					administration of B12 injections are necessary for symptomatic control, despite biochemical evidence of adequate treatment. This is a significant issue in primary care, and further adds to the workload associated with IM injections.	assumed as soon as a diagnosis is made treatment will be offered based on the recommendations in the guideline. While the committee agree oral vitamin B12 replacement may be as effective as intramuscular vitamin B12 replacement for some cases there wasn't the evidence to state this.
326	NICE GP panel	Guideline	013	007	1.5 Should treatment (long term/ loading doses etc) be stratified according to the severity of deficiency as well as the cause	Thank you for your comment. NICE does not generally include dosages in recommendations where they are available in the BNF or SPC. A dosage may be included if this information is not available, or the committee agrees that there needs to be a change to current recommended dosages, for example because of new evidence. Loading doses are covered in the BNF and therefore loading doses and stratification of treatment by severity were not considered as part of the guideline review therefore no recommendations have been made relating to this.
327	NICE GP panel	Guideline	013	007	1.5 Please provide information on whether older adults should take supplements despite normal B12 levels to reduce their risk of dementia. A couple of respondents independently reported that this has been advocated by 'expert' lecturers.	Thank you for your comment. Prevention of vitamin B12 deficiency was excluded as part of the guideline.
328	NICE GP panel	Guideline	013	014	1.5.3 Please clarify how to manage people with B12 deficiency who are high risk for autoimmune gastritis but in whom further tests are normal	Thank you for your comment. The committee agreed that the recommendation offering intramuscular injections if autoimmune gastritis is the suspected cause (as well as the cause) of vitamin B12 deficiency will capture some people at high risk of autoimmune gastritis. This reflects that a positive test result for anti-intrinsic factor antibody test is good for

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						identifying autoimmune gastritis, however a negative test result is not good at ruling people out. However, if the person has a confirmed deficiency and the cause is unknown then the committee recommend that intramuscular injections are considered over oral vitamin B12 replacement. Therefore anyone with a confirmed deficiency will be treated. The guideline review did not look at treatment for people at risk of autoimmune gastritis without a confirmed deficiency.
329	NICE GP panel	Guideline	013	014	1.5.3 Please clarify replacement regimens and if initial loading doses are required	Thank you for your comment. NICE does not generally include dosages in recommendations where they are available in the BNF or SPC. A dosage may be included if this information is not available, or the committee agrees that there needs to be a change to current recommended dosages, for example because of new evidence. Loading doses are covered in the BNF and therefore not included in the guideline.
330	NICE GP panel	Guideline	014	026	1.5.10 We suggest diet is considered early so reposition this recommendation higher up the page	Thank you for your comment. This was discussed at length and the committee agreed it was important to put the causes of deficiency with the more serious consequences first.
331	NICE GP panel	Guideline	014	027	1.5.4 The recommendations don't match BOMSS guidelines, which are more prescriptive about IM therapy for certain procedures	Thank you for your comment. The BOMSS guidelines are specific to bariatric surgery whereas these recommendations apply to major gastric and terminal ileal resection as well. We didn't stratify the evidence by type of surgery and therefore made a recommendation covering all types of surgery that cause malabsorption.

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						No evidence was identified to suggest that intramuscular injections are more effective than oral replacement. However, the committee agreed that it is likely to be the better option. We looked but didn't find evidence for combinations or sequences of oral and intramuscular vitamin B12 replacement.
332	NICE GP panel	Guideline	014	027	1.5.10 Do patients correcting a dietary (or medication-related) cause need such frequent treatment as recommended?	Thank you for your comment. The committee has not stated the frequency of medications. They have advised assessing the person's symptoms to determine the response to treatment as part of the ongoing care and follow up recommendations. Depending on this response the committee have also recommended that treatment may need to be changed, continued or stopped.
333	NICE GP panel	Guideline	015	009	1.5.12 Doses of over-the counter supplements would be advised by the seller but we suggest a specific daily dose is included in guidance	Thank you for your comment. A review of the effectiveness of over-the-counter (OTC) supplements was not included as part of the scope of the guideline and therefore no recommendations have been made on whether to suggest them and what dosage to use. The recommendation relating to OTC oral supplements is to highlight which supplements are appropriate. This is because some oral supplements that are labelled as containing vitamin B12 do not contain a form that is appropriate to use as vitamin B12 replacement.
334	NICE GP panel	Guideline	016	008	1.5.15 Concerns about adherence: please add a bullet point on financial hardship	Thank you for your comment. Financial hardship alone was not considered a reason to offer intramuscular injections over oral replacement. The committee were aware that people on low incomes get free prescriptions which would cover financial hardship.
335	NICE GP panel	Guideline	016	018	1.5.16 Management of unknown causes of B12 deficiency: thankyou, this is clear	Thank you for your comment.

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336	NICE GP panel	Guideline	017	001	1.6 Please include advice on when to recheck B12 levels in those with a normal result but have a recurrence of symptoms and a change in risk factors	Thank you for your comment. The recommendation related to this is in the section on thresholds for test results. The committee recommend that if the person's initial test result suggests that vitamin B12 deficiency is unlikely then other causes of their symptoms should be investigated. If the person is still experiencing symptoms or signs 3 to 6 months later, consider a repeat of the initial test.
337	NICE GP panel	Guideline	017	001	1.6 Is there any benefit at all from monitoring B12 levels in the drug compliant and well? Those on oral treatment? Those on IM treatment? People post-gastric surgery have routine monitoring, but others usually not.	Thank you for your comment. Following stakeholder feedback the recommendation for repeating oral testing has been removed from the guideline. There was no evidence to recommend monitoring B12 concentrations for people on oral or intramuscular vitamin B12 replacement.
338	NICE GP panel	Guideline	017	002	1.6.1 A quote from one respondent: "If you ask anyone 'do you feel tired, depressed or anxious?' 100% of people respond with a yes. We suggest you replace this statement."	Thank you for your comment. The committee agreed it was important to ask about symptoms as a change in these gives the healthcare professional an idea of whether or not treatment is working. The recommendation has been rephrased to state 'At each follow-up appointment, ask the person if their symptoms have improved or worsened, or if they are experiencing new symptoms that could be linked to vitamin B12 deficiency.'
339	NICE GP panel	Guideline	017	012	1.6.2 suggests retesting 1-3months – many local labs refuse to repeat B12 within 6 months	Thank you for your comment. Following stakeholder comments the recommendation for repeating the initial test for people on oral vitamin B12 replacement has been removed from the guideline.
340	NICE GP panel	Guideline	019	004	1.6.11 Please clarify why would someone consider initial diagnostic tests at follow-up?	Thank you for your comment. The recommendation's aim is to ensure the initial diagnostic test is not repeated to see if the result has changed. The reason not to repeat it is because the intramuscular injections will influence the test

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						and the result will not be an accurate reflection of how well it is working. The recommendation is to make it clear that there is no value in retesting.
341	NICE GP panel	Guideline	019	006	1.6.12 Please add 'if symptoms not improved consider additional causes of symptoms'. When people have vague symptoms low B12 might be coincidental and other more serious causes may be missed.	Thank you for your comment. The recommendation has been updated to add an additional point on thinking about alternative diagnoses as the cause of the person's symptoms.
342	NICE GP panel	Guideline	019	011	1.6.13 Is there a rationale for annual follow-up on those who have a clear diagnosis and are compliant with treatment? Formal follow-up is unusual in primary care	Thank you for your comment. The recommendation has been updated to 'advise them to come back if symptoms get worse, reappear, or they get new symptoms'.
343	NICE GP panel	Guideline	019	024	1.6.15: please specify the reduced frequency	Thank you for your comment. No evidence was identified for the frequency of intramuscular injections and the committee made a research recommendation for this. The committee were aware that people could be started on a dose at 3 monthly intervals and the BNF suggests these could be reduced to 2 monthly intervals. The recommendation is meant to reflect this.
344	NICE GP panel	Guideline	033	026	and evidence E p 44– Please summarise the information on the effectiveness and cost effectiveness of oral and intramuscular treatment for suitable patients in the main body of the guideline to aid decision making	Thank you for your comment. We have made it clear in the rationale, how the evidence and experience of the committee have informed the recommendations and now explicitly refer to the guideline model. Details of the modelling are in Evidence report E, as you have noted.
345	NICE GP panel	Guideline	035	009	Consider rechecking (annually?), instead of 'blindly continuing'?	Thank you for your comment. A new recommendation has been added which states 'Review the need for vitamin B12 replacement if the person stops using nitrous oxide

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						recreationally and they no longer have symptoms of vitamin B12 deficiency.'
346	NICE GP panel	Guideline	039	004	Could we possibly link this statement to recommendation 1.6.7	Thank you for your comment. Repeating the initial test at the first follow up appointment has been removed from the guideline and the rationale updated to reflect this.
347	NICE GP panel	Guideline	041	010 - 014	'this is primarily diagnosed in primary care', but this may not be true after the guideline is published?	Thank you for your comment. The committee believe it will still be primarily diagnosed in primary care.
348	NICE GP panel	Guideline	041	020	relates to page 5 line 16 – please alter to match our suggestions as above.	Thank you for your comment. We have added your suggestions to the context.
349	Northumbria Pharma Ltd	Guideline	General	General	Regarding the review question 1.1 'What is the clinical and cost effectiveness of vitamin B12 replacement, including the dose, frequency and route of administration?', the Guideline currently doesn't include dose recommendation other than for parenteral administration and for oral vitamin B12 replacement prescribed during pregnancy or breastfeeding (minimum 1000mcg daily, page 16 line 1 and page 26 line 3). Will NICE consider a recommended dose of 1000mcg whenever oral vitamin B12 replacement is prescribed; for similar reasons of setting a minimum dose to ensure that enough vitamin B12 is being absorbed, and in line with content of Evidence E summarised below?	Thank you for your comment. NICE does not include dosage in recommendations where they are available in the BNF or SPC. A dosage may be included if this information is not available, or the committee agrees that there needs to be a change to current recommended dosages, for example because of new evidence. The guideline has been updated to recommend at least 1mg a day when oral vitamin B12 replacement is prescribed in cases of malabsorption. This is because all comparisons for oral with intramuscular vitamin B12 replacement used 1mg of oral replacement. The committee also agreed that there was no evidence to suggest a lower dose would be effective in this group and that using this dose is likely to be current practice for this group. The dosage is stated to ensure that these patients receive the appropriate treatment. There wasn't evidence to recommend a 1mg dose for people with medicine or nitrous oxide induced deficiency. Oral

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					-Evidence E (page 58, lines 38 to 43) describes 'use of 1000mcg cyanocobalamin tablets will be at least as effective as lower strength tablets as well as cyanocobalamin being generally well tolerated and unlikely to cause harm.' -Evidence E (1.1.6) includes tables of evidence that 1000mcg cyanocobalamin generally achieves better haemalological values than lower doses -Evidence E (page 22, lines 9 to 12) describes 'For oral vitamin B12, only costs of Orobalin are included as this is lower cost as well as having 20 times the strength of the generic 50mcg tablet. Orobalin is the only licensed 1 mg oral tablet currently and hence this is why this medicine is selected for analysis as other versions of the 1 mg tablet would be considered unlicensed.'	vitamin B12 replacement can be prescribed at lower doses for a dietary deficiency.
350	Northumbria Pharma Ltd	Guideline	General	General	To ensure that patients always receive a licensed cyanocobalamin preparation of known strength and safety, we would suggest a recommendation that prescriptions should always be written as a named brand of licensed product. NICE will be aware that there are numerous unlicensed cyanocobalamin supplements available. Generic prescribing of	Thank you for your comment. The expectation is that healthcare professionals follow relevant guidance about which medicines should be prescribed by brand. When making decisions about the use of unlicensed medicines, users should follow General Medical Council's prescribing guidance: prescribing unlicensed medicines and the MHRAs drug safety update for off-label or unlicensed use of medicines.

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					cyanocobalamin tablets is currently common practice and often results in the dispensing of unlicensed vitamin B12 supplements (approximately 43% of prescriptions for 1mg cyanocobalamin tablets were incorrectly dispensed with unlicensed supplements rather than the licensed product, Orobalin in May 2023*) As stated in EvidenceE, in the case of cyanocobalamin 1mg the contractor is reimbursed at the price of Orobalin 1mg even if a cheaper unregulated supplement is dispense, we believe that it is important to ensure that only the licensed formulation, as required, and as paid for, is dispensed. *Sources: Comparison of NHS English Prescribing Data (EPD) with NHSBSA Prescription Cost Analysis (PCA Dispensing Data), and Orobalin sales data.	
351	Northumbria Pharma Ltd	Guideline	General	General	Prescribing of 'modified-release' cyanocobalamin 1mg tablets is currently common (c.25,900 packs per month in England*). These are all unlicensed supplements and there is no published evidence for the use of cyanocobalamin MR in preference to immediate-release tablets**. Will NICE consider dissuading the prescribing of unlicensed supplements where licensed preparations exist	Thank you for your comment. The expectation is that healthcare professionals follow the BNF when prescribing oral vitamin B12 supplements and only use licenced medications. Advising healthcare professionals not to use unlicenced preparations is beyond the remit of NICE. When making decisions about the use of unlicensed medicines, users should follow General Medical Council's prescribing guidance: prescribing unlicensed medicines and the MHRAs drug safety update for off-label or unlicensed use of medicines.

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					*English Prescribing Data (EPD Feb 2023) **https://www.sps.nhs.uk/wp-content/uploads/2020/06/UKMI_QA_Oral-Vitamin-B12-preparations_May-2020.pdf	
352	Northumbria Pharma Ltd	Guideline	016 036	008 to 014 017 to 018	The draft guideline gives examples of concerns about adherence to oral treatment. Will examples of concerns about adherence to intramuscular treatment be included? Needle phobia is considered very common, affecting at least 1 in 10* people, and can be a cause of missed treatment / appointments (DNAs). Would NICE consider mentioning this specifically as an important consideration when deciding upon intramuscular or oral vitamin B12 replacement based on clinical judgement and the person's preference. *https://www.guysandstthomas.nhs.uk/health-information/needle-phobia-and-overcoming-your-fear	Thank you for your advice. The NICE guidelines on Patient experience in adult NHS services and Shared decision making cover general recommendations on discussing treatments and listening to the person's fears. Needle phobia would be part of the discussions with the person. NICE guidelines do not generally link to other medical association or patient support group guidelines or websites from the recommendations because these may change and NICE has no control over the content.
353	Northumbria Pharma Ltd	Guideline	021	008 to 011	We agree with the definition of 'vitamin B12 replacement'. However we think that it could be made clearer within section 1.5 'Managing vitamin B12 deficiency', that treatment should be with prescribed doses rather than potentially left to people to shop for OTC product, which could be subject to error; particularly affecting those for whom English is not a first language or spoken,	Thank you for your comment. The expectation is that healthcare professionals follow the BNF when prescribing oral vitamin B12 replacement. The recommendation relating to OTC oral supplements is to highlight which supplements are appropriate. This is because some oral supplements that are labelled as containing vitamin B12 do not contain a form that is appropriate to use as vitamin B12 replacement.

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					those with learning difficulties,, some elderly, and those on low incomes.	
354	Northumbria Pharma Ltd	Guideline	035	022 to 026	We welcome that the only consideration of OTC purchase of vitamin B12 supplements by people is in the context of 'should they wish to buy supplements'. However we think that the guideline can more clearly advise against clinicians recommending to people who require vitamin B12 replacement to buy an OTC product. Self purchase of an OTC product will no doubt lead to confusion, as recognised in Draft Guiideline and incorrect treatment amongst some, and some level of increased health inequality, particularly affecting those for whom English is not a first language or spoken, those with learning difficulties, some elderly, and those on low incomes.	Thank you for your comment. A review of the effectiveness of over-the-counter (OTC) supplements was not included as part of the scope of the guideline and therefore no recommendations have been made on whether to suggest them and what dosage to use. The recommendation relating to OTC oral supplements is to highlight which supplements are appropriate. This is because some oral supplements that are labelled as containing vitamin B12 do not contain a form that is appropriate to use as vitamin B12 replacement. This guideline has not gone into the details on how to communicate with people because this is covered in section 1.5 Enabling patients to actively participate in their care of the NICE guideline on Patient experience in adult NHS services. This is cross referred to in the first guideline recommendation 1.1.1. Users should refer to Guidance on conditions for which over the counter items should not routinely be prescribed in primary care.
355	Northumbria Pharma Ltd	Guideline	035	025	We are a bit concerned that the recommendation to 'list the types of vitamin B12 that people should look out for' can still lead to confusion and potential health inequality particularly affecting those for whom English is not a first language or	Thank you for your comment. A review of the effectiveness of over-the-counter (OTC) supplements was not included as part of the scope of the guideline and therefore no recommendations have been made on whether to suggest them and what dosage to use. The recommendation relating to OTC oral supplements is to highlight which supplements

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					spoken of lower education level, some elderly, and those on low incomes.	are appropriate should a person wish to buy them. This is because some oral supplements that are labelled as containing vitamin B12 do not contain a form that is appropriate to use as vitamin B12 replacement. This guideline has not gone into the details on how to communicate with people because this is covered in section 1.5 Enabling patients to actively participate in their care of the NICE guideline on Patient experience in adult NHS services. This is cross referred to in the first guideline recommendation 1.1.1.
356	Northumbria Pharma Ltd	Guideline	037	006	it may be challenging to implement the draft recommendations if it leads to a marked increase in injections administered in primary care. We are concerned that whilst the cost calculation is one consideration, so too is the general burden on primary care staff time. According to NHS English Prescribing Data (EPD) for May 2023, there were 349,944 hydroxocobalamin injections prescribed in May 2023, and if assuming that each took 10 minutes of healthcare professional time to administer, this already accounts for 58,324 hours in that month alone.	Thank you for your comment. Intramuscular injections are only recommended where the committee believe it was necessary. Where intramuscular injections are recommended over oral it is because the committee agree they are likely to be the most effective and cost-effective option.
357	Northumbria Pharma Ltd	Evidence E	058 059	044 to 045	To ensure that the licensed formulation is dispensed it is essential that the prescription is written as the licensed brand, rather than generically as cyanocobalamin.	Thank you for your comment. We do not refer to drug brand names in our guidance. The expectation is that healthcare professionals follow the BNF when prescribing oral vitamin B12 supplements and only use licenced medications.

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				001 to 002	NICE will be aware that there are numerous unlicensed cyanocobalamin supplements available. Generic prescribing of cyanocobalamin tablets is currently common practice and often results in the dispensing of unlicensed vitamin B12 supplements (approximately 43% of prescriptions for 1mg cyanocobalamin tablets were incorrectly dispensed with unlicensed supplements rather than the licensed product, Orobalin in May 2023*) As stated in EvidenceE, in the case of cyanocobalamin 1mg the contractor is reimbursed at the price of Orobalin 1mg even if a cheaper unregulated supplement is dispense, we believe that it is important to ensure that only the licensed formulation, as required, and as paid for, is dispensed. *Sources: Comparison of NHS English Prescribing Data (EPD) with NHSBSA Prescription Cost Analysis (PCA Dispensing Data), and Orobalin sales data.	Advising healthcare professionals not to use unlicenced preparations is beyond the remit of NICE. When making decisions about the use of unlicensed medicines, users should follow General Medical Council's prescribing guidance: prescribing unlicensed medicines and the MHRAs drug safety update for off-label or unlicensed use of medicines. In our economic analysis, we have used the NHS drug tariff price, which, as you note, is the price of Orobalin.
358	Nottingham and Nottinghamshire ICB	Guideline	General	General	The offer of oral or IM treatment is based in most cases on patient reference, what about basing it also on cost effectiveness?	Thank you for your comment. There was no clear indication of oral or intramuscular replacement being more clinically effective than the other. For people with autoimmune gastritis, IM was found to be less costly. For other causes it was less clear and some patients are needle-phobic.

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						Therefore, in some cases the committee recommended either treatment. In these circumstances, NICE likes to make it clear that the person has a choice.
359	Nottingham and Nottinghamshire ICB	Guideline	010	010	Diagnose deficiency if a total B12 of less than 180 nanogram per litre. This level seems high. Our local labs report deficiency when less than 150. We are concerned this will result in many more patients ending up on treatments	Thank you for your comment. Several stakeholders commented on the thresholds. Some thought they were too low, others thought they were too high and there was also some support that they are about right. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not. Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests. The committee also recommend considering MMA as a further test for people with an indeterminate active or total B12 test result. This is to capture people who may have a vitamin B12 deficiency when their test result doesn't meet the criteria for deficiency. An indeterminate result covers an active B12 of between 25 and 70 pmol per litre, and a total B12 of between 180 and 350 nanograms (133 and 258 pmol) per litre.

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						The committee has also added a recommendation to use the laboratory's reference ranges to decide if vitamin B12 deficiency is likely when interpreting serum MMA and plasma homocysteine test results.
360	Nottingham and Nottinghamshire ICB	Guideline	010	018	We are concerned that the use of MMA testing will be difficult and costly to implement within an already stretched primary care. Has the resource impact of the test this been factored in into the costing template for uptake of the guidance?	Thank you for your comment. Economic modelling showed that serum MMA is likely to be cost effective for people with a B12 measurement in the indeterminate range. Implementing these recommendations will require some reallocation of resources, including investment in pathology services, so that testing can become more widely available. A resource impact report and tool will be published alongside this guideline.
361	Nottingham and Nottinghamshire ICB	Guideline	018	016	If the repeated test suggests the person no longer has a vitamin B12 deficiency and their symptoms have not improved, one option is to increase the dose of oral treatment which seems irrational	Thank you for your comment. The committee agreed this was an important option because some people may have started on the lowest licenced dose for oral vitamin B12 replacement and a higher dose may improve symptoms.
362	Nottingham and Nottinghamshire ICB	Guideline	035	022 - 026	There is no recommendation as to what situation may warrant self-care with OTC products. Is this outside the scope of this guideline? The offer and consider advice implies it should be on FP10 (especially relevant to dietary deficiency) whereas advice to seek treatment OTC would fit better with NHSE Guidance on 'conditions for which over the counter items should not routinely be prescribed in primary care'	Thank you for your comment. A review of the effectiveness of over-the-counter (OTC) supplements was not included as part of the scope of the guideline and therefore no recommendations have been made on whether to suggest them and at what dose. The recommendation relating to OTC oral supplements is to highlight which supplements are appropriate. This is because some oral supplements that are labelled as containing vitamin B12 do not contain a form that is appropriate to use as vitamin B12 replacement. Users should refer to Guidance on conditions for which over the

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						counter items should not routinely be prescribed in primary care.
363	Office for Health improvement and Disparities (OHID)	Guideline	General	General	The Office for Health Improvement and Disparities (OHID) at the Department of Health and Social Care (DHSC) is supportive of this guideline. You may wish to note that the Scientific Advisory Committee on Nutrition (SACN) concluded in its 2006 report on folate and disease prevention that folic acid intakes up to 1 mg day are not associated with masking anaemia associated with vitamin B12 deficiency and SACN's 2017 updated recommendations on folic acid concluded that evidence published since the 2006 report does not provide a substantive basis to change the conclusions of the previous risk assessment with regard to these outcomes. In September 2021, following SACN's 2017 updated recommendations on folic acid and a UK wide public consultation, the UK government and devolved administrations announced their intention to proceed with arrangements to require the mandatory fortification of non-wholemeal wheat flour	Thank you for your comment and support for this guideline. Thank you as well for the information about folic acid.

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					with folic acid to help prevent neural tube defects. In accordance with SACN recommendations, a monitoring plan is being implemented to monitor folic acid intakes following fortification. We are happy to provide any support as needed post consultation.	
364	Oxford Project to Investigate Memory and Ageing (OPTIMA)	Guideline	General	General	We suggest that the Committee might recognise that **B12-insufficiency (**defined as values of serum total B12 above the cut-off for deficiency but up to about 300/350pmol/L), is a significant population health problem since it can be associated with a variety of symptoms. Seventeen different adverse outcomes were identified in a recent review (Table 4, Smith et al 2018). A particularly striking example is the finding that the rate of atrophy of the brain in the elderly increases as the serum total B12 level declines over the range 600 pmol/L to 160 pmol/L (Vogiatzoglou et al. 2008). Smith, A.D., M.J. Warren, & H. Refsum, *Vitamin B12. Adv Food Nutr Res*, 2018. **83**: 215-279.	Thank you for your comment. Vitamin B12 insufficiency as a concept was not discussed during scoping or development, and treating people without a deficiency was not part of the scope of the guideline. There was little evidence for signs and symptoms, treatment or thresholds for test results, so the committee used expert opinion to make recommendations for thresholds for diagnostic test results. The committee agreed that it is difficult to determine absolute cut-offs for thresholds. With this in mind they recommended an indeterminate range to reflect this uncertainty and advise further testing for people whose test results fall into this category. Without evidence for treating symptomatic people outside the thresholds the committee were unable to make recommendations in this area.

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					DOI: 10.1016/bs.afnr.2017.11.005 Vogiatzoglou A. et al. Vitamin B12 status and rate of brain volume loss in community-dwelling elderly. *Neurology* 2008. **71**:826-832 DOI: 10.1212/01.wnl.0000325581.26991.f2 We hope that the committee will recognise B12-insufficicncy and recommend treatment in such synptomatic cases. Indeed, treatment when the total B12 is in the insufficient range might anyway be recommend even without signs or symptoms since it may prevent the development of symptoms	We checked the cited references to make sure we had not missed them in our searches. The citation from Smith et al., is not a peer reviewed publication, instead coming from a textbook. Such literature is not considered in evidence reviews. The study from Vogiatzoglou et al., was conducted in people that did not have vitamin B12 deficiency, thus not meeting the inclusion criteria for this guideline.
365	Oxford Project to Investigate Memory and Ageing (OPTIMA)	Guideline	General	General	The question above: 'Would it be challenging to implement of any of the draft recommendations?' We consider that setting up clinical chemistry assays for MMA (methylmalonic acid) might be challenging, but that homocysteine assays are standardised and commercial and ought to be more widely available	Thank you for your comment. Economic modelling showed that MMA is likely to be cost effective for people with a B12 measurement in the indeterminate range although there may be a resource impact. Implementing these recommendations will require some reallocation of resources, including investment in pathology services, so that testing can become more widely available. A resource impact report and tool will be published alongside this guideline.
366	Oxford Project to Investigate Memory and	Guideline	General	General	The question above: 'Would implementation of any of the draft recommendations have significant cost implications? We suggest that costs could be reduced if the Committee did not recommend ithe use of	Thank you for your comment.

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	Ageing (OPTIMA)				intramuscular B12 treatment so often. Oral B12 at 1-2 mg per day has been shown to be as effective in almost all situations. About 1% of an oral dose is absorbed passively into the bloodstream. Parenteral B12 is only required to correct the initial very poor B12 status when pernicious anaemia is first diagnosed. Later, although some patients prefer regular injections, oral high-dose (1–2mg/day) maintenance treatment is adequate for most patients with pernicious anaemia (Vidal-Alaball et al 2005). In Sweden, for example, oral B12 is the prescribed treatment of choice for the vast majority of patients. Vidal-Alaball et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency Cochrane Database Syst Rev 2005 CD 004655 DOI: 10.1002/14651858.CD004655.pub2	The guideline's economic modelling showed that oral B12 treatment was more costly than intramuscular B12 treatment unless treatment is only required for a short period. The guideline conducted its own systematic review. The cited Cochrane review was published in 2005 and the review was checked for studies that matched the guideline review protocol to be included in the guideline. The guideline committee considered the paper by Vidal-Alaball et al. However, using the current drug tariff for oral B12, intramuscular treatment is less costly.
367	Oxford Project to Investigate Memory and Ageing (OPTIMA)	Guideline	009	001	Section 1.3. **Diagnosing vitamin B12 deficiency.** We suggest that a preamble here might reflect the Committee's 'evidence review' and acknowledge that, in spite of much research, the diagnosis of B12 deficiency remains challenging. A similar view was expressed in the Information Sheet on B12 published by the American Society for Nutrition which	Thank you for your comment. The following statement has been added to the rationale and committee discussion to make this clear "The committee noted that there is currently no established 'gold standard' test for diagnosing vitamin B12 deficiency. This means that while tests can be a

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					concluded "Overall, as there is no gold-standard test to define deficiency, we recommend that a positive clinical response to vitamin B-12 treatment should be an important guide to the diagnosis of deficiency" (Sobczyńska-Malefora & Smith 2022),. Accordingly, we suggest that NICE consider including a positive clinical response to treatment as one of the aids to diagnosis, in particular in relation to less common symptoms, such as psychosis. Sobczyńska-Malefora, A. and A.D. Smith, *Vitamin B-12. Adv Nutr*, 2022. **13**:. 2061-3. DOI: 10.1093/advances/nmac030	diagnostic aid, they cannot be relied on completely to confirm or rule out deficiency." Thank you for the citation. This study is a narrative review and was checked to see if any studies that fitted our review protocol and should therefore be included in the guideline. No new studies were identified.
368	Oxford Project to Investigate Memory and Ageing (OPTIMA)	Guideline	010	010	Section 1.3.8. **Thresholds for initial test results.** It is not clear to us why the committee chose a value of total B12 of 133 pmol/L as the cut-off for deficiency since internationally by far the commonest value is 148 pmol/L. We could not find an explanation of this decision.	Thank you for your comment. Several stakeholders commented on the thresholds. Some thought they were too low, others thought they were too high and there was also some support that they are about right. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not. Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The

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						committee also noted that either active or total B12 are recommended as tests. The committee also recommend considering MMA as a further test for people with an indeterminate active or total B12 test result. This is to capture people who may have a vitamin B12 deficiency when their test result doesn't meet the criteria for deficiency. An indeterminate result covers an active B12 of between 25 and 70 pmol per litre, and a total B12 of between 180 and 350 nanograms (133 and 258 pmol) per litre. The committee has also added a recommendation to use the laboratory's reference ranges to decide if vitamin B12 deficiency is likely when interpreting serum MMA and plasma homocysteine test results.
369	Oxford Project to Investigate Memory and Ageing (OPTIMA)	Guideline	010	017	Section 1.3.10. It is good that the committee recognises that indeterminate results require further work since people with total B12 values in the range 133-258 pmol/L often show symptoms and will benefit from treatment. We suggest that the committee considers using the term **'B12-insufficiency'** when total B12 values are above the cut-off for deficiency but below a value of about 300/350 pmol/L. The prevalence of B12-isufficiency (or B12-inadequacy) so defined is surprisingly high: a recent survey found that it occurred in	Thank you for your comment. The committee did not consider the term B12 insufficiency when developing the protocols or recommendations. Therefore, it has not been added to the guideline. Also, no other stakeholders have suggested using the term and we do not want to introduce a new concept without other stakeholders having the opportunity to comment on it.

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					between 29% and 60% of people in different categories see Table 3 in review by Smith et al. (2018). Smith, A.D., M.J. Warren, & H. Refsum, *Vitamin B12. Adv Food Nutr Res*, 2018. **83**: 215-279. DOI: 10.1016/bs.afnr.2017.11.005	
370	Oxford Project to Investigate Memory and Ageing (OPTIMA)	Guideline	011	023	Section 1.3.14. **Test results indicating vitamin B12 deficiency is unlikely.** We are concerned that the Committee has chosen such a relatively low value (258 pmol/L) of total B12 as the cut-off to define a lack of deficiency. B12-insufficiency may manifest signs or symptoms at values ot total B12 of up to 300/350 pmol/L as summarised in Table 4 of Smith et al (2018). Smith, A.D., M.J. Warren, & H. Refsum, *Vitamin B12. Adv Food Nutr Res*, 2018. **83**: 215-279. DOI: 10.1016/bs.afnr.2017.11.005	Thank you for your comment. Several stakeholders commented on the thresholds. Some thought they were too low, others thought they were too high and there was also some support that they are about right. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not. Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests. The committee also recommend considering MMA as a further test for people with an indeterminate active or total B12 test result. This is to capture people who may have a vitamin B12 deficiency when their test result doesn't meet the criteria for deficiency. An indeterminate result covers an active B12 of between 25 and 70 pmol per litre, and a total

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						B12 of between 180 and 350 nanograms (133 and 258 pmol) per litre. The committee has also added a recommendation to use the laboratory's reference ranges to decide if vitamin B12 deficiency is likely when interpreting serum MMA and plasma homocysteine test results.
371	Oxford Project to Investigate Memory and Ageing (OPTIMA)	Guideline	012	001	Section 1.3.15. We strongly suggest that in addition to repeating the test and measuring MMA (methylmalonic acid), the patient should be treated with B12 if they continue to experience symptoms or signs. This is surely good clinical practice. A positive response to treatment is a way of revealing B12 deficiency/insufficiency.	Thank you for your comment. The recommendation has been updated to advise investigating other causes as well as considering a repeat of the initial test if they are still experiencing symptoms or signs 3 to 6 months later. MMA has been removed because the committee agreed that most laboratories would not allow for an MMA without testing total or active B12 first. A trial of vitamin B12 deficiency was not one of the options considered in the review. Therefore, no recommendations have been made advising healthcare professionals whether or not to trial vitamin B12 replacement in this scenario.
372	Pernicious Anaemia Society	Guideline	General	General	Pernicious Anaemia Society is a charitable organisation with a mission to improve the diagnosis of pernicious anaemia and treatment of people with this condition. One of the symptoms of Pernicious Anaemia is B12 deficiency. The Pernicious Anaemia Society was instrumental in commissioning these guidelines. We are a patient advocacy group with over 8500 members, and we host the Pernicious	Thank you for your responses.

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					Anaemia forum on www.healthunlocked.com with over 30000 followers. We have extensive experience in commissioning, funding, and organising research into Pernicious Anaemia.	
373	Pernicious Anaemia Society	Guideline	General	General	We strongly object to the use of the term "autoimmune gastritis" as it is not synonymous with Pernicious Anaemia. Throughout the document references are to autoimmune gastritis only whilst neglecting Pernicious Anaemia. This seriously impacts the usefulness of the guidelines for healthcare professionals since Pernicious Anaemia is the term by which the condition causing the majority of B12 deficiency issues is currently known. Patients are unfamiliar with the term autoimmune gastritis to describe their condition. Autoimmune gastritis is a misnomer for the condition of Pernicious Anaemia since some patients will not present with symptoms of gastritis. We acknowledge the term pernicious anaemia also inadequately describes the condition (because most patients do not have anaemia and the condition is no	Thank you for your comment. The guideline has been updated to acknowledge the difference between autoimmune gastritis and pernicious anaemia and provide a more detailed reason as to why the term 'pernicious anaemia' has not been used. This explains that autoimmune gastritis is sometimes referred to as pernicious anaemia which is a separate condition that can be a consequence of chronic, severe vitamin B12 deficiency, including deficiency caused by autoimmune gastritis. However, pernicious anaemia in its true sense (that is 'a life-threatening anaemia') is now extremely rare because of developments in testing and treatment for, and greater awareness of, vitamin B12 deficiency. For this reason, and to prevent any confusion with autoimmune gastritis, we have not used the term 'pernicious anaemia' in the recommendations. Please be reassured that anyone who searches for the term 'pernicious anaemia' using either the NICE website or another search engine, will find it appears in their search results. This is because the term 'pernicious anaemia' appears in the main body of the guideline, even if it does not appear in the recommendations themselves. We have also included a brief reference to the terminology used in this guideline on its main overview page (sometimes

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					longer fatal if treated), but the term Pernicious Anaemia has become a known and accepted descriptor in both health care and for patients in the UK. To not use the term Pernicious Anaemia in the guideline does a disservice to users of the document and will hinder and delay the diagnosis and treatment of patients with this condition. Health care professionals use and already are familiar with the term pernicious anaemia. It is specifically used in the system of coding of conditions on medical records. The guideline must use this term to ensure healthcare professionals find advice when searching NICE guidelines. When carrying out a search amongst NICE guidelines, a health care professional will likely not use the terms gastritis or autoimmune because they are not educated that these terms are, in these guidelines, being used (incorrectly) as synonymous with the term pernicious anaemia.	called the landing page) both for clarity and to further aid anyone who is searching for this guideline.

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					Numerous research publications and existing guidelines refer to Pernicious Anaemia and not to autoimmune gastritis which establishes a convention of using the term Pernicious Anaemia. Pernicious Anaemia is also frequently used to describe patients who are unable to absorb B12 through diet and oral B12 supplementation but who respond to treatment of Injections of Intra-Muscular hydroxocobalamin even if they have a negative result for the Intrinsic Factor/IFA test. We believe that many of these patients are likely also to have Pernicious Anaemia because although highly specific, the intrinsic factor antibody assay has a low sensitivity only picking up 40-60% of patients. It would be remiss, at this opportunity to improve diagnosis and treatment guidelines for Pernicious Anaemia, for NICE and the Committee to underestimate the psychological importance for patients (who may have had a long journey to diagnosis) to have a label which they understand and which they can research and discuss with patient groups and their health care	

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					provider. It is vital that NICE and the healthcare profession provide a correct umbrella name for their condition. Until a suitable name is universally accepted, NICE must use and refer to pernicious anaemia in these guidelines to ensure patients are properly treated. This guideline is NOT the place to try to change the name of the condition. We would welcome a better understanding and awareness of both terms in the medical profession and when, and if, there is scientific proof and agreement that autoimmune gastritis includes patients with pernicious anaemia, or another suitable term is agreed upon, then we will be willing to help educate both patients and public on this topic. **We urge you to use the term "Autoimmune Gastritis including Pernicious Anaemia" to make sure it is abundantly clear throughout the Guideline that the treatment of Pernicious Anaemia is covered.**	

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					We respectfully submit that it is insufficient to simply refer to this as part of the explanation. In practice a health care professional or patient will not read the document in its entirety when looking for guidance but will look only at specific sections. Your removal of the term Pernicious Anaemia from the title and the text of the document seriously damages the chances of patients with a B12 deficiency being properly diagnosed and treated. What is Pernicious Anaemia | Pernicious Anaemia Society (pernicious-anaemia-society.org) We believe this point goes to the fundamental credibility of this document with patients and healthcare professionals alike. To miss this opportunity to make a better guideline for the people in the UK living with Pernicious Anaemia and those awaiting a diagnosis is a travesty. It is especially important since statistics show that this condition is more prevalent in women who are already commonly the subject of gaslighting from the medical profession.	

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					'It's All in Your Head': The Dangers of Medical Gaslighting | Psychology Today United Kingdom Vitamin B12 or folate deficiency anaemia - Causes - NHS (www.nhs.uk) (prevalence in women)	
374	Pernicious Anaemia Society	Guideline	General	General	We are surprised by the frequent use of the term "Clinical Judgement" throughout the document and having consulted with our health care professional members, their feedback is that this term is unhelpful in a Guideline. The guideline should be much clearer in pointing clinicians in the direction of further tests, treatment, or referrals. The initial diagnosis of B12 deficiency and, in particular, Pernicious Anaemia, is left to primary care who are not experts in vitamin B12 deficiency symptoms, diagnosis and management. There is a significant need for education in this area during training of health care professionals and for existing health care professionals to have better access to current accurate information.	Thank you for your comment. In the absence of evidence, the committee made consensus recommendations. The term 'clinical judgement' is used where there is a choice of interventions, and it is not clear which is better. Further testing and change of treatment are recommended in some instances. However, without evidence of benefit of further testing or referral the committee were unable to recommend these options in all circumstances. Training of healthcare professionals is beyond the remit of this guideline.
375	Pernicious Anaemia Society	Guideline	General	General	The word "consider" is not helpful in these guidelines. In almost every case in this guideline a "consider X" actually means "do X". Feedback from our healthcare	Thank you for your comment. The word 'consider' is used in NICE guidelines to denote recommendations for activities or interventions that could be offered. Its use reflects the lack of available evidence to make a strong recommendation.

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					professional members supports this. These guidelines would greatly benefit from providing more clarity on the steps to be taken and by removing the word "consider". The aim of the guidelines is to ensure that practitioners provide optimal care, which can be achieved through clear and concise language. This draft guidance uses the word "consider" 25 times. One example is "consider further investigations to explore other causes of vitamin B12 deficiency if, during discussion, the person suggests or gives information that raises that the deficiency is not linked to their diet. In clinical practice, it is expected that if a B12 deficiency isn't suggestive of arising from dietary factors, clinicians proactively explore other potential causes. This approach should not be "considered" but must be a definitive action. Numerous cases involving patients with Pernicious Anaemia or other malabsorption issues underscore the importance of this approach. Often, these patients are identified or suggested as having a vitamin	However, it signifies that the committee agreed this was the best choice although they do not have clear evidence to show it is cost-effective. The committee have looked at the recommendations again but there isn't the evidence to strengthen them. Recommendations are made to identify the cause of the deficiency, the 'consider' recommendations in this context reflect the uncertainty in the test result. As people diagnosed with vitamin B12 deficiency would be offered treatment, there is a recommendation to consider switching treatments should the treatment not work.

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					B12 deficiency, yet the cause of deficiency isn't adequately investigated, leading to prolonged periods before an accurate diagnosis is established. Such delays further result in extended intervals before receiving the appropriate treatment. Recent survey findings involving 1182 members of the Pernicious Anaemia Society support this issue. The survey revealed that 40% of participants waiting longer than 3 years, while 27% waited between 1 to 3 years before finally securing a correct diagnosis whilst experiencing symptoms. This is unacceptable as it significantly impacts patients' quality of life and can cause irreversible symptoms. The impacts extend beyond patient well-being by putting a strain on the healthcare system. The number of appointments and tests that patients have during these prolonged years will be expensive. Overall, it is important for both patients' quality of life and the healthcare system's efficiency that the practice of investigation into vitamin B12 deficiencies becomes standard procedure in clinical practice.	

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					We respectfully pose the question "what is the impact of over diagnosing B12 Deficiency rather than under diagnosing it"? A patient with Pernicious Anaemia who is left untreated will get worse and may have irreversible neurological symptoms. The cost of clinical time and investigations will increase higher than the cost of dosing the patient with B12 which is non-toxic and cannot be overdosed. If the patient responds to treatment of replacement B12 then clearly, they were deficient. Whilst health care professionals know that some nutrients are toxic in excess this is not the case for B12 and greater education of the health care profession is needed about this.	
376	Pernicious Anaemia Society	Guideline	General	General	The Pernicious Anaemia Society is a charitable organisation with a mission to improve the diagnosis of pernicious anaemia and improve treatment of people with this condition, whether it has been formally diagnosed by the known to be inaccurate Intrinsic Factor/IFA test or by symptoms and low B12 serum blood test. These guidelines in their current draft form do a disservice to existing patients with Pernicious Anaemia and potentially will lead to people being misdiagnosed or diagnosed	Thank you for your comment. The committee made recommendations based on the available evidence. Some have been updated following stakeholder consultation.

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					late leaving them with irreversible symptoms which are debilitating and life changing for many. We urge the committee to take this opportunity to improve the guidelines and the lives of people with Pernicious Anaemia.	
377	Pernicious Anaemia Society	Guideline	001	005	Over 16s Our members are disappointed that these guidelines exclude those under the age of 16 who have a B12 deficiency especially in relation to those who have or are suspected to have Pernicious Anaemia. By leaving out this group of people, especially where there is a family history of Pernicious Anaemia/B12 deficiency, we believe that these guidelines wrongly imply that Pernicious Anaemia is not found in people within this age group. Even if the scope of these guidelines and the depth of medical research and knowledge is currently inadequate to address detailed guidance for under 16s, the Guidelines should at least point health care professionals in the direction of specialisms or advice for what to do when presented with a young person with symptoms of B12 Deficiency and a family history of Pernicious Anaemia. The	Thank you for your comment. Unfortunately we were unable to recruit all the expertise necessary to be able to develop recommendations in relation to children. It also became apparent there was little evidence in relation to paediatrics. In these circumstances committees will often extrapolate the evidence from adults to children. However, for this guideline there was also a lack of good quality evidence for adults. Overall, the decision NICE made was that it was better to focus on adults. No statements or links to other guidance have been made in relation to under 16s in this guideline because this group was excluded from the scope.

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					committee must recommend is that separate guidelines for under 16s and B12 deficiency need to be commissioned. 216.full.pdf (bmj.com) Megaloblastic Anemia in Children (stanfordchildrens.org) Vitamin B12 or folate deficiency anaemia - Causes - NHS (www.nhs.uk) (people of any age can have Pernicious Anaemia) The Pernicious Anaemia Society helpline regularly gets enquiries from health care professionals and family members with children under 16 who are reporting fatigue, lacking in motivation and energy sometimes with a family history of pernicious anaemia or B12 deficiency due to malabsorption and where their diet contains adequate B12 from animal products. This must be a red flag to the health care professionals that requires further investigation. **Since there are no other adequate guidelines on B12 deficiency in young people from NICE, it must be made clear in these Guidelines that it is possible for people under 16 to have Pernicious Anaemia**	
378	Pernicious Anaemia Society	Guideline	001	005 - 006	We still believe it is unhelpful in a guideline about B12 Deficiency to not mention Pernicious Anaemia in the title.	Thank you for your comment. The guideline has been updated to acknowledge the difference between autoimmune gastritis and pernicious anaemia and provide a more detailed reason as to why the term 'pernicious anaemia' has not been

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					Pernicious Anaemia is the most common cause of non-dietary B12 deficiency in the UK. Currently there is inaccuracy of testing for this condition. The intrinsic factor (IF)/intrinsic factor antibody (IFA) test is inaccurate in 40%+ of cases and a negative IF/IFA test does not prove you do not have Pernicious Anaemia. We see limited knowledge within primary care of this condition and there is an obvious need for clear and improved guidelines in its diagnosis and treatment in the UK. The current guidelines from NICE and British Society of Haematology are, in our experience, already largely not adequately followed by primary care providers and the level of knowledge about the essential vitamin B12 in the health care profession is currently inadequate.	used. This explains that autoimmune gastritis is sometimes referred to as pernicious anaemia which is a separate condition that can be a consequence of chronic, severe vitamin B12 deficiency, including deficiency caused by autoimmune gastritis. However, pernicious anaemia in its true sense (that is 'a life-threatening anaemia') is now extremely rare because of developments in testing and treatment for, and greater awareness of, vitamin B12 deficiency. For this reason, and to prevent any confusion with autoimmune gastritis, we have not used the term 'pernicious anaemia' in the recommendations.
379	Pernicious Anaemia Society	Guideline	004	003 - 006	The guidelines need to clarify what they mean on Page 4 by trying to link a connection between the terms "autoimmune gastritis" and "pernicious anaemia". This poses challenges due to insufficient awareness within the healthcare profession of these terms and their link.	Thank you for your comment. The guideline has been updated to acknowledge the difference between autoimmune gastritis and pernicious anaemia and provide a more detailed reason as to why the term 'pernicious anaemia' has not been used. This explains that autoimmune gastritis is sometimes referred to as pernicious anaemia which is a separate condition that can be a consequence of chronic, severe vitamin B12 deficiency, including deficiency caused by

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					Furthermore, these terms cannot be accurately used interchangeably and should be rephrased to emphasise that autoimmune gastritis and Pernicious Anaemia are not synonymous. Autoimmune gastritis can manifest with or without Pernicious Anaemia (including vitamin B12 deficiency). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8414617/ . Typically, autoimmune gastritis can progress to Pernicious Anaemia in its advanced phases. When referring to the stage of autoimmune gastritis (AIG) resulting in vitamin B12 deficiency, this essentially refers to Pernicious Anaemia as this would be the point of severe parietal cell destruction and intrinsic factor deficiency. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2773890/. Pernicious anaemia is estimated to onset in 15-20% of those with AIG (https://pubmed.ncbi.nlm.nih.gov/32647173/ , https://pubmed.ncbi.nlm.nih.gov/27671008/)	autoimmune gastritis. However, pernicious anaemia in its true sense (that is 'a life-threatening anaemia') is now extremely rare because of developments in testing and treatment for, and greater awareness of, vitamin B12 deficiency. For this reason, and to prevent any confusion with autoimmune gastritis, we have not used the term 'pernicious anaemia' in the recommendations.

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					Patients with Pernicious Anaemia may not present with gastric symptoms. This could delay or mislead diagnosis of Pernicious Anaemia if the health care professional does not connect B12 deficiency with this condition and does not find it referenced properly in the guidelines. Pernicious Anaemia is the name the disease has been known by since it was first described by Thomas Addison in 1849. In other countries it is referred to as Addison's or Biermer's disease. It is important to acknowledge the existence of Pernicious Anaemia in the guidelines for B12 deficiency for these reasons: ● Many patients have an existing diagnosis of Pernicious Anaemia or "PA" on their records and due the current lack of education of the health care profession and the public it will not be understood that the term you use, namely autoimmune gastritis, is meant to cover the same condition. ● Many patients seeking a diagnosis or with a diagnosis will come to	

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					learn that they have a family history of pernicious anaemia. It is important that both patients and health care professionals do not stop using or understanding the term Pernicious Anaemia until there is agreement on the appropriate name for non-dietary malabsorption of B12 and a thorough education of the medical profession and research community in this regard. A large body of research currently refers to Pernicious Anaemia not autoimmune gastritis including Pernicious Anaemia.	
380	Pernicious Anaemia Society	Guideline	004	005 - 006	"The consequence of this is vitamin B12 deficiency, and this can lead to pernicious anaemia" is not an accurate statement. We are not aware of any research that proves or suggests this. B12 deficiency does not lead to Pernicious Anaemia. B12 deficiency is a consequence of Pernicious Anaemia. Pernicious Anaemia is a condition which results in B12 Deficiency if not adequately treated.	Thank you for your comment. The guideline has been updated to acknowledge the difference between autoimmune gastritis and pernicious anaemia and provide a more detailed reason as to why the term 'pernicious anaemia' has not been used. This explains that autoimmune gastritis is sometimes referred to as pernicious anaemia which is a separate condition that can be a consequence of chronic, severe vitamin B12 deficiency, including deficiency caused by autoimmune gastritis. However, pernicious anaemia in its true sense (that is 'a life-threatening anaemia') is now extremely rare because of developments in testing and treatment for, and greater awareness of, vitamin B12 deficiency. For this reason, and to prevent any confusion

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					Pernicious Anaemia as a condition is much wider than just B12 deficiency. It is important the guidelines make this clear because even if the B12 deficiency is managed well by treatment in patients with Pernicious Anaemia, other consequences are relevant for the ongoing management of a Pernicious Anaemia patient's health including iron deficiency anaemia and gastric cancer. Patients with Pernicious Anaemia are at a greater risk of developing Neuro-endocrine Tumours (NETs) and of stomach cancer. Systematic review: gastric cancer incidence in pernicious anaemia - PubMed (nih.gov)	with autoimmune gastritis, we have not used the term 'pernicious anaemia' in the recommendations.
381	Pernicious Anaemia Society	Guideline	004	007 - 021	The information in this section is so vague it raises serious concerns that it provides no help or guidance to a Health Care Professional. This section should state: ● B12 deficiency is potentially a serious condition that can lead to neurological symptoms some of which may be irreversible if not treated promptly and adequately. https://www.sciencedirect.com/science/article/pii/S1568997214000548	Thank you for your comment. These recommendations are written to provide a brief overview of what the committee agreed needs to be highlighted to people with suspected or confirmed deficiency. The section on 'Information for the public' on this guideline's web page also provides links to other organisations' websites which provide more detailed advice directly written for people with suspected or confirmed vitamin B12 deficiency.

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					● It is vital to find the cause of the B12 deficiency as this will affect how it will be best treated. ● B12 deficiency can result from ○ lifestyle choices such as diet which excludes animal products, excess alcohol or misuse of nitrous oxide. ○ medical conditions such as Pernicious Anaemia, stomach surgery, coeliac disease, infections, or other reasons for malabsorption of B12 through the stomach or ○ use of medications to treat other conditions which may deplete B12 such as PPIs, Metformin or Nitrous Oxide in medical use. ● Fatigue as a symptom may require further investigation for other conditions but fatigue combined with symptoms identified as those related to B12 deficiency must lead to a test for adequate B12 levels.	There is a bullet point highlighting the importance of continuing treatment so that symptoms do not get worse or return. The committee agreed that it is not always possible to identify the cause. They made recommendations for unknown causes where treatment is given and reviewed at a later date to see if it resolves symptoms. Stating that it is vital to find a cause would contradict this section. The bullet point noting that vitamin B12 deficiency 'has various causes' has been updated to state that it 'can be caused by a lack of vitamin B12 in the diet, or problems with the way the body processes the vitamin linked to certain medications, operations, conditions or the recreational use of nitrous oxide'. Testing is recommended for people with unexplained fatigue and one of the risk factors. However, the committee do not agree that people with fatigue and other symptoms should always be tested for vitamin B12 deficiency. The recommendations related to dietary deficiency advise that diet (for example, a vegetarian or vegan diet) may not be the cause, or the only cause, of a person's vitamin B12 deficiency. The rationales related to diagnosing vitamin B12 deficiency highlight the problems with testing.

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					Clinicians should be aware that diet (e.g., a vegan or vegetarian diet) may not be the only cause for a B12 deficiency. It is vital the healthcare profession understand that standard testing for Serum B12 is beset with problems due to varying levels of ranges throughout the UK, and due to misleading results if a patient is supplementing, maybe unwittingly, through fortified drinks or foods or over-the-counter vitamins. Clinical judgement must rely primarily on thorough symptomology examinations, not serum levels, until a more accurate test to rule out Pernicious Anaemia is developed. https://pubmed.ncbi.nlm.nih.gov/17363419/ Re: Pernicious anaemia - Serum B12 test has poor sensitivity | The BMJ The serum B12 test | Stichting B12 Tekort Evidence review | Active B12 assay for diagnosing vitamin B12 deficiency | Advice | NICE	Recommendations related to ongoing care and follow up have been updated to emphasise assessing symptoms when reviewing treatment.
382	Pernicious Anaemia Society	Guideline	004	020 - 021	the use of the word "are" in this sentence should be changed to "may be"	Thank you for your comment. The recommendation has been updated as suggested.

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383	Pernicious Anaemia Society	Guideline	005	003 - 004	"most people only need 1 blood test to diagnose vitamin B12 deficiency but some may need further tests." It is misleading to leave this statement here without clarification. This sentence should state which blood test is being referred to. Serum B12 is not a standard test within the full blood count (FBC). A B12 Serum blood test will not indicate that there is sufficient active B12 being used by the body at a cellular level. A request for a Serum B12 blood test from a health care professional will not diagnose the cause of the B12 deficiency. A Serum B12 blood test may be a useful indicator alongside patient symptoms that a B12 deficiency exists. At best, the Serum B12 blood test may lead to an indication that there is insufficient B12 in the total blood serum. This line should be changed to read. **Whilst some people may be diagnosed as B12 deficient from a Serum B12 blood test, this test, in itself, does not explain**	Thank you for your comment. The aim of this bullet point is just to highlight how many tests a person may need rather than go into all the details about testing. The bullet point has been updated to state 'a single blood test can be enough to support a diagnosis of vitamin B12 deficiency but some people may need further tests to diagnose the condition'. The presence of B12 in fortified food and drinks is mentioned in the recommendations and rationales for risk factors and managing dietary vitamin B12 deficiency. The committee made recommendations for an indeterminate range to reflect the uncertainty in test results because they were aware that the initial test results from total or active B12 may not be accurate. The committee also discussed the thresholds in light of stakeholder comments. They agreed that there are four main manufacturers of the tests. Three out of the four have thresholds similar to those recommended in the guideline, however one does not. Therefore they added a bullet point to the threshold recommendations for active and total B12 test results to state that where there is substantial local variation in validated thresholds, the clinician should use those set by the laboratory doing the testing. Investigating and managing complications related to vitamin B12 deficiency and cofactors were not included as part of the scope of the guideline. Therefore they were not included as

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					the cause of the B12 deficiency nor whether rectifying the B12 serum level with supplements will address the symptoms. B12 appears in fortified foods and energy drinks and multi-vitamins many of which patients may be taking to relieve their fatigue or to supplement their diet. The health care professional needs to be aware that these can significantly affect the results of a Serum B12 test. The guidelines must make it clear that the initial Serum B12 blood test may be inaccurate, the ranges vary considerably throughout the United Kingdom and people with an underlying cause for their B12 deficiency symptoms may be symptomatic even with a "within range Serum B12 level". An Active B12 level test may give a more accurate picture but is also not adequate to understand the cause or recommend the appropriate treatment of B12 Deficiency. High folate levels may also mask a B12 deficiency and give a misleading Serum B12 result.	part of the guideline reviews and no recommendations have been made related to this. The committee agreed that clinicians will still test folate and vitamin B12 together despite there being no mention of folate in this guideline. Evidence was not available to recommend active B12, MMA and homocysteine tests ordered together as part of the initial diagnosis. However, further testing is recommended if the test result is indeterminate, and in some circumstances at the follow-up appointment if the person's symptoms have not improved after treatment.

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					Vitamin B12 or folate deficiency anaemia - Diagnosis - NHS (www.nhs.uk) In order to best diagnose B12 deficiency and provide an indication of the cause, health care professionals should be authorised to order Active B12, MMA and Homocysteine tests as these, together with symptoms reported by the patient are going to present the best indication of B12 deficiency and the way to treat it.	
384	Pernicious Anaemia Society	Guideline	005	007 - 008	B12 deficiency affects each person differently and has various causes. **The use of the word "various" is misleading in this context.** There are only three causes of vitamin B12 deficiency namely: ● insufficient intake or depletion due to lifestyle choices ● drug-induced depletion ● malabsorption due to a medical condition or surgery Using the word "various" implies that diagnosis of the route cause is more complex than it needs to be.	Thank you for your comment. The recommendation has been updated to state 'it can be caused by a lack of vitamin B12 in the diet, or problems with the way the body processes the vitamin linked to certain medications, operations, conditions or the recreational use of nitrous oxide'.

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					The clinician must investigate the patient, their lifestyle and their family history to support finding a cause of the B12 deficiency because the treatment for malabsorption will require lifelong ongoing and sufficient B12 replacement through IM injections. Lifestyle choices and drug-induced deficiencies may be successfully treated with oral supplementation since these patients will be able to absorb vitamin B12 via Intrinsic Factor. However, where neurological symptoms present, then treating by IM injection is likely to resolve the patient's symptoms more quickly.	
385	Pernicious Anaemia Society	Guideline	005	016 - 017	The statement "some causes of vitamin B12 deficiency will need (and receive) lifelong treatment, such as deficiency caused by autoimmune gastritis" is misleading. The Guidelines MUST specifically mention pernicious anaemia here to ensure that people with this diagnosis are correctly treated for life. Pernicious Anaemia is not curable nor reversible. We are concerned by the number of reports from our members	Thank you for your comment. The recommendation has been updated to change 'lifelong treatment' to 'lifelong vitamin B12 replacement' to make it clear the committee are not talking about treatment of other conditions. The committee agreed that they wanted to emphasise autoimmune gastritis only in this point as an example of

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					of heath care professionals stopping, threatening to stop, or reducing treatment because they can no longer find a record of a positive Pernicious Anaemia diagnosis on a patient's file. In some cases, the health care professional has removed the reference to Pernicious Anaemia. This often happens when patients move house and must register with a new surgery. These guidelines need to state categorically that for people with Pernicious Anaemia, discontinuation of treatment of B12 Replacement therapy is not an option. Further, these guidelines would be improved, as would the experience of many of our members, if they stated that treatment for Pernicious Anaemia including IM B12 Hydroxocobalamin should continue for pregnant women. The Expert Testimony confirms this expert-testimony (nice.org.uk)	someone who is likely to need lifelong vitamin B12 replacement. The term pernicious anaemia is not used in the recommendations and a further description as to why is included in the section on Terms used in this guideline. Continuing with vitamin B12 replacement if it was started before pregnancy and breastfeeding is recommended at the start of the recommendations for managing vitamin B12 deficiency. This applies to both oral and intramuscular vitamin B12 replacement and is irrespective of the cause of their deficiency.
386	Pernicious Anaemia Society	Guideline	005	018 - 020	Explain to pregnant women and pregnant people who are receiving vitamin B12 replacement that using nitrous oxide with air (gas and air) during labour is unlikely to make their vitamin B12 deficiency worse.	Thank you for your comment. Several stakeholders commented on this suggesting that without evidence to support this the statement should not be made. The

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					There is not sufficient evidence to support this claim. Your evidence comes from the testimony of 1 expert witness but does not seem to refer to recent research in this area as per the below. This statement is potentially dangerous to people with pernicious anaemia or malabsorption issues. It is clear from our membership and the research we link below, Nitrous Oxide has a significant impact on people with Pernicious Anaemia. Patients with Pernicious Anaemia should be offered alternatives to Gas and Air or be given additional B12 IM hydroxocobalamin. Nitrous oxide in labour predicted newborn screening total homocysteine and is a potential risk factor for infant vitamin B12 deficiency - Ljungblad - 2022 - Acta Paediatrica - Wiley Online Library Nitrous oxide–induced vitamin B12 deficiency - PMC (nih.gov) The Link between Nitrous Oxide Uptake and Vitamin B12 Deficiency - Today's RDH (todaysrdh.com) we submit the following wording is clearer: **Explain to pregnant people that there is insufficient evidence to make a clear**	committee agreed and the recommendation relating to this has been removed from the guideline. Recommendations related to pregnant patients on gas and air are covered by MHRA guidance on Nitrous oxide: neurological and haematological toxic effects.

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					statement about the use of nitrous oxide for pain relief in pregnancy but that it is recommended for people with Pernicious Anaemia or B12 malabsorption issues that they consider alternatives.	
387	Pernicious Anaemia Society	Guideline	006	003 – 004	"Offer an initial diagnostic test for vitamin B12 deficiency to people who have:" This statement must specify which diagnostic test is to be offered. The current initial diagnostic test for B12 deficiency available in primary care is not fit for purpose (Serum B12) Laboratory Performance of Serum B12 Assay in the United Kingdom (UK) As Assessed By the UK National External Quality Assessment Scheme for Haematinics: Implications for Clinical Interpretation – ScienceDirect A B12 Serum blood test will only indicate whether total B12 in the blood is low, within range or high. Health care professionals need to be aware that, at best, a B12 serum blood test can only suggest that there is insufficiency or deficiency of B12 in the total blood serum. High levels are often	Thank you for your comment. The recommendations on which test to use are further down in the section on diagnosing vitamin B12 deficiency. The committee were limited in what they could recommend for testing for vitamin B12 by the available evidence. They agreed that more research is needed and made a key research recommendation in this area.

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					secondary to treatment and cannot be used to assess efficacy of B12 in the body. Normal or within range levels do not exclude B12 deficiency.	
388	Pernicious Anaemia Society	Guideline	006	005 – 007	By using the word "and" rather than "or" these guidelines risk missing many potentially B12 Deficient patients who may need multiple appointments and tests further down the line adding to the cost and delay in treatment.	Thank you for your comment. No evidence was identified to make a strong recommendation that people with one of the symptoms or signs without a risk factor, or one of the risk factors without a symptom or sign, should be tested. The committee agreed that the symptoms and signs associated with vitamin B12 deficiency vary and can also be indicative of other conditions. Without the evidence, making a recommendation to test people with just one of the symptoms or signs or risk factor would hugely increase resource impact without any evidence of benefit. The committee recognise that there may be people in whom there is a suggestion of vitamin B12 deficiency without a risk factor, however this would vary and need to be assessed on a case-by-case basis. Consequently, they recommended that clinical judgement would need to be used to decide if a person should be tested in these circumstances.
389	Pernicious Anaemia Society	Guideline	006	008	"Use clinical judgement when deciding whether to test people who have at least 1 symptom or sign but no risk factors" We respectfully submit that the term "clinical judgement" is not helpful advice or guidance in Guidelines. The guideline should state:	Thank you for your comment. No evidence was identified to make a strong recommendation that people with one of the symptoms or signs without a risk factor, or one of the risk factors without a symptom or sign, should be tested. The committee agreed that the symptoms and signs associated with vitamin B12 deficiency vary and can also be indicative of other conditions. Without the evidence, making a recommendation to test people with just one of the

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					Symptoms of B12 deficiency are often insidious and complex and tests for B12 deficiency should be explored for people who have at least 1 symptom or sign but no risk factors. This is especially important if the patient has neurological symptoms or a family history of pernicious anaemia. Pernicious anaemia: recognition, diagnosis and management – The Pharmaceutical Journal (pharmaceutical-journal.com)	symptoms or signs or risk factor would hugely increase resource impact without any evidence of benefit. The committee recognise that there may be people in whom there is a suggestion of vitamin B12 deficiency without a risk factor, however this would vary and need to be assessed on a case-by-case basis. Consequently, they recommended that clinical judgement would need to be used to decide if a person should be tested in these circumstances.
390	Pernicious Anaemia Society	Guideline	006	011	"Do not rule out a diagnosis of vitamin B12 deficiency based solely on the absence of anaemia or macrocytosis." We agree this is an important statement to include in the guideline. Many people with pernicious anaemia or malabsorption of B12 do not have anaemia and it is vital that their symptoms are treated promptly and with sufficiently regular B12 replacement treatment before any macrocytosis presents. However this statement should also include "not to rule out a vitamin B12 deficiency based solely on the a normal serum B12 level".	Thank you for your comment and support for the recommendation. Regarding your point about normal serum B12 results, a statement has been added to the rationale for the initial test recommendations noting that there is currently no 'gold standard' test for diagnosing vitamin B12 deficiency. This means that while tests can be a diagnostic aid, they cannot be relied on completely to confirm or rule out deficiency. The committee also recommends that if there is an indeterminate serum B12 test result then further testing should be considered. This reflects their view that the thresholds for serum B12 results, while generally accepted, are not always reliable.

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					A multicenter retrospective analysis of the clinical features of pernicious anemia in a Korean population – PubMed (nih.gov) Autoimmune gastritis, with or without pernicious anemia: epidemiology, risk factors, and clinical management – PMC (nih.gov)	
391	Pernicious Anaemia Society	Guideline	006	017	We respectfully submit that the guideline would be more helpful if it read "may not be exclusive to vitamin B12 Deficiency"	Thank you for your comment. The committee agreed that a lot of the symptoms are recognised as common in other conditions and therefore agreed this was an important statement to make. Getting a correct diagnosis is important whether it is vitamin B12 deficiency or another cause for the symptoms.
392	Pernicious Anaemia Society	Guideline	007		**Box 1** Several symptoms /symptom descriptions that patients commonly mention appear to be absent from the guidelines. Our surveys of individuals with Pernicious Anaemia and vitamin B12 deficiency indicate the regular occurrence and use of these symptoms within this group of individuals. **Brain Fog (Cognitive difficulties)** – we find it important in this section to use terms which the patient may report, the most frequent of which for pernicious anaemia patients is "brain fog". Whilst not an accepted medical term we believe that this term could be a good	Thank you for your comment. The recommendations and box have been updated to make it clear that these are common symptoms and signs. The symptoms and sign box has been updated to state 'cognitive difficulties such as difficulty concentrating or short-term memory loss (sometimes referred to as brain fog)' which can be symptoms of delirium or dementia. The committee discussed changing the term 'unexplained fatigue' to 'profound fatigue without an obvious lifestyle cause'. However, they agreed that this may not be the only description for the person's fatigue and not everyone would describe their fatigue as 'profound'.

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					trigger word in the guidelines for clinicians to understand what the patient is describing since it is an often-used shorthand to describe a collection of cognitive impairment symptoms Long COVID: Brain fog | Long-term effects of COVID-19 (nhsinform.scot) What is brain fog? | Journal of Neurology, Neurosurgery & Psychiatry (bmj.com) Low Vitamin B12 Levels: An Underestimated Cause Of Minimal Cognitive Impairment And Dementia – PMC (nih.gov) **Unexplained fatigue** We find it important to refer to the nature of the fatigue rather than that it is "unexplained". It is our experience as a patient advocacy and patient support group that many patients with Pernicious Anaemia or with B12 deficiency, especially women, are gaslighted around the use of the word "fatigue" and are often dismissed or given wrong advice. Fatigue from a B12 deficiency is not the same as being tired or even "tired all the time". It is an overwhelming physical and emotional feeling that is not resolved with more or better-quality sleep. It significantly	

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					impacts the person's life, often resulting in the inability to function, to be or remain employed, maintain relationships etc. This symptom should be described as **Profound fatigue without a obvious lifestyle cause.**	
393	Pernicious Anaemia Society	Guideline	008		**Page 8 Box 2** Pernicious Anaemia and a family history of Pernicious Anaemia must be listed as a specific risk factor. The guidelines should also list the most common autoimmune diseases associated with Pernicious Anaemia and vitamin B12 deficiency which include, autoimmune thyroid diseases, type 1 diabetes, and vitiligo. Many clinicians are unaware of the overlap with auto-immune diseases and a list in this guideline would be very helpful. Vitiligo and associated autoimmune disease: retrospective review of 300 patients – PubMed (nih.gov) Vitiligo and Pernicious Anemia | JAMA Dermatology | JAMA Network **Recreational nitrous oxide use**	Thank you for your comment. Autoimmune conditions are included as a risk factor in the box. Only three examples of these are given to avoid suggesting the list is comprehensive. The effects of medicinal nitrous oxide use is covered in MHRA guidance https://www.gov.uk/drug-safety-update/nitrous-oxide-neurological-and-haematological-toxic-effects and therefore has not been included in this guideline. Only the most common symptoms and signs were included in the guideline review therefore the recommendations have been restricted to these. The recommendations and box have been updated to make it clear that these are common symptoms and signs.

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					We are concerned that this refers only to recreational use. Although this is a known term for misuse, it should also not be overlooked that single time misuse can also have devastating effects especially if the user is already low in B12. This term also potentially leaves out here prolonged use during labour or sedation for which there is currently insufficient research. We submit that a further risk factor to consider should be suspected bacteria like H.Pylori, ulcers, symptom of low or high stomach acid, self-dosing with excessive OTC antacids	
394	Pernicious Anaemia Society	Guideline	009	003 – 005	"Use either total B12 (serum cobalamin) or active B12 (serum holotranscobalamin) as the initial test for suspected vitamin B12 deficiency unless" This statement is inaccurate and misleading. Serum and Active B12 tests are not interchangeable, and they measure different things. We understand that primary care health care providers cannot or will not order	Thank you for your comment. In the absence of high-quality evidence, the committee agreed that either total B12 (serum cobalamin) or active B12 (serum holotranscobalamin) should be the initial diagnostic test for most people. The committee noted that, in their experience, active B12 is a more accurate test than total B12, however active B12 is also significantly more costly. They also agreed that using active B12 would not require a change in practice for GP surgeries because it can be carried out on the same serum sample as for total B12. However, recommending active B12 over total B12 would lead to a notable change in practice and would be difficult to justify without evidence of cost effectiveness.

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					Active B12 tests as routine in their current practice. A Serum B12 test may give an indication that the patient is low in B12, and this may be sufficient if diet is suspected as the cause of the deficiency. A simultaneous Active B12 test (and potentially MMA and homocysteine) should be recommended when any one of the risk factors are present. This paragraph should read: **Use total B12 (serum cobalamin) as the initial test for suspected vitamin B12 deficiency as an indication that deficiency is likely to be present.** **Use active B12 (serum holotranscobalamin) as the initial test where the vitamin B12 deficiency is suspected where one or more of the risk factors is the suspected cause of the deficiency and during pregnancy and breastfeeding. Further testing of homocysteine or MMA at the same time may also be useful in these circumstances to help the overall picture**	MMA testing is recommended when the test results are indeterminate. However, there wasn't evidence to support recommending homocysteine in this group and the committee agreed that this is less practical because it requires testing in hospital phlebotomy.

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					but will not, in isolation, prove B12 deficiency or otherwise. B_{12} deficiency is best diagnosed using a combination of tests because none alone is completely reliable. The symptoms and features of B_{12} deficiency are variable and may be atypical. Timely diagnosis is important, and treatment is often quick to resolve thereby gratifying for the patient. Failure to diagnose B_{12} deficiency can have dire consequences, usually neurological. Vitamin B12 deficiency from the perspective of a practicing hematologist | Blood | American Society of Hematology (ashpublications.org)	
395	Pernicious Anaemia Society	Guideline	009	015 - 016	Take blood samples for diagnostic tests before starting vitamin B12 replacement. This should be further clarified by the point in lines 20-22 We suggest this wording is: **Take blood samples for diagnostic tests before starting vitamin B12 replacement and take into account the patient response to whether or not they are supplementing with over-the-counter**	Thank you for your comment. The points you suggest are in two separate recommendations because they occur at different points in the pathway. The second of the two recommendations is just to highlight that oral vitamin B12 supplements may affect test results. It has been updated to include all forms of vitamin B12 supplementation including vitamin B12 tablets, injections or transdermal patches. Assessing the person's dietary intake is included as part of the risk factors in the section on 'When to recognise vitamin B12 deficiency'. This includes by the section on recognising vitamin B12 deficiency and has been updated to include food or drinks fortified with vitamin B12.

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					B12 supplements, multi-vitamins or have a diet high in B12 fortified food and drinks.	
396	Pernicious Anaemia Society	Guideline	009	017 – 019	"Do not delay vitamin B12 replacement while waiting for the test results of people with suspected severe megaloblastic anaemia or sub-acute combined degeneration of the spinal cord**"**. The use of the word "replacement" in this statement needs to read "IM Injections" as replacement is too vague and implies that other treatments such as oral or over-the-counter medications may be sufficient which is clearly not the case when these symptoms or manifestations present.	Thank you for your comment. Both oral and intramuscular injections are options within the treatment recommendations and therefore this recommendation has been kept as 'vitamin B12 replacement'.
397	Pernicious Anaemia Society	Guideline	009	020 – 022	"When offering an initial diagnostic test to a person who is already taking an over-the-counter supplement that contains vitamin B12, ask them what dosage they are taking." This statement does not offer guidance. We respectfully submit that Guidelines should help the health care professional know what to do with the information. This statement should read:	Thank you for your comment. This recommendation is to ensure clinicians get the information about supplementation because some people buy supplements over the counter if they think they will help before going to the doctor. It ties in with the following recommendation which advises using caution when interpreting test results in people already taking over the counter supplementation as it is likely to increase B12 concentrations. The recommendation for retesting when people are using oral vitamin B12 replacement at the first follow up

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					When offering an initial diagnostic test to a person already taking an over-the-counter supplement that contains vitamin B12, inform them that this will likely lead to misleading results and ask them if they would consider delaying the diagnostic test until they have stopped B12 supplementation for at least 4 weeks so that a more accurate test result is likely to be forthcoming. The patient and clinician need to be aware that if the patient has symptoms and/or risk factors, stopping any potential source of vitamin B12 for 4 weeks could lead to further deterioration. If any deterioration is seen, treatment should be restarted immediately along with monitoring of the patient's symptom response. Since it is difficult to interpret accurately the results of Serum B12 if the patient has taken B12 supplements, if the clinician is unsure, they should seek expert advice. This applies also to re-testing. The Rationale notes that "The committee emphasised the need to take blood samples from people before they start	appointment has been removed from the guideline following stakeholder comments. The committee agreed they would still need to test the person if they are suspected of vitamin B12 deficiency even if they are taking supplements. A trial of vitamin B12 replacement without testing was not one of the options considered in the review. Therefore, no recommendations have been made advising healthcare professionals in this area. Recommendations to consider further testing with serum MMA are also made for people with an indeterminate test result. The committee agreed that the supplements would affect the active and total B12 results but not the MMA result.

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					vitamin B12 replacement treatment, because this could affect their test results. They also highlighted the need to ask people which vitamin B12 supplements they are taking (if any) and at what dosage, because higher doses can elevate vitamin B12 concentrations in the blood and affect test results." Therefore, a SYMPTOMS NOT SERUM approach with an empirical trial of B12 injections to look for a positive clinical response offers the best potential for accurate diagnosis and would be cost saving." Since red blood cells have an average life span of 120 days, 4 weeks without supplementation or a diet in B12 fortified food and drink may still skew the results.	
398	Pernicious Anaemia Society	Guideline	010	001 – 003	"Factors that can affect initial test results Use caution when interpreting the test results of anyone who is: • already taking an over-the-counter supplement containing vitamin B12" The phrase "use caution" here is not sufficient as a guideline.	Thank you for your comment. This recommendation is to highlight factors the healthcare professional may not be aware of when assessing a person for vitamin B12 deficiency. Evidence was not available to be more specific. However, further testing with MMA is also recommended for

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					People who are already supplementing with B12 will have results that are misleading. The guideline should state: **Advice should be given to anyone already taking an over-the-counter supplement containing B12 that their serum B12 blood test result is likely to be inaccurate and they should be free from B12 supplementation for at least 4 weeks prior to being tested. If this is likely to result in a significant increase or return of symptoms and the patient is concerned by this potential delay to testing, then alternative testing to B12 serum should be considered such as Active B12 and MMA and Homocysteine. If the clinician is unsure they should seek expert advice.**	people with an indeterminate test result and that could include testing people with one of these factors. Stopping any vitamin B12 replacement or supplements before testing was not included as a review in this guideline and no recommendations have been made in this area.
399	Pernicious Anaemia Society	Guideline	010	007 – 014	We have serious concerns about what seem to us to be arbitrary levels to confirm diagnosis of B12 deficiency. Ranges vary significantly throughout the UK and the accuracy of lab tests also varies significantly. Current ranges are based on test results of the population in the area. This means that if there is a high proportion of people with low B12 such as elderly in	Thank you for your comment. Several stakeholders commented on the thresholds. Some thought they were too low, others thought they were too high and there was also some support that they are about right. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not.

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					the area, a low B12 will be considered normal or within range. This exposes patients who live in areas where the range average is lower, to misdiagnosis or delayed treatment. Reference intervals and cut off limits are method dependant and throughout the UK there is significant difference in Serum B12 lab results due to differing vitamin B12 assays. Different areas of the UK use different assays and cut off values. Serum vitamin B12 levels and symptoms are not correlated. Someone with Pernicious Anaemia can have mid to high B12 serum levels yet still be experiencing symptoms of B12 deficiency. Low folate, low iron and B12 in fortified foods as well as B12 supplements can all affect B12 test results. https://pubmed.ncbi.nlm.nih.gov/25959209/ Vitamin B12 and folate levels increase during treatment of iron deficiency anaemia in young adult woman – Remacha – 2015 – International Journal of Laboratory Hematology – Wiley Online Library	Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests. The committee also recommend considering MMA as a further test for people with an indeterminate active or total B12 test result. This is to capture people who may have a vitamin B12 deficiency when their test result doesn't meet the criteria for deficiency. An indeterminate result covers an active B12 of between 25 and 70 pmol per litre, and a total B12 of between 180 and 350 nanograms (133 and 258 pmol) per litre. The committee has also added a recommendation to use the laboratory's reference ranges to decide if vitamin B12 deficiency is likely when interpreting serum MMA and plasma homocysteine test results. The committee noted that there is no universal international threshold with which to define deficiency; it will vary according to how deficiency is diagnosed, the population studied and assay used for each country.

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					These guidelines make no mention of issues resulting from B12 analogues and pseudo B12 which have a very similar structure to B12 but which are not functional and cannot be utilised by cells. A clinician must be informed and consider the patients B12 result may be skewed due to non-functional B12 analogues. Beware of the Ailments of Vitamin B12 Deficiency | Semantic Scholar Since the B12 Serum test also measures B12 analogues it cannot provide reliable information about the proportion of biologically usable B12. Additionally with the change in the type of vitamin B12 assay now performed there are many false normal values (https://www.nejm.org/doi/full/10.1056/nejmc1204070, https://pubmed.ncbi.nlm.nih.gov/1546692) Around the world vitamin levels, especially B12 and D are sub-optimal and better levels would help improve preventable diseases such as dementia, hypertension, cancer, thyroid.	

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					https://www.sciencedirect.com/science/article/pii/S2212958815001226 In Japan, one of the healthiest countries in the world, anything under 370 pmol/l is considered deficient and 500 pmol/l is considered optimal. Over 1000 is recommended for the elderly. This is an area that should be further researched. In the UK there is no consensus on ranges as the four B12 assay labs are all using different ranges. Our members report that a "normal" level of Vitamin B12 in the bloodstream can be considered as being between 190 and 950 pg/ml. Some have been told that even under 190 they do not need to be concerned! It is our recommendation that the guidelines state that below 200 pg/ml is absolute deficiency and further investigation as to the cause is vital. Between 200 and 350 pg/ml is borderline and requires more testing or investigation depending on the presenting symptoms, the risk factors, and patient history.	

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					In view of the inaccuracy of Serum B12 blood tests we respectfully submit that the flag for deficiency should be set higher than that proposed by this guideline. We believe that earlier treatment of B12 deficiency and low B12 will benefit the patient in the short term but also lead ultimately to less costs relating to potentially invasive tests and repeat appointments.	
400	Pernicious Anaemia Society	Guideline	010	015 – 016	"When interpreting homocysteine test results, use clinical judgement to determine what reference range to use**."** With respect, this statement is not guidance and is unlikely to help the practitioner. Practitioners should be guided with reference ranges for homocysteine results. Instructing a clinician to make a "clinical judgement" when interpretating homocysteine results is insufficient guidance and needs to state what factors need to be taken into account and what the recommendation is with a high homocysteine result and B12 deficiency symptoms.	Thank you for your comment. We have updated this to make it more specific. The recommendation now states 'Use laboratory reference ranges to interpret plasma homocysteine test results when deciding if vitamin B12 deficiency is likely, but take into account additional factors that may increase plasma homocysteine levels (such as folate deficiency).' The committee has also updated the diagnosis recommendations so that either MMA or homocysteine are recommended for testing when recreational nitrous oxide use is suspected. The management recommendations advise using intramuscular vitamin B12 replacement where malabsorption is the cause or suspected cause of vitamin B12 deficiency. The committee did not have the evidence to show reference ranges for MMA and homocysteine and in their experience

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					Homocysteine can be raised due to issues other than malabsorption. This statement needs to state that B12 Deficiency leads to a build-up of MMA and Homocysteine and where these tests indicate that levels are raised, the patient should be treated as if they have a malabsorption issue and given IM hydroxocobalamin. Referral to a specialist haematologist with knowledge of Pernicious Anaemia is advisable. MMA levels greater than 350 nmol/L and homocysteine level greater than 15 µmol/L and Serum B12 level lower than 200pg/mL is a clear indication of B12 deficiency. Methylmalonic Acid and Homocysteine as Indicators of Vitamin B12 Deficiency in Patients with Gastric Cancer after Gastrectomy – PMC (nih.gov) Folate deficiency also increases homocysteine. MMA and homocysteine tests can be a useful tool to aid diagnosis, but they are not in themselves a diagnostic tool for B12 Deficiency.	agreed it would be better to use the laboratory reference ranges. Further text has been added to the rationale to make it clear that 'there is currently no established 'gold standard' test for diagnosing vitamin B12 deficiency. This means that while tests can be a diagnostic aid, they cannot be relied on completely to confirm or rule out deficiency (for example, a person could still have a vitamin B12 deficiency even if their test result suggests this is unlikely).'

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					MMA and Homocysteine results within normal ranges does not mean there is no B12 deficiency	
401	Pernicious Anaemia Society	Guideline	010	021 - 026	There is insufficient evidence for there to be a different level for B12 deficiency in Pregnancy and Breastfeeding. **A range with 180 at the lowest point it too low. B12 deficiency finding should start at 200 and anything between 200 and 350 should be cause for concern.** We do not understand on what basis there has been a recommendation for a higher threshold of holoTC in pregnancy or breastfeeding. Whilst holoTC does decline in pregnancy a level of 25 pmol/L should also be an appropriate level.	Thank you for your comment. Several stakeholders commented on the thresholds. Some thought they were too low, others thought they were too high and there was also some support that they are about right. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not. Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests. The committee also recommend considering MMA as a further test for people with an indeterminate active or total B12 test result. This is to capture people who may have a vitamin B12 deficiency when their test result doesn't meet the criteria for deficiency. An indeterminate result covers an active B12 of between 25 and 70 pmol per litre, and a total B12 of between 180 and 350 nanograms (133 and 258 pmol) per litre.

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						The committee has also added a recommendation to use the laboratory's reference ranges to decide if vitamin B12 deficiency is likely when interpreting serum MMA and plasma homocysteine test results. Following stakeholder comments the committee agree that there is no need for a higher threshold during pregnancy or breastfeeding and have removed the recommendation from the guideline.
402	Pernicious Anaemia Society	Guideline	010	027	Incidence of auto-immune disease in black and Asian population may be an additional risk factor to consider as patients are likely to have more than one auto-immune condition. Pernicious Anaemia is often mistakenly considered a predominantly white disease. Further research is called for in this area. Racial Patterns in Pernicious Anemia — Early Age at Onset and Increased Frequency of Intrinsic-Factor Antibody in Black Women | NEJM	Thank you for your comment. The presence of autoimmune conditions in different population groups was not included as part of a review in this guideline. However, the committee agreed that as well as this recommendation autoimmune conditions are included as a risk factor in the section on When to recognise vitamin B12 deficiency. This should hopefully capture the right people with vitamin B12 deficiency.
403	Pernicious Anaemia Society	Guideline	011	023 - 028	This section must make it clear that this applies only to a new diagnosis. If a patient is already on B12 injections because they have Pernicious Anaemia or malabsorption then these test levels are irrelevant and the guideline needs makes it clear that testing Serum B12, Active B12 or MMA while on IM B12 injections should not	Thank you for your comment. There is a recommendation in the ongoing care and follow up section about not repeating the initial test in people already receiving intramuscular injections. There are also recommendations earlier in the guideline advising healthcare professionals to ask people what over-the-counter supplementation they are taking and this has

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					be carried out as the results will not indicate anything of useful value in diagnosis, treatment or monitoring. It is crucial for practitioners to enquire whether patients have been using any oral supplements or receiving B12 injections. If these treatments are in use before doing the initial test, these guidelines will not be applicable, and alternative measures should be considered. Exploring functional markers like MMA and homocysteine, coupled with a thorough assessment of symptoms, can support a diagnosis. When there's an indication of vitamin B12 deficiency, initiating a treatment trial is recommended, followed by assessing the treatment's impact on symptomology. Should the treatment show no discernible effect, it should become essential to investigate alternative diagnoses.	been cross referred to here. This has been updated to make it clear that it includes any over-the-counter supplement containing vitamin B12, including any vitamin B12 tablets, injections and transdermal patches. A trial of vitamin B12 replacement for people whose test results suggest they don't have a deficiency was not included as part of the guideline review. Therefore, no recommendations have been made advising healthcare professionals whether or not to trial vitamin B12 replacement in this scenario.
404	Pernicious Anaemia Society	Guideline	012	001 - 005	If a patient has low Serum B12 and symptoms, MMA concentrations should be measured earlier than 3-6 months. MMA test while on supplementation will not give an accurate result	Thank you for your comment. The recommendation has been updated to advise investigating other causes as well as

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						considering a repeat of the initial test if they are still experiencing symptoms or signs 3 to 6 months later. MMA has been removed because the committee agreed that most laboratories would not allow for an MMA without testing total or active B12 first.
405	Pernicious Anaemia Society	Guideline	012	006	Identifying the cause of vitamin B12 deficiency The test for intrinsic factor is inaccurate. https://ashpublications.org/blood/article/112/6/2214/24841/How-I-treat-cobalamin-vitamin-B12-deficiency It is important that clinicians are aware of this and that whilst a positive IF/IFA test will lead to a diagnosis of Pernicious Anaemia, a negative test does not prove that the patient does not have pernicious anaemia. What is Pernicious Anaemia | Pernicious Anaemia Society (pernicious-anaemia-society.org) Limited value of testing for intrinsic factor antibodies with negative gastric parietal cell	Thank you for your comment and the references about the inaccuracy of the anti-intrinsic factor antibody test. The committee were aware of this and highlighted in the rationale that 'a positive anti-intrinsic factor antibody test strongly suggests autoimmune gastritis, a negative test is less reliable so cannot be used to rule out the condition'.

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					antibodies in pernicious anaemia - PubMed (nih.gov)	
406	Pernicious Anaemia Society	Guideline	012	007	Consider an anti-intrinsic factor antibody test for people with vitamin B12 deficiency if autoimmune gastritis is suspected and they have not previously had: this statement should read: **Conduct an anti-intrinsic factor antibody test for people with vitamin B12 deficiency if autoimmune gastritis or pernicious anaemia is suspected or if there is a family history reported of pernicious anaemia and they have not previously had:**	Thank you for your comment. Family history of an autoimmune condition which would include autoimmune gastritis is included as a risk factor and therefore likely to be a reason to suspect autoimmune gastritis. We did not look at testing everyone with a family history of autoimmune gastritis with an anti-intrinsic factor antibody test and therefore have not made a recommendation in this area.
407	Pernicious Anaemia Society	Guideline	012	019 - 022	If auto-immune gastritis including pernicious anaemia is suspected, then the tests should be as follows: Gastroscopy with gastric biopsy – a finding of atrophic gastritis supports an impaired capacity for active B12 uptake, Investigations for Coeliac disease, H-pylori, tapeworm, achlorhydria – any of which may require additional B12 supplementation.	Thank you for your comment. The committee agreed that an anti-intrinsic factor antibody test is the best first option to use. It is good at determining that people have a diagnosis if the test is positive. It is also widely available to and used by GPs. In the absence of evidence of cost effectiveness, the committee agreed to put the further investigations in order of cost per test unit. An anti-gastric parietal cell antibody test has the lowest unit cost whereas gastroscopy has the highest.

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					A Gastrin test may help indicate the presence of abnormal cells, ulcers or tumours but does not confirm a diagnosis of B12 Deficiency. A CobaSorb test can help prove that a patient can absorb low dose crystalline cobalamin in oral supplementation but it is of no use to patients with a malabsorption from food. A CobaSorb test can be used to clarify whether the patient has lost the capacity for an active uptake of B12 or not. It should also be highlighted that the CobaSorb test is not able to answer the question of causes of B12 malabsorption, especially those related to food cobalamin malabsorption (e.g. in the elderly)."	Investigations for coeliac disease are covered in the NICE guideline on Coeliac disease and this is cross referred to rather than repeating the recommendations here.
408	Pernicious Anaemia Society	Guideline	013	007 - 008	Managing vitamin B12 deficiency "how long it usually takes for treatment to take effect and when they are likely to see an improvement in their symptoms" This guidance is inadequate since there is large variation in the length of time for symptoms to improve amongst patients with many different factors affecting this. A survey of 2798 respondents with vitamin B12 deficiency from multiple causes looked	Thank you for your comment. Following stakeholders' comments this recommendation has been updated to provide more detail. It now states: Explain to people starting treatment with vitamin B12 replacement: • that response to treatment can vary and depends on the cause of the vitamin B12 deficiency • that their symptoms could start to improve within 2 weeks, but this may take up to 3 months

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					at the length of time patients started to see improvements in symptoms once starting treatment. They found respondents took as little as less than two weeks to to over 3 months to see an improvement in symptoms. Therefore we see an massive interindividual variation in symptom improvement (https://stichtingb12tekort.nl/enquete-2015/herstel/). It is important to manage expectations and explain that the road to recovery from symptoms resulting from B12 deficiency can be long and is not always straightforward. It may, at times, not progress in a positive way. Many patients will suffer setbacks along the way and may encounter other problems such as other nutrient deficiencies. It is our member's experience that health care practitioners currently do not have the knowledge to provide accurate information about this matter or even offer guidance. A universal information sheet could significantly benefit both clinicians and patients. Such a resource would aid clinicians in effectively conveying	• that it can take much longer for symptoms to disappear altogether, and that although their symptoms could get worse initially during treatment, this should improve • when to seek medical help (without waiting for any scheduled appointments) if their symptoms have not improved, get worse or return, or they get new symptoms, after starting treatment.

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					information to patients and empower patients to carry essential knowledge home.	
409	Pernicious Anaemia Society	Guidelines	013	014 - 016	"deficiency caused by malabsorption 1.5.3 Offer lifelong intramuscular vitamin B12 replacement to people if autoimmune gastritis is the cause, or suspected cause, of vitamin B12 deficiency" The word "offer" is misleading. People with Pernicious Anaemia or malabsorption issues need B12 replacement for life. This section must refer to pernicious anaemia as well as autoimmune gastritis because these terms are not interchangeable. This section needs to give an explanation and guidance on the frequency of treatment and make it clear to clinicians that there is insufficient research to explain why some patients need more frequent injections than others and that clinicians should be led by the patient feedback on reversal of symptoms. The current NICE guidelines and those from the British Society of Haematologists (BSH) are frequently reported by our	Thank you for your comment. The use of the word 'offer' is standard NICE practice. NICE uses 'offer' (or words such as 'measure', 'advise', or 'refer') to reflect a strong recommendation. The guideline has been updated to acknowledge the difference between autoimmune gastritis and pernicious anaemia and provide a more detailed reason as to why the term 'pernicious anaemia' has not been used. This explains that autoimmune gastritis is sometimes referred to as pernicious anaemia which is a separate condition that can be a consequence of chronic, severe vitamin B12 deficiency, including deficiency caused by autoimmune gastritis. However, pernicious anaemia in its true sense (that is 'a life-threatening anaemia') is now extremely rare because of developments in testing and treatment for, and greater awareness of, vitamin B12 deficiency. For this reason, and to prevent any confusion with autoimmune gastritis, we have not used the term 'pernicious anaemia' in the recommendations. With regard to your specific bullet points: • NICE does not generally include dosages in recommendations where they are available in the BNF or SPC. Loading doses are covered in the BNF and therefore not included in the guideline.

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					members as being unknown to, or misunderstood by, primary care physicians. This guideline needs to state that people with Pernicious Anaemia should: • receive every other day IM injections until symptoms resolve or until no further improvement is reached. • receive sufficiently regular IM injections which continue to keep their symptoms at bay or under control based on patient feedback. The BSH guidelines suggest every 12 weeks or every 8 weeks for those with neurological symptoms but our members report this is frequently insufficient for many patients with Pernicious Anaemia. • review symptoms and frequency of IM injections with the patient and adjust frequency according to the patient's feedback and clinical review of their symptoms. • Treatment should be for life and may need to vary in frequency and dosage from time to time according	• No evidence was identified relating to frequency of vitamin B12 replacement and the committee made a research recommendation relating to this. • The recommendations on ongoing care and follow up cover when to review symptoms and when to consider changing the frequency of injections. • Lifelong intramuscular vitamin B12 replacement is recommended for people if autoimmune gastritis is the cause or suspected cause of vitamin B12 deficiency. • There is a recommendation not to repeat the initial test for people who are receiving intramuscular injections.

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					to the patient's needs and symptoms. Testing Serum B12 whilst on IM injections is not required.	
410	Pernicious Anaemia Society	Guidelines	014	003 - 004	"offer either intramuscular or oral vitamin B12 replacement, based on the person's preference." For patients with Pernicious Anaemia, the delivery of B12 should not be a matter of "preference" but based on the treatment which resolves the symptoms and should take account of the patient's needs and likely compliance. Newly diagnosed patients are not usually sufficiently informed to make the most appropriate choice. Most people if given a choice between a potentially painful IM injection and a tablet would opt for the tablet but we already know that oral supplementation is insufficient for those with Pernicious Anaemia and for those with low B12 and neurological symptoms. A clinician cannot leave it to the patient to express a preference unless it is made clear that a tablet might not (and indeed is unlikely to) work.	Thank you for your comment. Following stakeholder comments the recommendations have been updated. Intramuscular injections are offered to people with autoimmune gastritis or who have had a total gastrectomy or complete terminal ileal resection. For all other people with vitamin B12 deficiency because of malabsorption intramuscular injections are considered over oral replacement.

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411	Pernicious Anaemia Society	Guideline	014	005	"Medicine-induced vitamin B12 deficiency" This section needs to acknowledge that those with Pernicious Anaemia may also be on other medication for autoimmune diseases or diabetes and/or may have been prescribed PPIs. In these cases, the need for more frequent B12 IM injections may arise or alternative treatments or the cessation of PPIs should be offered to support the treatment of other conditions	Thank you for your comment. No evidence was identified for the frequency of doses therefore no recommendations have been made in this area.
412	Pernicious Anaemia Society	Guideline	014	020 - 021	"vitamin B12 deficiency caused by nitrous oxide, based on the person's preference." The treatment of B12 deficiency by oral or IM is not a matter of preference, it should be based on the root cause, reversal of symptoms and patient compliance.	Thank you for your comment. There is no clear evidence to distinguish which out of oral or intramuscular vitamin B12 replacement was more clinically or cost effective for medicine induced vitamin B12 deficiency. Therefore the committee agreed to recommend either oral or intramuscular vitamin B12 replacement.
413	Pernicious Anaemia Society	Guideline	015	013 - 014 023 - 024	"Explain that supplements contain varying amounts and types of vitamin B12 and tell them where to find information on how to improve their intake of the vitamin including information about sources of vitamin B12 in food" This section should clarify that it does not relate to patients with a diagnosis of Pernicious Anaemia.	Thank you for your comment. The recommendations related to management of vitamin B12 deficiency have been split into separate sections to make it clearer which apply to which cause. There is a separate section for people where malabsorption is the cause or suspected cause of vitamin B12 deficiency. A review of the effectiveness of over-the-counter (OTC) supplements was not included as part of the scope of the guideline and therefore no recommendations have been

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					Over-the-counter (OTC) Supplements in the UK are unregulated and not necessarily an adequate solution to B12 deficiency and are insufficient to treat Pernicious Anaemia. If recommending an OTC supplement, the clinician needs to suggest a dose range and preferred type of cobalamin. They also need to ensure they are verified supplements. The guidance that OTC products may contain cyanocobalamin, adenosyl-cobalamin or methyl-cobalamin or hydroxocobalamin without explaining the difference between these types in terms of absorption and why a patient should choose one over the other has little value. There is insufficient research to indicate that each of these forms of cobalamin are equally effective and in what dose. This section should include an explanation particularly for vegans that analogue or pseudo B12 supplements such as spirulina, nori etc can be harmful to the absorption of B12. We are concerned in general by this guidance because there is a general lack of	made on whether to suggest them and what dosage to use. The recommendation relating to OTC oral supplements is to highlight which supplements are appropriate. This is because some oral supplements that are labelled as containing vitamin B12 do not contain a form that is appropriate to use as vitamin B12 replacement. Further detail has been added to the rational explaining that pseudo supplements or vitamin B12 analogues are not appropriate for treating a vitamin B12 deficiency. The section on 'Information for the public' on this guideline's web page also provides links to other organisations' websites which provide more detailed advice directly written for people with suspected or confirmed vitamin B12 deficiency. Investigating and managing complications related to vitamin B12 deficiency and cofactors were not included as part of the scope of the guideline. Therefore they were not included as part of the guideline reviews and no recommendations have been made related to this.

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					knowledge about good sources of B12 in the health care profession and a significant amount of misinformation online. Clinicians need to advise patients to seek assistance from credible sources according to their cause of B12 deficiency such as reputable Patient Advocacy and Support Groups, the Vegan Society etc. Clinicians need to make it clear to patients that B12 does not work in isolation in the body and that an increase in B12 is likely to require adequate folate, iron, potassium and magnesium intake through a healthy diet, suitable blood test monitoring and supplementation where required. Vitamin D is also often low in people with B12 deficiency.	
414	Pernicious Anaemia Society	Guideline	016	017 - 021	Unknown causes of vitamin B12 deficiency This should clearly state that the clinician should be led by symptoms and the resolution of symptoms with B12 supplementation	Thank you for your comment. The expectation is that healthcare professionals will take symptoms into account when considering treatment. Symptoms are also covered in the recommendations related to ongoing care and follow up.
415	Pernicious Anaemia Society	Guideline	017	001	1.6 Ongoing care and follow-up We believe the guidelines must distinguish between the appropriate follow up for people with Pernicious Anaemia (and other	Thank you for your comment. The ongoing care and follow up recommendations have been updated to make them clearer.

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					malabsorption issues) and those with dietary B12 deficiency. With dietary deficiency one can assume that with compliance and the cessation of deficiency symptoms, the patient need only further consult their primary care giver if symptoms return. For those who are on Intra-muscular (IM) B12 for life due to Pernicious Anaemia or other malabsorption reasons, advice should be given about the advisability of adequate folate intake through diet and supplementation and repeat blood tests for folate and iron should be conducted if symptoms are slow to resolve, return or increase. Regular iron blood tests are advisable for individuals with Pernicious Anaemia and autoimmune gastritis. This recommendation is due to destruction of parietal cells, which not only leads to a deficiency in intrinsic factor required for vitamin B12 absorption but also affects the production of hydrochloric acid. This acid essential for dissociating iron from its food-bound protein, leading to a poor absorption of iron. A study showed that 20% of individuals with Pernicious Anaemia have	The committee agreed the decision to optimise, change, continue or stop treatment should be based on the symptoms. Investigating and managing complications related to vitamin B12 deficiency and cofactors were not included as part of the scope of the guideline. Therefore they were not included as part of the guideline reviews and no recommendations have been made related to this. The guideline recommends not repeating the initial test for people on intramuscular injections. The recommendations have been updated to make it clearer that if a person has or is suspected of having an irreversible cause of vitamin B12 deficiency then treatment should continue even if symptoms improve. The committee hope this guideline will raise awareness of vitamin B12 deficiency among healthcare professionals. No evidence was found related to the adverse events of intramuscular injections, therefore no recommendations have been made in this area. No evidence was found for screening for gastric cancer and therefore the committee made a research recommendation in this area.

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					iron deficiency (https://pubmed.ncbi.nlm.nih.gov/3806900/.) Once on IM B12 injections of hydroxocobalamin no further testing of Serum B12 level is appropriate. Patients with Pernicious Anaemia on regular IM injections likely will show a high level of Serum B12, this is not an indication to reduce frequency of, or stop, treatment. Education of clinicians needs to be improved around the non-toxicity of B12 for Pernicious Anaemia patients alongside ensuring clinicians are aware that B12 is not addictive and that high levels caused by injection (rather than high B12 levels naturally occurring) are not a concern or risk indicator for cancer. Patients with pernicious anaemia should be made aware of the increase in risk of NETs and stomach cancer, told what signs to look out for and be offered routine gastroscopy check-ups at suitable intervals.	
416	Pernicious Anaemia Society	Guideline	018	011 - 017	Please make it clear that for patients with PA, treatment with Intra-Muscular B12 is for life and if their symptoms have not	Thank you for your comment. Intramuscular injections are recommended for people with confirmed or suspected malabsorption. The follow up recommendation for people

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					improved, increasing the frequency of injections, and monitoring their iron and folate levels is required.	with an irreversible cause of vitamin B12 deficiency has been updated to state 'continue with lifelong intramuscular injections, even if their symptoms have improved, or are no longer present'. No evidence was identified on the frequency of injections and the committee made a recommendation for research in this area. Investigating and managing complications related to vitamin B12 deficiency and cofactors were not included as part of the scope of the guideline. Therefore they were not included as part of the guideline reviews and no recommendations have been made related to this.
417	Pernicious Anaemia Society	Guideline	019	004 - 005	"Do not repeat the initial diagnostic test in people who are having intramuscular vitamin B12 replacement." This should state specifically that the B12 Serum blood test that should not be repeated or the result must be ignored. Please make it clear in the guidelines that people on Intra-Muscular injections are likely to show high levels of Serum B12 and this is NOT a reason to stop or reduce treatment. Our members regularly report that healthcare professionals are woefully	Thank you for your comment. The recommendation's aim is to reflect that none of the tests done at the initial diagnosis should be repeated. The committee agreed there was no reason to repeat testing for people having intramuscular injections and that response to treatment should be based on the change in symptoms.

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					ignorant about B12 levels and often lecture or mislead patients about toxicity or overdosing and threaten to stop treatment if the patient is additionally supplementing alongside NHS prescribed treatment.	
418	Pernicious Anaemia Society	Guideline	019	006 - 020	Increasing the frequency of injections is important for people with Pernicious Anaemia. We do not agree with the statement to increase the "dose". Increasing the dose is likely only to result in excess being excreted in urine and excess B12 will not be absorbed into cells.	Thank you for your comment. The recommendation has been updated so it only refers to the frequency of injections and not the dose.
419	Pernicious Anaemia Society	Guideline	019	21 - 23	"If the cause, or suspected cause, of vitamin B12 deficiency has been resolved and the person's symptoms have improved, or are no longer present" This statement should start with "other than in the case of Pernicious Anaemia or Autoimmune Gastritis" as patients with these conditions require vitamin B12 therapy for life.	Thank you for your comment. As autoimmune gastritis is an irreversible cause of vitamin B12 deficiency the cause would not have been resolved. The recommendation for follow up on people with an irreversible cause of vitamin B12 replacement whose symptoms have improved has been updated to state: 'continue with lifelong intramuscular injections, even if their symptoms have improved or are no longer present'.
420	Pernicious Anaemia Society	Guideline	020	008	The word consider must not be used. A referral to a gastrologist or an endoscopy should be offered as routine if any symptoms present, specifically upper GI	Thank you for your comment. We did not have the evidence to make a recommendation that all people should be referred for gastrointestinal endoscopy. Therefore, the strength of the recommendation in this guideline matches the strength of the

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					symptoms. This is a very important area that needs to be improved in the UK. Most gastric cancers are found in stages 3 and 4 in which curative care is usually not available, and we only provide palliative care. The 5-year survival rate is 20% at the later stages. Patients should be referred for an endoscopy upon diagnosis of pernicious anaemia to rule out stomach cancer. A patient with pernicious anaemia and upper GI symptoms present MUST be referred to gastroenterology and undergo an endoscopy. Other countries have guidelines including EUs Management of epithelial precancerous conditions and lesions in the stomach (MAPS II) however the UK currently lacks a system for monitoring for these patients. Stomach cancer is difficult but vital to detect in the early stages. If patients have an increased risk such as is the case for Pernicious Anaemia this should be flagged and discussed with a gastroenterologist without delay	recommendations on upper gastrointestinal tract cancers in NICE's guideline on suspected cancer.

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					Vitamin B12 or folate deficiency anaemia - Complications - NHS (www.nhs.uk) Stomach cancer statistics | Cancer Research UK Cancer statistics, 2014 - PubMed (nih.gov) Gastric cancer in autoimmune gastritis: A case-control study from the German centers of the staR project on gastric cancer research - PubMed (nih.gov) Weis	
421	Pernicious Anaemia Society	Guideline	020 021	014 - 016 001 - 002	The definition of irreversible cause must include pernicious anaemia. Pernicious Anaemia is a lifelong, irreversible condition.	Thank you for your comment. The guideline has been updated to acknowledge the difference between autoimmune gastritis and pernicious anaemia and provide a more detailed reason as to why the term 'pernicious anaemia' has not been used. This explains that autoimmune gastritis is sometimes referred to as pernicious anaemia which is a separate condition that can be a consequence of chronic, severe vitamin B12 deficiency, including deficiency caused by autoimmune gastritis. However, pernicious anaemia in its true sense (that is 'a life-threatening anaemia') is now extremely rare because of developments in testing and treatment for, and greater awareness of, vitamin B12 deficiency. For this reason, and to prevent any confusion with autoimmune gastritis, we have not used the term 'pernicious anaemia' in the recommendations.
422	Pernicious Anaemia Society	Guideline	021	008 - 011	This statement wrongly implies that B12 replacement (IM injections) and oral	Thank you for your comment. This section is used to describe how specific terms have been used in the guideline recommendations. Therefore, when the guideline

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					supplementation are interchangeable as treatment for B12 deficiency. This is incorrect and will lead to wrong treatment for patients with Pernicious Anaemia and malabsorption issues. There is insufficient research to suggest that even high dose oral supplementation of B12 helps resolve neurological symptoms such as those encountered by patients with Pernicious Anaemia. High dose oral supplementation is also likely ineffective since large amounts are excreted without absorption even by people with no malabsorption issue.	recommendations state 'vitamin B12 replacement' this could be either oral or intramuscular. Where one of those two options is recommended it has been made clear within the recommendations. There is no intention in this section to imply one method of vitamin B12 replacement, whether oral or intramuscular, is better than the other.
423	Pernicious Anaemia Society	Guideline	021	008 - 012	We believe the use of the term "B12 Replacement" here is too vague to be a useful guideline. It should be clear that replacement is either B12 IM injections or prescribed 1000mcg B12 oral tablets. Too often health care professionals refer Pernicious Anaemia patients with B12 deficiency to purchase their own over-the-counter oral tablets as a replacement therapy to reduce costs, particularly in England where prescription	Thank you for your comment. This section is used to describe how specific terms have been used in the guideline recommendations. Therefore, when the guideline recommendations state 'vitamin B12 replacement' this could be either oral or intramuscular. Where one of those two options is recommended it has been made clear within the recommendations. There is no intention in this section to imply one method of vitamin B12 replacement, whether oral or intramuscular, is better than the other, nor what dose should be used.

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					charges apply. OTC supplements are not subject to any regulation and often do not contain sufficiently high level B12 to reverse symptoms caused by B12 deficiency. People with a dietary deficiency and no other reason for malabsorption may respond to OTC B12 supplements or changes to their diet.	
424	Pernicious Anaemia Society	Guideline	021	018 - 020	**Vitamin B12 replacement What is the clinical and cost effectiveness of vitamin B12 replacement for vitamin B12 deficiency, including the dose, frequency, and route of administration.** This is not an adequately expressed research question. There are far too many variables in such a question due to the different reasons for B12 Deficiency, the lack of existing research into the causes of malabsorption, the inadequate tests to determine B12 deficiency and the test for Intrinsic Factor/IFA as well as the huge variation in symptoms and resolution of symptoms in the individual patient. The James Lind Alliance Priority Setting Partnership with the Pernicious Anaemia	Thank you for your comment. The research recommendations here are written as broad questions giving an indication of what area and interventions are considered for further research. More detail is provided in the appendix of the evidence report linked to just below the research recommendation.

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					Society listed the Top 10 Priority research questions determined by those with Pernicious Anaemia Pernicious Anaemia Top 10 | James Lind Alliance (nihr.ac.uk) We encourage research into these 10 Uncertainties because this will greatly help people with Pernicious Anaemia and B12 Deficiency. The other areas of research identified in this guideline are welcomed.	
425	Pernicious Anaemia Society	Guideline	022	005	We strongly support research into the area of self-administration as we believe that patient led self-care and control of symptoms will both improve the patient experience and reduce cost to the NHS,	Thank you for your support for the recommendation.
426	Pernicious Anaemia Society	Guideline	022	030 - 031	With respect, the statement "This could prevent the effects of vitamin B12 deficiency becoming permanent" is not an accurate reflection of what happens. B12 Deficiency cause neurological, gastric, and psychological symptoms. There is a high risk that without treatment neurological symptoms are irreversible. Many of our members live with numbness, affected gait, tinnitus etc due to delayed diagnosis and inadequate treatment.	Thank you for your comment. We believe this applies to page 33 lines 30 to 31 rather than page 22. The statement is meant to imply that people who are suspected of having autoimmune gastritis should be treated as though they have autoimmune gastritis. This would then hopefully prevent the effects of the deficiency becoming permanent.

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427	Pernicious Anaemia Society	Guideline	024 - 025	009 onwards	"Why the committee made the recommendations. The committee agreed it was important to give people information about vitamin B12 deficiency that is tailored to their individual circumstances, including the condition's various symptoms and causes, and what they can expect from investigations and treatment. They also highlighted difficulties in diagnosing vitamin B12 deficiency because its symptoms are also linked to many other conditions. Based on their experience and expertise, the committee also agreed that the limitations of diagnostic tests should be explained to people with suspected vitamin B12 deficiency. In addition, they highlighted situations where it could be difficult to interpret the test results, such as results that are indeterminate or are affected by the use of over-the-counter supplements. Having these discussions would mean people know what to expect from testing and could prevent any distress or concern if their results are unclear." Whilst we support and acknowledge the sentiment of this paragraph above in the guidelines, unfortunately these points have not translated through to the draft	Thank you for your comment. The recommendations have been made based on the available evidence. Recommendations related to tailoring healthcare services to the individual are covered in the patient experience guideline which is cross referred to in this guideline. The guideline does not recommend a specific frequency for injections. Where the frequency of injections is mentioned in the guideline it is to illustrate the cost of treatment and when intramuscular injections are likely to be cost effective. NICE does not generally include dosages in recommendations where they are available in the BNF or SPC. A dosage may be included if this information is not available, or the committee agrees that there needs to be a change to current recommended dosages, for example because of new evidence. Loading doses are covered in the BNF and therefore not included in the guideline. The guideline did look for clinical evidence relating to the frequency of intramuscular injections, however no evidence was identified and the committee made a research recommendation.

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					guidelines. There are two key elements here: • INDIVIDUAL CIRCUMSTANCES • DIFFICULTY IN DIAGNOSING (including inaccurate tests) It is our view that these two points are inadequately expressed in the guidelines and unless our comments are included, we do not believe that they will be addressed making the guidelines not fit for purpose. Currently, the guidelines do not effectively convey the importance of tailored treatment and there is urgent need for precise alignment between rationale and guideline content. Present Guidelines recommend 1mg IM B12 every 2-3 months. This regimen is insufficient for a substantial number of patients. Guidelines should clearly state that treatment should be tailored to individual requirements in section 1.5 Managing vitamin B12 deficiency. Practitioners should feel encouraged to optimise IM B12 treatment frequency. If symptoms return or their severity increases before the next scheduled injection, an increased treatment regimen should be	

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					implemented and an assessment of symptomatology to evaluate its impact.	
428	Pernicious Anaemia Society	Guideline	025	012 - 014	How the recommendations might affect practice. The recommendations reflect current practice and are therefore unlikely to have a big resource impact. With respect these, guidelines do not reflect current practice for our members either in the diagnosis or treatment of B12 deficiency whether arising from Pernicious Anaemia or otherwise. There is a general lack of knowledge and awareness about B12 Deficiency and an even greater number of misunderstandings about Pernicious Anaemia in the healthcare profession. We believe that if these guidelines, adopting our recommendations, are communicated to primary care, not only will the experience of the patient improve but importantly there will be a reduced cost to the NHS. Women with B12 deficiency are routinely offered costly anti-depressants which are often unnecessary. Our members report repeated visits to their health care professional which are a waste	Thank you for your comment. This statement relates to the recommendations on providing people with suspected or confirmed vitamin B12 deficiency with information about their condition. The committee agreed that providing information is current practice and therefore there would not be a resource impact. The statement has been updated to make it clear that it is providing information and support that will not lead to a resource impact. The likely impact of specific recommendations related to diagnosis and treatment are discussed in those rationales.

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					of valuable resource. Patients with Pernicious Anaemia or B12 deficiency who are more speedily diagnosed and treated can return more quickly to a functional role in the economy and society.	
429	Pernicious Anaemia Society	Guideline	025	020 - 024	Using the word "and" rather than "or" this guideline will miss or delay a large number of B12 deficient patients.	Thank you for your comment. No evidence was identified to make a strong recommendation that people with one of the symptoms or signs without a risk factor, or one of the risk factors without a symptom or sign, should be tested. The committee agreed that the symptoms and signs associated with vitamin B12 deficiency vary and can also be indicative of other conditions. Without the evidence, making a recommendation to test people with just one of the symptoms or signs or risk factor would hugely increase resource impact without any evidence of benefit. The committee recognise that there may be people in whom there is a suggestion of vitamin B12 deficiency without a risk factor, however this would vary and need to be assessed on a case-by-case basis. Consequently, they recommended that clinical judgement would need to be used to decide if a person should be tested in these circumstances.
430	Pernicious Anaemia Society	Guideline	026	008 - 009	Unexplained fatigue would be better expressed as profound fatigue without obvious lifestyle cause.	Thank you for your comment. The committee discussed changing the term 'unexplained fatigue' to 'profound fatigue without an obvious lifestyle cause'. However, they agreed that this may not be the only description for the person's fatigue and this guideline covers dietary deficiency and not everyone would describe their fatigue as 'profound'.

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431	Pernicious Anaemia Society	Guideline	026 029	015 - 019 030 - 031	With respect, the evidence of one health care professional on this point is insufficient and this area needs a call for further research.	Thank you for your comment. As well as the testimony from the expert witness the guideline looked for evidence in this area. The committee also discussed this based on their experience before writing the recommendations. There was no evidence to suggest that symptoms, signs or risk factors would be different during pregnancy.
432	Pernicious Anaemia Society	Guideline	027	008	"Autoimmune gastritis" and "Pernicious Anaemia", these terms are not interchangeable. Pernicious Anaemia is the known and used term by health care professionals and patients and appears on medical records and in research papers.	Thank you for your comment. The guideline has been updated to acknowledge the difference between autoimmune gastritis and pernicious anaemia and provide a more detailed reason as to why the term 'pernicious anaemia' has not been used. This explains that autoimmune gastritis is sometimes referred to as pernicious anaemia which is a separate condition that can be a consequence of chronic, severe vitamin B12 deficiency, including deficiency caused by autoimmune gastritis. However, pernicious anaemia in its true sense (that is 'a life-threatening anaemia') is now extremely rare because of developments in testing and treatment for, and greater awareness of, vitamin B12 deficiency. For this reason, and to prevent any confusion with autoimmune gastritis, we have not used the term 'pernicious anaemia' in the recommendations.
433	Pernicious Anaemia Society	Guideline	027	022 024 - 025	Nitrous oxide is known to inactivate vitamin B12 in the body. Nitrous Oxide has a significant impact on people with Pernicious Anaemia. Patients with Pernicious Anaemia should be offered alternatives to Gas and Air or be given additional B12 IM hydroxocobalamin.	Thank you for your comment. Recommendations related to nitrous oxide use during labour were not covered in this guideline as they are covered in MHRA guidance on Nitrous oxide: neurological and haematological toxic effects.

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434	Pernicious Anaemia Society	Guideline	028	011	Asking about supplementation without specific guidance as to what to do about carrying out blood tests does not provide sufficient help to the practitioner. A practitioner should advice to stop supplementation before the test, or if this is likely to result in a worsening of symptoms, to take this into account when interpreting the results.	Thank you for your comment. This recommendation is to highlight factors the healthcare professional may not be aware of when assessing a person for vitamin B12 deficiency. Evidence was not available to be more specific. However, further testing with MMA is also recommended for people with an indeterminate test result and that could include testing people with one of these factors. A review on stopping medications before testing was not included as part of the guideline.
435	Pernicious Anaemia Society	Guideline	028	015 – 016	With respect, the committee for this guideline is unlikely to have sufficient experience in determining the difference in accuracy of Serum and Active B12 tests. There is not sufficient scientific evidence to suggests an Active B12 test is more accurate or reliable and it remains fraught with the same issues as a Serum B12 test when B12 is supplemented.	Thank you for your comment. The committee made the statement based on their experience. However, they have also made it clear that there is not the evidence to support one test over the other and have also made a research recommendation in this area.
436	Pernicious Anaemia Society	Guideline	029	021	We are concerned by the arbitrary levels of the ranges, the variation in assays throughout the UK and the inaccuracy of results due to supplementation make blood tests for B12 no more than an indicator to be considered alongside symptoms. There needs to be an attitude shift towards a presumption of B12 deficiency at low levels even within range	Thank you for your comment. Several stakeholders commented on the thresholds. Some thought they were too low, others thought they were too high and there was also some support that they are about right. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not.

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						Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests. The committee also recommend considering MMA as a further test for people with an indeterminate active or total B12 test result. This is to capture people who may have a vitamin B12 deficiency when their test result doesn't meet the criteria for deficiency. An indeterminate result covers an active B12 of between 25 and 70 pmol per litre, and a total B12 of between 180 and 350 nanograms (133 and 258 pmol) per litre. The committee has also added a recommendation to use the laboratory's reference ranges to decide if vitamin B12 deficiency is likely when interpreting serum MMA and plasma homocysteine test results.
437	Pernicious Anaemia Society	Guideline	029	027 - 028	Treatment with vitamin B12 replacement is not expensive, nor is it thought to be harmful. There is no evidence to suggest that treatment with B12 is harmful and the resolving of symptoms must take priority for the benefit of the patient's health and wellbeing.	Thank you for your comment. The committee agree that resolving symptoms is a priority.

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438	Pernicious Anaemia Society	Guideline	031 032	027 - 029 001	The committee should refer to Pernicious Anaemia as well as autoimmune gastritis, they are not the same condition, and it is dangerous to patients with an existing diagnosis and those who will be diagnosed with Pernicious Anaemia for these guidelines to neglect to mention this condition.	Thank you for your comment. The guideline has been updated to acknowledge the difference between autoimmune gastritis and pernicious anaemia and provide a more detailed reason as to why the term 'pernicious anaemia' has not been used. This explains that autoimmune gastritis is sometimes referred to as pernicious anaemia which is a separate condition that can be a consequence of chronic, severe vitamin B12 deficiency, including deficiency caused by autoimmune gastritis. However, pernicious anaemia in its true sense (that is 'a life-threatening anaemia') is now extremely rare because of developments in testing and treatment for, and greater awareness of, vitamin B12 deficiency. For this reason, and to prevent any confusion with autoimmune gastritis, we have not used the term 'pernicious anaemia' in the recommendations.
439	Pernicious Anaemia Society	Guideline	032	011 - 012	The committee are wrongly using the term autoimmune gastritis in this context. Positive Intrinsic Factor Antibodies is indicative of pernicious anaemia. Negative IFA result does not mean you do not have Pernicious Anaemia.	Thank you for your comment. The guideline has been updated to acknowledge the difference between autoimmune gastritis and pernicious anaemia and provide a more detailed reason as to why the term 'pernicious anaemia' has not been used. This explains that autoimmune gastritis is sometimes referred to as pernicious anaemia which is a separate condition that can be a consequence of chronic, severe vitamin B12 deficiency, including deficiency caused by autoimmune gastritis. However, pernicious anaemia in its true sense (that is 'a life-threatening anaemia') is now extremely rare because of developments in testing and treatment for, and greater awareness of, vitamin B12 deficiency. For this reason, and to prevent any confusion

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						with autoimmune gastritis, we have not used the term 'pernicious anaemia' in the recommendations. The rationale includes the statement that 'The evidence also showed that, while a positive anti-intrinsic factor antibody test strongly suggests autoimmune gastritis, a negative test is less reliable so cannot be used to rule out the condition'
440	Pernicious Anaemia Society	Guideline	032	026 - 028	We agree that there is no impact on cost here. However, the use of autoimmune gastritis is wrong, currently primary care providers use the term pernicious anaemia as do research papers, medical records, and patients.	Thank you for your comment. The guideline has been updated to acknowledge the difference between autoimmune gastritis and pernicious anaemia and provide a more detailed reason as to why the term 'pernicious anaemia' has not been used. This explains that autoimmune gastritis is sometimes referred to as pernicious anaemia which is a separate condition that can be a consequence of chronic, severe vitamin B12 deficiency, including deficiency caused by autoimmune gastritis. However, pernicious anaemia in its true sense (that is 'a life-threatening anaemia') is now extremely rare because of developments in testing and treatment for, and greater awareness of, vitamin B12 deficiency. For this reason, and to prevent any confusion with autoimmune gastritis, we have not used the term 'pernicious anaemia' in the recommendations.
441	Pernicious Anaemia Society	Guideline	033	004 - 012	Our member experience is that there is no follow up, discussion of reversal of symptoms, and a significant amount of lack of empathy or understanding about the debilitating nature of B12 deficiency symptoms in primary care. Contrary to providing optimal care, many people with B12 Deficiency are left to take matters in	Thank you for your comment. The committee hope this guideline will improve awareness of vitamin B12 deficiency and improve outcomes for patients.

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					their own hands and resort to alternative methods of obtaining sufficient B12. It is not without irony that we point out that a B12 injection can be obtained in the UK through a beauty salon with no restriction on frequency or dose and without prior testing.	
442	Pernicious Anaemia Society	Guideline	034	024 - 026	Simply listing the different types without explaining their different purpose or efficacy is not helpful in this guideline. We do not believe there is sufficient research available yet to provide the answer to this point.	Thank you for your comment. We think this relates to page 35 lines 24 to 26 where the draft guideline stated "Therefore, the committee agreed to list the types of vitamin B12 people should look out for should they wish to buy supplements". This relates to recommendation 1.5.13 of the draft guideline. The aim of this recommendation is to ensure people are aware that should they wish to purchase supplements then only some would be considered suitable as a vitamin B12 replacement. We have added a statement to the recommendation advising that 'some supplements do not contain enough, or the right type, of vitamin B12 to be effective' to make the purpose of the recommendation clearer.
443	Pernicious Anaemia Society	Guideline	039	010 - 020	We fully support the committee's view that based on symptoms reported by the patient, increasing the frequency of IM injections for patients who are on the treatment is the correct recommendation.	Thank you for your comment and support for the recommendation.
444	Pernicious Anaemia Society	Guideline	039 040	023 - 024 003	It is our members experience that patients with Pernicious Anaemia are not offered a routine annual appointment.	Thank you for your comment. The recommendation has been updated to 'advise them to come back if symptoms get worse, reappear, or they get new symptoms'. The guideline recommends not retesting people who are having

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					This recommendation needs to be communicated as education to primary care. Further this recommendation must not be used as an opportunity to mistakenly re-test for IF/IFA or blood serum where a diagnosis of Pernicious Anaemia or malabsorption has been made and treatment is working. With respect, this would have an impact on current practice and would contribute to increased appointments as routine which may not be necessary. We suggest that patients with Pernicious Anaemia or malabsorption of B12 on long term IM B12 injections are encouraged to return to their health care professional when symptoms return, increase or change to discuss the appropriate change to their frequency and that patients with Pernicious Anaemia are, in particular, given routine gastro consultations.	intramuscular vitamin B12 replacement and the committee hope this will be adhered to.
445	Pernicious Anaemia Society	Evidence Review C	007	015	The evidence review indicates that there is no "gold standard" clinical or biochemical test available to diagnose B12 deficiency but the Guideline fails to mention this.	Thank you for your comment. This has been added to the rationales in the diagnosis section.

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446	Pernicious Anaemia Society	Evidence Review C	009		Chart The summary of studies chart specifically gives the references: Deficient: serum total vitamin B12 levels below 200 pg/mL Borderline: serum total vitamin B12 levels ranging from 200 to 350 pg/mL The guideline has arbitrarily taken a lower value of 190 to determine deficiency which all other evidence and experience suggests is too low. We are concerned that by using average reference ranges based on tested population, the figure for deficiency will become lower and that people who live in certain areas will be disadvantaged if the bottom range is low due to population age or high incidence of B12 deficiency testing which reduces the average.	Thank you for your comment. Several stakeholders commented on the thresholds. Some thought they were too low, others thought they were too high and there was also some support that they are about right. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not. Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests. The committee also recommend considering MMA as a further test for people with an indeterminate active or total B12 test result. This is to capture people who may have a vitamin B12 deficiency when their test result doesn't meet the criteria for deficiency. An indeterminate result covers an active B12 of between 25 and 70 pmol per litre, and a total B12 of between 180 and 350 nanograms (133 and 258 pmol) per litre. The committee has also added a recommendation to use the laboratory's reference ranges to decide if vitamin B12 deficiency is likely when interpreting serum MMA and plasma homocysteine test results.The committee noted that there is

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						no universal international threshold with which to define deficiency; it will vary according to how deficiency is diagnosed, the population studied and assay used for each country.
447	Pernicious Anaemia Society	Evidence Review C	036		Chart Economic evidence in this section fails to recognise repeat visits to primary care providers for tests an return of symptoms where proper diagnosis has not been made and suitable treatment has not been given. Giving primary care providers the ability to order Active B12, MMA and Homocysteine, would, we submit save time and money as the results of the tests together could enable earlier diagnosis, suggest better treatment and avoid repeat consultations.	Thank you for this comment. We have added this to the list of limitations. Stakeholders have indicated to us that the cost of additional testing arising from this guideline will be considerable without multiple tests. We do not have evidence that multiple testing would improve diagnosis significantly enough to justify the cost.
448	Pernicious Anaemia Society	Evidence Review D	General	General	The quality of evidence in this review for people with Pernicious Anaemia is low	Thank you for your comment. The quality of the evidence was noted in the review and considered by the committee when reviewing the evidence and making recommendations.
449	Pernicious Anaemia Society	Evidence Review D	006	009 - 012	We agree the cause of the B12 deficiency is most important. We do not believe that this has been sufficiently advised in the draft guidelines. Ironically this review states "the consequences of not identifying malabsorption conditions in people with B12 deficiency can be severe, including irreversible neurological damage and pernicious anaemia" whereas "pernicious	Thank you for your comment. The committee were restricted by the available evidence in making more detailed recommendations than they have. Therefore they have made research recommendations in this area.

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					anaemia" as a term in your guideline has been completely neglected.	
450	Pernicious Anaemia Society	Evidence Review E	General	General	The quality of evidence in this review for people with Pernicious Anaemia is low	Thank you for your comment. The low quality of the evidence was considered by the committee when reviewing the evidence and making recommendations. This has also been mentioned in the committee discussion in the evidence report.
451	Pernicious Anaemia/B12d Support Group	Guideline	General	General	**Frequency of IM Treatment** - We are disappointed not to see any reference or guideline as to the recommended treatment, dosages and frequency of IM injections as are currently in the CKS for the treatment of Pernicious Anaemia, particularly in relation to the advice that every other day loading injections should continue in cases where there is neurological involvement (advice which in our experience is either not known or just ignored) We would hope that the current guidance will remain with the added proviso that continuing injections at 8-12 weekly intervals can be adjusted if required.	Thank you for your comment. No evidence was identified for increased frequency of intramuscular injections despite this being specified in the protocol. Therefore the committee did not specify particular time intervals for injections. They also made a research recommendation covering the dose, frequency and route of administration. The committee also recommend that frequency of injections are increased in line with the summary of product characteristics if symptoms have not improved.
452	Pernicious Anaemia/B12d Support Group	Guideline	General	General	**Strategy & Policy for dealing with B12 Deficiency in primary care** – It has also become apparent from the experience of our members that within individual primary care settings there may not be a clear strategy or policy for dealing with B12 deficiency and that individual GP's within	Thank you for your comment. The committee hope the guideline will raise awareness of vitamin B12 deficiency and improve outcomes for people with the condition.

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					each practice can offer varying testing and/or treatment options without clinically based cause and without reference to the current CKS and NHS guidance. It is also generally felt by our members that their concerns about their condition and treatment are not taken seriously and they are not listened to. This can result in a lottery lucky dip as to which Doctor within a practice the patient gets to see as to what further testing may be considered as well as the outcome of any treatment offered. Whilst we would hope that the new guidelines will be used as a base on which Doctors will diagnose and treat B12 deficiency we do feel that some of the draft guidelines to do go far enough nor give enough advice and information on what is a very complicated condition. Given the current pressures and constraints on primary care, we do not believe that General Practitioners are able to give the time to researching to help their patients so that when referencing the guidelines everything needs to be in black and white and crystal clear to enable them to make informed decisions quickly	

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453	Pernicious Anaemia/B12d Support Group	Guideline	General	General	**Patient Disatisfaction** - A recently published study and research project of patients diagnosed with both Autoimmune Gastritis and PA, which a number of members participated in, showed that: • Diagnosis: Diagnosis was consistently described as "difficult" with 80% of patients stating diagnostic delays of 1-10 years. • Treatment: Was reported as sub-optimal by 64% of patients with 51% stating their care was poor or very poor. • Quality of Life: This showed that most people with both conditions experienced low health related quality of life and psychological well-being. • Patient Disempowerment: Data provided via Patient forums indicated that lack of awareness in healthcare about both conditions resulted in lack of help to patients to understand their conditions, complications and management. Benefits from self-administering B12 in	Thank you for your comment and information on the recent study. The committee hope this guideline will help improve care for people with a vitamin B12 deficiency. We checked the cited study for inclusion in our review. The study did not meet the inclusion criteria due to methodological factors, namely the lack of validation of the themes identified due to the nature of the data source and no indication of ethical approval for the research, so has not been included in the guideline.

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					response to symptom recurrence were described but also reported was a lack of approval and support from healthcare providers, creating self-doubt and concern. • Patient/Provider Relationships: Participants expressed dissatisfaction with medical care, poor doctor relationships, and disengagement from healthcare. Many described symptoms that were frequently trivialized, leaving them feeling misunderstood and they found a perceived gender bias in patient-provider relationships with females commonly told their symptoms were stress-based, psychosomatic, or hormonal. Complaints concerning fragmented care and lack of patient-centred care were also common. Link to the full research document: https://journals.sagepub.com/doi/10.1177/23743735231151767?fbclid=IwAR2IyK6q_7f	

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					vIr_REnUEzbGo_1KCzC5gZrJwtTBPVGAVHgHfZ_C5rZuz5Qw We would like to think that the new guidelines will be effective in going some way towards improving the patients experience and outcomes because quite frankly the issues highlighted in this research are not acceptable	
454	Pernicious Anaemia/B12d Support Group	Guideline	General	General	**Training in Primary Care** – Given that B12 deficiency is normally diagnosed and treated in primary care we feel that there are many health care providers with little knowledge of the condition, who hold misconceptions about testing and treatment, who fail to recognise the severity of lifelong disability which can be caused by their failure to diagnose in a timely manner or treat correctly, nor the impact that the illness can have on a patients life. We understand that in general medical students receive very little training in vitamin deficiencies and that given the complexity and nature of this particular deficiency that training is an issue that we feel needs to be addressed in order to improve the outcomes for many patients. Is this a recommendation that could be considered and written into the guidelines?	Thank you for your comment. Training of GPs is beyond the scope of this guideline.

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455	Pernicious Anaemia/B12d Support Group	Guideline	005	016	**Information and Support** We believe that this should be made clearer in that the majority of causes (other than some causes) will require lifelong treatment, if the cause of deficiency is not dietary related.	Thank you for your comment. The recommendation has been updated to change 'lifelong treatment' to 'lifelong vitamin B12 replacement' to make it clear the committee are not talking about treatment of other conditions. The committee agreed that they wanted to emphasise autoimmune gastritis only in this point as an example of someone who is likely to need lifelong vitamin B12 replacement. The committee do not agree that the majority of causes will require lifelong vitamin B12 replacement.
456	Pernicious Anaemia/B12d Support Group	Guideline	005	018	**Information and Support** We believe this to be incorrect. Given the recent incidences of the use of nitrous oxide (gas and air) being withdrawn in maternity units due to safety concerns for staff suffering B12d due to inhalation of polluted air it does not seem reasonable to assume that its use is unlikely to affect a patient or that a patient already suffering from B12d will not suffer a detrimental effect. If it is not safe for members of staff how can it be for patients?	Thank you for your comment. Several stakeholders commented on this suggesting that without evidence to support this the statement should not be made. The committee agreed and the recommendation relating to this has been removed from the guideline. Recommendations related to pregnant patients on gas and air are covered by MHRA guidance on Nitrous oxide: neurological and haematological toxic effects.
457	Pernicious Anaemia/B12d Support Group	Guideline	006	005	**Recognising Vitamin B12 Deficiency** Given that the list of symptoms and risk factors is not exhaustive and that there are many symptoms of deficiency which medical professionals may not be aware of or associate with B12d perhaps this line could read **and/or**	Thank you for your comment. No evidence was identified to make a strong recommendation that people with one of the symptoms or signs without a risk factor, or one of the risk factors without a symptom or sign, should be tested. The committee agreed that the symptoms and signs associated with vitamin B12 deficiency vary and can also be indicative of other conditions. Without the evidence, making a recommendation to test people with just one of the symptoms or signs or risk factor would hugely increase

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						resource impact without any evidence of benefit. The committee recognise that there may be people in whom there is a suggestion of vitamin B12 deficiency without a risk factor, however this would vary and need to be assessed on a case-by-case basis. Consequently, they recommended that clinical judgement would need to be used to decide if a person should be tested in these circumstances.
458	Pernicious Anaemia/B12d Support Group	Guideline	006	014	**Medicine induced vitamin B12 Deficiency –** Is there any research on each individual medicine known to cause deficiency whether or not stopping or changing the medicine will rectify the failure to absorb B12 naturally or whether the medicine in question has permanently inhibited the ability of the body to absorb B12.	Thank you for your comment. We assume this comment relates to the recommendations on managing medicine-induced vitamin B12 deficiency. Evidence was not identified on whether stopping or changing the medicine would rectify the deficiency. The committee made their recommendation on the basis that in some situations there may be an alternative medicine that could be used that does not cause a deficiency, and that stopping treatment will remove the cause of deficiency. However, they recommended reviewing the need for vitamin B12 replacement rather that stopping it if the medicine causing the deficiency is stopped. This is because it was not clear to the committee how long the effects of the medicine would last.
459	Pernicious Anaemia/B12d Support Group	Guideline	007	001	**Recognising Vitamin B12 Deficiency (Symptoms & Signs)** This is not an exhaustive list, there are many other signs and symptoms of deficiency for example chronic pain, unexplained muscle/joint pain are common. Perhaps the final symptom in the list of "unexplained fatigue" could be amended to read "**unexplained**	Thank you for your comment. Only the most common symptoms and signs were included in the guideline review therefore the recommendations have been restricted to these. Unexplained pain was not one of the symptoms. The recommendations and box have been updated to make it clear that these are common symptoms and signs.

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					fatigue/unexplained pain". We feel that the fact that this is not an exhaustive list should also be made clearer in this section	
460	Pernicious Anaemia/B12 2d Support Group	Guideline	008	001	**Recognising Vitamin B12 Deficiency (Risk Factors)** Again this is not an exhaustive list so we feel this should be made clearer. We also think it is important that it be made stringently clear that it is perfectly possible to become deficient without any known risk factors.	Thank you for your comment. The recommendations and box have been updated to make it clear that these are common symptoms and signs. The recommendation advising using clinical judgement in deciding when to test when there are no risk factors covers situations where a person may not have a risk factor. However, the committee also advised using clinical judgement when deciding whether to test because symptoms and signs of vitamin B12 deficiency are shared by many other conditions.
461	Pernicious Anaemia/B12 2d Support Group	Guideline	009	007	**Diagnosing Vitamin B12 Deficiency** This section 1.3.1 states that either B12 Serum or Active B12 should be the initial test when recreational Nitrous Oxide use is the suspected cause of deficiency. However on line (12) of the section 1.3.3 it states that Homocysteine should be used as the initial test for recreational Nitrous Oxide use. This looks to be an error??	Thank you for your comment. Recommendation 1.3.1 recommends that total or active B12 are used when recreational nitrous oxide is not suspected to be the cause of the vitamin B12 deficiency. Recommendation 1.3.3 recommends what to use if recreational nitrous oxide use is suspected to be the cause of vitamin B12 deficiency.
462	Pernicious Anaemia/B12 2d Support Group	Guideline	009	020	**Diagnosing Vitamin B12 Deficiency** This does not indicate a clear purpose for asking the question as to what dosage of OTC supplements may have been taken and how the response would need to be interpreted	Thank you for your comment. This recommendation is to ensure clinicians get the information about supplementation because some people buy supplements over the counter if they think they will help before going to the doctor. It ties in with the following recommendation which advises using caution when interpreting test results in people already

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						taking over the counter supplementation as it is likely to increase B12 concentrations.
463	Pernicious Anaemia/B12d Support Group	Guideline	009 – 011		**General Observation** **Diagnosing vitamin B12 Deficiency** Given the historical difficulty in obtaining a diagnosis due to lack of reliable testing, that many of our members who are who are now undergoing necessary lifelong treatment for B12 deficiency have faced, we welcome the recommendations for additional testing such as Active B12, Homocysteine and MMA which may help to diagnose a deficiency and possibly help to identify a cause	Thank you for your comment and support for the recommendations.
464	Pernicious Anaemia/B12d Support Group	Guideline	010	010	**Confirmed Deficiency** – Whilst we welcome standardisation on what Serum and Active B12 levels should be considered deficient, as opposed to the current situation where these are set by area or laboratory we do feel that these are set too low	Thank you for your comment. Several stakeholders commented on the thresholds. Some thought they were too low, others thought they were too high and there was also some support that they are about right. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not. Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests.

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						The committee also recommend considering MMA as a further test for people with an indeterminate active or total B12 test result. This is to capture people who may have a vitamin B12 deficiency when their test result doesn't meet the criteria for deficiency. An indeterminate result covers an active B12 of between 25 and 70 pmol per litre, and a total B12 of between 180 and 350 nanograms (133 and 258 pmol) per litre. The committee has also added a recommendation to use the laboratory's reference ranges to decide if vitamin B12 deficiency is likely when interpreting serum MMA and plasma homocysteine test results.
465	Pernicious Anaemia/B12d Support Group	Guideline	010	015	**Confirmed Deficiency** – The advice to use clinical judgement to determine what reference range to use when interpreting Homocysteine test results appears ambiguous. Would the clinical judgement not have to take place before ordering this test due to consideration of testing being necessary with the results being interpreted as normal or abnormal by the parameters as laid down by the testing provider?	Thank you for your comment. We have updated this to make it more specific. The recommendation now states 'Use laboratory reference ranges to interpret plasma homocysteine test results when deciding if vitamin B12 deficiency is likely, but take into account additional factors that may increase plasma homocysteine levels (such as folate deficiency).'
466	Pernicious Anaemia/B12d Support Group	Guideline	011	012	**Indeterminate Test Results** – Given that severe cognitive impairment caused by B12 deficiency does not just affect those aged over 65, we believe that the age should be removed from this guideline	Thank you for your comment. The committee discussed this and removed the bullet point for people 'aged 65 or over and have cognitive impairment'. This is because it is covered by the preceding bullet point which states 'condition or symptom that may deteriorate rapidly and have a major effect on

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						quality of life (for example, neurological or haematological conditions like ataxia or anaemia)'. When making this decision the committee also agreed that age and cognitive impairment alone did not warrant starting treatment before waiting for a test result as most test serum MMA results would be available within two weeks.
467	Pernicious Anaemia/B12 2d Support Group	Guideline	012	001	**Test Results indicating Vitamin B12 Deficiency is unlikely** – As it is known that there are various factors that mean that initial tests may not be reliable to confirm deficiency, we would like to suggest that this guideline includes the proviso that further testing be carried out if any of the symptoms that are being experienced are severe and of a neurological nature	Thank you for your comment. The recommendation has been updated to advise investigating other causes as well as considering a repeat of the initial test if they are still experiencing symptoms or signs 3 to 6 months later. MMA has been removed because the committee agreed that most laboratories would not allow for an MMA without testing total or active B12 first. It is anticipated this would be for anyone with symptoms regardless of their severity.
468	Pernicious Anaemia/B12 2d Support Group	Guideline	012	006	**General Reference Identifying the Cause of B12 Deficiency** – The diagram in Table 1 of the Article from the Canadian Medical Association Journal shows areas and causes of B12 malabsorbtion https://www.cmaj.ca/content/171/3/251?fbclid=IwAR0N-nOtS9PrX-fCMwhRUgYf-rAdMt9qJp3LIDCD2ia48gQwuPwC2hdADfw	Thank you for the citation. We have checked this to ensure we are not missing any studies that fit the guideline review protocols.

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469	Pernicious Anaemia/B12d Support Group	Guideline	012	007	**Identifying the Cause of B12 Deficiency** – We question why this guideline only recommends IF testing if autoimmune gastritis is suspected. Pernicious Anaemia is caused by lack of Intrinsic Factor or antibodies to Intrinsic Factor and it is possible to have Pernicious Anaemia without having autoimmune gastritis and we therefore feel that this guideline should state "suspicion of autoimmune gastritis or pernicious anaemia" https://www.mdpi.com/2072-6643/14/8/1672?fbclid=IwAR3n2aZzUrnp_Ll2MtCCfBbRXZKfM2gM6qDrHzHZqsSkL-K5MI9guOe7jkw Due to the unreliability of IFA testing whereby a negative test cannot confirm that a patient does not have Pernicious Anaemia we believe it important that this fact is detailed and made clear to Health Professionals in this section. Patients are commonly told that they DO NOT have Pernicious Anaemia due to a negative IF test but this may well not be the case due to the lack of appropriate accurate testing or a single test that can categorically diagnose this nor do many Primary Care practitioners	Thank you for your comment and the citations about the difference between autoimmune gastritis and pernicious anaemia. The guideline has been updated to acknowledge the difference between autoimmune gastritis and pernicious anaemia and provide a more detailed reason as to why the term 'pernicious anaemia' has not been used. This explains that autoimmune gastritis is sometimes referred to as pernicious anaemia which is a separate condition that can be a consequence of chronic, severe vitamin B12 deficiency, including deficiency caused by autoimmune gastritis. However, pernicious anaemia in its true sense (that is 'a life-threatening anaemia') is now extremely rare because of developments in testing and treatment for, and greater awareness of, vitamin B12 deficiency. For this reason, and to prevent any confusion with autoimmune gastritis, we have not used the term 'pernicious anaemia' in the recommendations. The rationale in the guideline does state that the evidence 'showed that, while a positive anti-intrinsic factor antibody test strongly suggests autoimmune gastritis, a negative test is less reliable so cannot be used to rule out the condition.' This is why the committee recommended further tests. The committee also recommend lifelong intramuscular vitamin B12 replacement is offered to people if autoimmune gastritis is the suspected cause. This is the same as the recommendation for those with a confirmed diagnosis to take

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					show any inclination to carry out further testing in an attempt to find the cause of deficiency. There are also factors such as patients that have the CBILF gene who will test negative for IFA but do not have intrinsic factor. https://www.ncbi.nlm.nih.gov/gtr/conditions/C1394891/ Whilst the rationale and impact section on identifying the cause of B12 Deficiency stresses the importance of finding the cause of deficiency unfortunately the unreliability of the IFA test to do this is not stated clearly in the draft guidelines. Our feeling is that if this is not stated clearly in black and white in the new guidelines then this will not be taken seriously and carried out.	account of the lack of certainty in the outcome of a negative test result.
470	Pernicious Anaemia/B12d Support Group	Guideline	013	009 - 010	**Managing Vitamin B12 deficiency** Whilst we agree and support the concept that patients should be given information regarding their treatment, we have concerns regarding the inclusions of "how long it usually takes to work" and "when they are likely to see an improvement". In our experience there is no answer to these questions. Every patient is different and	Thank you for your comment. Following stakeholders' comments this recommendation has been updated to provide more detail. It now states: Explain to people starting treatment with vitamin B12 replacement: • that response to treatment can vary and depends on the cause of the vitamin B12 deficiency

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					how long these may take is going to be dependent on each individual, the severity of their deficiency, symptoms experienced and the damage already caused, particularly neurological as well as whether they are given enough of the correct treatment to resolve these at all. Are healthcare providers going to be given guidance to as to what this information should be and if so, what will this guidance be based on?	• that their symptoms could start to improve within 2 weeks, but this may take up to 3 months • that it can take much longer for symptoms to disappear altogether, and that although their symptoms could get worse initially during treatment, this should improve • when to seek medical help (without waiting for any scheduled appointments) if their symptoms have not improved, get worse or return, or they get new symptoms, after starting treatment.
471	Pernicious Anaemia/B12 2d Support Group	Guideline	013	013	**Managing B12 deficiency caused by malabsorption** What will the guidance to "consider" intramuscular injections" instead of oral replacement in this section be based upon and how should health professionals decide this? We believe that oral replacement is not suitable for these causes of malabsorption and patients are unlikely to benefit from any form of oral replacement and thereby leaving patients at risk of suffering neurological impairment. We feel this guidance is ambiguous and requires further clarity and that the guidance for this should be IM injections only	Thank you for your comment. The recommendations have been updated. Intramuscular injections are offered to people with autoimmune gastritis or who have had a total gastrectomy or complete terminal ileal resection. For all other people with vitamin B12 deficiency because of malabsorption intramuscular injections are considered over oral replacement. The committee agreed that in their experience intramuscular injections are better than oral replacement. However, there was no evidence to suggest that oral replacement could not be effective too. The weaker recommendation to 'consider intramuscular instead of oral vitamin B12 replacement' reflects this. The committee also made a research recommendation in this area to address the uncertainty.
472	Pernicious Anaemia/B12	Guideline	014	001	**Managing B12 deficiency caused by malabsorption** – Whilst we agree with the guidance that for other causes of	Thank you for your comment. Following stakeholder comments the recommendations have been updated. Intramuscular injections are offered to people with

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	2d Support Group				malabsorption that patients should have their wishes taken into account and treatment and the different treatment options discussed with them, we think it is also important that it be properly explained to them the implications of the fact that oral treatment, whilst it might normalise their serum levels, is unlikely to resolve symptoms and put them at risk of suffering further complications of deficiency. Most patients on being given a diagnosis have not heard of this deficiency, have no knowledge about how serious it is or the life changing symptoms and neurological issues it can cause when not treated appropriately. It is human nature that in this scenario a patient without knowing or being given the facts is going to choose the option to swallow a tablet rather than have an injection. Whilst we are aware of the licensing of the higher strength Orabalin supplements it is recognised that only approximately 1% of each dosage is absorbed to cellular level. Research as to the effectiveness of oral supplementation is old and poor quality and based on normalisation of serum levels with no account being taken of resolution of	autoimmune gastritis or who have had a total gastrectomy or complete terminal ileal resection. For all other people with vitamin B12 deficiency because of malabsorption intramuscular injections are considered over oral replacement. A recommendation has also been added to recommend that if oral vitamin B12 replacement is offered then it should be at a dose of 1mg a day. The recommendations for ongoing care and follow up make it clear that symptoms need to be taken into account when assessing a person's response to treatment. There wasn't evidence to suggest that oral or intramuscular injections were better for people with a vitamin B12 deficiency caused by medicines or recreational nitrous oxide use and the committee agreed that either option could be offered.

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					symptoms, quality of life, nor the costs of ongoing future investigations, treatment and care when patients suffer serious health deterioration due to not being treated correctly. As referenced by the 2018 Cochrane Report and cautioned by the B12 Institute: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004655.pub3/full#:~:text=Low%20quality%20evidence%20shows%20oral,as%20IM%20vitamin%20B12 https://b12-institute.nl/caution-note-about-oral-supps/ The problems caused by the inappropriate use of oral supplements are further exacerbated by the failure of Healthcare Providers to recognise and accept the fact that a normalised biochemical picture does not necessarily reflect the fact that a patient is not absorbing enough B12, is not cured and that their ongoing symptoms could be caused by B12 deficiency. This is a very common problem suffered by our members and we therefore believe that it should be referenced clearly in the new guidelines	

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					that caution should be applied when prescribing oral supplements for any form of malabsorption or B12 deficiency other than caused by diet and that it should also be made totally clear that normalisation of serum levels following any form of oral treatment should not be used solely to assess B12 status alongside the importance of taking symptoms into account. We strongly believe that the new guidelines should state that IM treatment should be given for all forms of B12 deficiency and malabsorption other than those of a dietary nature but in particular where neurological symptoms are already present as there is in our opinion no evidence that anything other than IM treatment will resolve such symptoms. We also feel that it should be made clear in the guidelines as it currently is in the CKS guidance and the BNF that this should be injections every other day until such time as neuro symptoms have completely resolved or there is no further improvement. This is based on the experience of our members and the fact that some are still	

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					seeing improvement as long as 5 years into this treatment.	
473	Pernicious Anaemia/B12 2d Support Group	Guideline	014	019	**Nitrous Oxide induced Deficiency** - The recreational use of NO to cause deficiency is likely to not be diagnosed promptly or until neurological symptoms appear, especially given that this is a common use by children and young people who will initially be unlikely to be discussing symptoms or problems with parents or seeking medical help, we feel that it is particularly important in this group of people that treatment should be IM initially as opposed to oral to negate the risk of them suffering permanent neurological deficit	Thank you for your comment. There is no clear evidence to distinguish which out of oral or intramuscular vitamin B12 replacement was more clinically or cost effective for vitamin B12 deficiency caused by recreational nitrous oxide use. Therefore the committee agreed to recommend either oral or intramuscular vitamin B12 replacement.
474	Pernicious Anaemia/B12 2d Support Group	Guideline	015	028	**Dietary Vitamin B12 deficiency** Whilst it might be assumed that a deficiency may be dietary in nature but not necessarily be the case, we feel that during pregnancy or breastfeeding IM treatment should be administered rather than high strength oral	Thank you for your comment. There wasn't the evidence to suggest that intramuscular instead of oral vitamin B12 replacement should be used for a dietary deficiency in any group, including during pregnancy and breastfeeding. The committee agreed that in their experience if a dietary deficiency is suspected then oral vitamin B12 replacement should work. The ongoing care and follow up recommendations also recommend switching treatment should oral vitamin B12 replacement not work.
475	Pernicious Anaemia/B12 2d Support Group	Guideline	016	018	**Unknown causes of vitamin B12 deficiency** We strongly feel this proposed guideline is totally wrong. Many patients who are currently undergoing necessary lifelong IM treatment for B12 deficiency	Thank you for your comment. The recommendation has been updated to make clear that it applies to people where malabsorption is not suspected. It has also been updated to make it clear this is a trial of oral vitamin B12 replacement and the response to treatment should be reviewed at the first

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					have never been diagnosed with an identifying cause, many simply because of lack of availability of appropriate testing, flawed tests such as IF or failure by healthcare providers to carry out any testing other than a serum B12 test and possibly IF and PCA. If a patient is deficient and they eat a diet rich in B12 and are not malnourished then their deficiency is caused by some form of malabsorption or one of the many other causes of deficiency of which no mention at all has been made in the draft guidelines, nor suggested as requiring investigation, for example SIBO, H-Pylori, Parasites, Gallbladder removal and Lyme disease. If a patient has a confirmed deficiency of unknown cause then they should be treated in the same way as for known causes of malabsorption as well as taking symptoms into account. Not knowing a cause does not mean that a patient does not have a deficiency which requires IM treatment. We have yet to see any proof or research to suggest that high dose Oral replacement is effective for resolving neurological symptoms regardless of the cause of deficiency. This guideline will result in patients having their injections	follow up appointment. The committee agreed that there was no evidence that oral treatment would not work in this group. The expectation is that healthcare professionals will take symptoms into account when making a diagnosis. The recommendations for ongoing care and follow up also make it clear that symptoms need to be taken into account when assessing a person's response to treatment.

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					withdrawn and putting their long-term health and wellbeing at serious risk	
476	Pernicious Anaemia/B12 2d Support Group	Guideline	017	012	**Ongoing care and follow up** There should be recognition that with the current pressures on General Practice that it is common for patients to not even be seen by a GP to discuss diagnosis let alone have a follow up appointment unless they request this normally due to continuing or worsening symptoms, so we welcome the guidance that follow up appointments should take place but have concerns that this will not happen as the GP Practices just do not have available appointments!	Thank you for your comment. The committee agreed it is important to offer an initial appointment to check the person's response to treatment.
477	Pernicious Anaemia/B12 2d Support Group	Guideline	017	022	**Follow up appointments for people taking oral replacement** It is the experience of our members in the UK that when they request and have a follow up appointment to inform the GP of continuing/worsening symptoms that the normal course of action is to carry out a further B12 serum test, which if normalised is used to decide that they are no longer deficient or do not have a deficiency and to stop treatment and to blame symptoms onto another cause rather than acceptance that a normal serum level does not necessarily mean a resolution of symptoms. We feel strongly therefore that this	Thank you for your comment. Following stakeholder comments the recommendation for repeating the initial test for people on oral vitamin B12 replacement has been removed from the guideline. The ongoing care and follow up recommendations have also been updated to make it clearer that response to treatment should be made by assessing symptoms.

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					guideline should state that in the presence of continuing or worsening symptoms that consideration of switching to IM injections should be made regardless of whether a repeated test suggests they still have a deficiency or not and especially given the total lack of evidence that oral therapy is effective in doing anything other than normalising serum levels or that it will resolve neurological symptoms	
478	Pernicious Anaemia/B12 2d Support Group	Guideline	018	004	**Follow up appointments for people taking oral replacement** We believe that this guideline should contain the recommendation that IM should be considered if the cause of the deficiency has not been addressed and if they are still experiencing symptoms that would indicate that oral replacement is not working	Thank you for your comment. The follow up recommendations have been updated so that optimising oral vitamin B12 replacement or switching to intramuscular injections are both options if symptoms do not sufficiently improve, worsen or new symptoms develop.
479	Pernicious Anaemia/B12 2d Support Group	Guideline	018	008	**Follow up appointments for people taking oral replacement** We do not feel that treatment should be stopped if the patient is still experiencing symptoms even if the suspected cause has been addressed	Thank you for your comment. The recommendation relates to people whose symptoms have improved, not those who are still experiencing symptoms. The committee agreed that if both symptoms have improved and the cause has been addressed then stopping treatment should be considered.
480	Pernicious Anaemia/B12 2d Support Group	Guideline	018	011	**Follow up appointments for people taking oral replacement** Again if repeat testing shows normalised levels but symptoms have not improved or new symptoms have appeared we believe that the first line should be to trial IM loading	Thank you for your comment. Following stakeholder comments the recommendation for repeating the initial test for people on oral vitamin B12 replacement has been removed from the guideline. The ongoing care and follow up recommendations have also been updated to make it clearer

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					injections to see if improvement is experienced rather than to consider increasing dosage of oral which is clearly not resolving symptoms before engaging in further expensive testing to try to find another cause. Whilst we are of course aware that symptoms may have other causation if a patient has been tested with a proven B12 deficiency and has recognised symptoms of B12 deficiency then the probability is that ongoing symptoms are due to the deficiency not being treated sufficiently or with oral supplements, especially given the lack of evidence that oral supplements work for anything other than dietary deficiency.	that response to treatment should be made by assessing symptoms. The committee still recommend that further testing should be considered for people whose symptoms have worsened or they have new symptoms because this would help determine if the original diagnosis was correct. Treatment can then be adjusted based on the test results.
481	Pernicious Anaemia/B12 2d Support Group	Guideline	018	019	**Further Testing with MMA** – This guideline recommends consideration of an MMA test for the reasons detailed following oral treatment for the deficiency. Our belief is that for MMA to be accurate that this test should be performed before any B12 treatment has been administered due to the risk of oral supplements normalising levels without addressing symptoms.	Thank you for your comment. The committee agreed that for ongoing care and follow up, further testing with MMA is meaningful because it reveals whether B12 replacement is influencing B12 status at a metabolic level. In other words, a decrease in MMA concentration is a sensitive and specific way of demonstrating a positive impact on the function of one of the two B12-dependent enzymes.
482	Pernicious Anaemia/B12 2d Support Group	Guideline	020	001	**Monitoring for gastric cancer in people with autoimmune gastritis** – We believe that this section should include Pernicious Anaemia and not just autoimmune gastritis.	Thank you for your comment. We did not have the evidence to make a recommendation that all people should be referred for gastrointestinal endoscopy. Therefore, the strength of the recommendation in this guideline matches the strength of the

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					It is also our belief that those with PA and/or autoimmune gastritis should have regular monitoring for gastric cancer. Presumably the guideline to only carry out endoscopy due to new symptoms is based on economics but we strongly feel no aspect of a patients monitoring or treatment should be based on cost.	recommendations on upper gastrointestinal tract cancers in NICE's guideline on suspected cancer.
483	Pernicious Anaemia/B12d Support Group	Guideline	021	003	**Reversible cause** – Is the suggestion that reversible causes of B12 deficiency other than dietary, based on research or assumption, for example Coeliac disease which is mentioned as being a reversible cause in the draft guidelines? Unfortunately, it is the experience of our members that despite Coeliac disease being well managed that they continue to suffer B12 deficiency symptoms and require IM treatment	Thank you for your comment. The committee agreed that while coeliac disease is a reversible cause of vitamin B12 deficiency, its management will not always remove the deficiency. The recommendations for ongoing care and follow up reflect this. If someone has a reversible cause and it is not resolved then the committee recommend continuing with intramuscular vitamin B12 replacement. The recommendations for the management of vitamin B12 deficiency caused by malabsorption have been updated. For people with a deficiency because of malabsorption that is not caused by autoimmune gastritis or surgery (for example, malabsorption caused by coeliac disease) intramuscular injections are recommended over oral vitamin B12 replacement.
484	Pernicious Anaemia/B12d Support Group	Guideline	021	019	**Key recommendations for research (1. Vitamin B12 replacement)** – We believe that long term IM therapy both clinically and economically is preferential and that cost should not be prioritised over clinical need. We would certainly like to see research	Thank you for your comment. The research recommendations here are written as broad questions giving an indication of what area and interventions are considered for further research. More detail is provided in the appendix of the evidence report linked to just below the research recommendation.

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					based on frequency of IM therapy because as far as we are aware the current guidance for the administration of injections 8-12 weekly is not based on any research whatsoever and is inadequate for the majority of our members	
485	Pernicious Anaemia/B12 2d Support Group	Guideline	021	15	**Recommendations for research** – We welcome and support recommendations and research into B12 deficiency and Pernicious Anaemia as good quality research and evidence is sadly lacking at the current time which we feel is partly responsible for so many of our members being misdiagnosed/undiagnosed, inadequately treated and resulting in them continuing to suffer not only symptoms but the impact that this has on their daily lives. With many having no option other than to accept permanent invalidity or to resort to sourcing and carrying out their own injections. They should not have to do this and they should receive the help needed from the NHS and their healthcare providers	Thank you for your comment and support for the research recommendation.
486	Pernicious Anaemia/B12 2d Support Group	Guideline	022	001	**Key recommendations for research (2. Diagnosing vitamin B12 deficiency)** – Given that the recommendations for testing in the draft guidelines appear somewhat disjointed with different tests suggested for	Thank you for your comment. The evidence was not available for the committee to recommend a cascade of tests. The research recommendations for diagnosis and identifying the cause are further defined in the respective

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					different possible causes we believe that there should be a cascade of tests, starting with serum B12, homocysteine, MMA, Active B12 and if autoimmune suspected, both Intrinsic Factor AB and Parietal Cells AB should be included in that cascade. the costs of the extra tests would surely be less than the multiple visits, unnecessary medications, tests, consultant appointments, work time lost, benefits paid etc incurred by most undiagnosed patients as well as the longterm outcome of delayed -v- prompt treatment.	evidence reports. This includes the suggestion that these tests could be looked at alone and in combination.
487	Pernicious Anaemia/B12 2d Support Group	Guideline	022	005	**Key recommendations for research (3. Self-Administration)** – In our experience many sufferers are happy to administer their own injections, especially with the blessing, guidance and a prescription from their Doctors. Given the savings that would be made in terms of healthcare professional appointments for administration of IM therapy this must surely be more cost effective. We would like to see this research carried out quickly.	Thank you for your comment. The committee agree and would also like to see this research carried out quickly.
488	Pernicious Anaemia/B12 2d Support Group	Guideline	022	009	**Key recommendations for research (4. Identifying the cause of vitamin B12 deficiency)** – Any research is welcomed	Thank you for your support for the research recommendation.

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489	Pernicious Anaemia/B12 2d Support Group	Guideline	023	001	**Key recommendations for research (5. Follow up)** – If this research is carried out we feel that the most important aspect to be included in a follow up review should be symptoms. Unfortunately at the present time this is something that is woefully lacking with patients being dismissed when they report symptom return or worsening.	Thank you for your comment. The research recommendations here are written as broad questions giving an indication of what area and interventions are considered for further research. More detail is provided in the appendix of the evidence report linked to just below the research recommendation. Assessment of symptoms is included as part of the research protocol.
490	Pernicious Anaemia/B12 2d Support Group	Guideline	023	004	**Other recommendations for research** – All recommendations for research are welcomed	Thank you for your support.
491	Pernicious Anaemia/B12 2d Support Group	Guideline	025	001	**Rationale** We would question why there is acceptance here that use of OTC supplements can affect initial testing, despite the patient experiencing symptoms and being deficient yet once on prescribed oral supplementation that normalised levels indicate resolution of the deficiency?	Thank you for your comment. The recommendation to repeat the initial test for people receiving oral vitamin B12 replacement has been removed from the guideline following stakeholder comments.
492	Pernicious Anaemia/B12 2d Support Group	Guideline	025	005	**Rationale** Whilst is commendable that the Committee want to offer assurance to patients that their treatment can be adjusted and that their treatment will not be stopped in the future, the reality is that this is unlikely to happen.	Thank you for your comment. As well as the recommendation in the patient information section and this associated rationale, the committee have also made a recommendation in the ongoing care and follow up section. This advises that treatment should be continued for those

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					The current situation is that many GP's do not currently follow NHS or CKS guidance and whilst we would hope that this might change, we fear it will not.	with an irreversible cause of vitamin B12 deficiency even if their symptoms have improved or are no longer present.
493	Pernicious Anaemia/B12d Support Group	Guideline	026	004	**Rationale** We are pleased that this common misconception is being addressed!	Thank you for your comment.
494	Pernicious Anaemia/B12d Support Group	Guideline	026	017	**Rationale** We wonder why a poor response to iron treatment is recognised as a sign of vitamin B12 deficiency yet nowhere in the draft guidelines is there any mention of the important relationship between Folate and B12 and both deficiencies causing similar symptoms. Whilst we appreciate that the guidelines relate only to B12 deficiency we strongly believe that folate should always be tested alongside B12 and that if both deficiencies exist B12 therapy should not be delayed whilst folate deficiency is addressed and that both deficiencies should be treated accordingly at the same time.	Thank you for your comment. Investigating and managing complications related to vitamin B12 deficiency and cofactors were not included as part of the scope of the guideline. Therefore they were not included as part of the guideline reviews and no recommendations have been made related to this.
495	Pernicious Anaemia/B12d Support Group	Guideline	026	021	**Rationale** Whilst it has generally been recognised for some time that age is a risk factor for B12 deficiency and that older people are at	Thank you for your comment. Following stakeholder comments the committee discussed age as a risk factor again. Increasing age was included as a risk factor in the review and as a confounder for other factors. However, no

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					higher risk of suffering cognitive impairment and dementia which might impact their diet and eating habits, there appears to be little recognition of the fact that it is likely that it could be the B12 deficiency causing the cognitive impairment and dementia and that IM treatment may reverse these symptoms leaving the patient able to continue to lead a relatively normal life.	evidence was identified related to age. The committee discussed that the ageing process causes physiological changes in the gastrointestinal system that can affect dietary intake of vitamin B12 and can potentially cause malabsorption of the vitamin. Older people are also at higher risk of developing health problems such as cognitive impairment and dementia, which can impact on their diet and eating habits. Dietary factors, cognitive impairment and dementia are already listed as risk factors in the guideline and the committee agreed that age alone was not a risk factor that would warrant a test for deficiency without the presence of other risk factors. In light of this, the committee agreed to remove age as a risk factor from the risk factors box.
496	Pernicious Anaemia/B12 2d Support Group	Guideline	027	009	**Rationale** Given that B12 is processed via the terminal ileum surely it should be recognised that anything which can impact on this area should be a risk factor	Thank you for your comment. The committee made recommendations for procedures they know affected the absorption of vitamin B12. We are not sure what you mean by anything that can impact on this area.
497	Pernicious Anaemia/B12 2d Support Group	Guideline	027	028	**Rationale** Whilst this should be planned for at the time of surgery, we believe that there should be recognition of the fact that it is common that this does not actually happen	Thank you for your comment. The committee believe this does usually happen at the time of surgery and have not seen evidence that it is common for this not to happen. Therefore they have not made a statement in this area.
498	Pernicious Anaemia/B12 2d Support Group	Guideline	028	004	**Rationale** Whilst we hope that the new guidelines do lead to a greater awareness of the condition and accept that this in turn may have a potential resource impact on general	Thank you for your comment. The committee hope the guideline will raise awareness of vitamin B12 deficiency and the recommendations will be followed.

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					practice, we have concerns that the guidelines will not be followed or adhered to due to lack of resources	
499	Pernicious Anaemia/B12 2d Support Group	Guideline	028	012	**Rationale** It is disappointing that despite the experience of the committee that active B12 testing is a more accurate form of testing than serum B12 that it has been decided not to recommend this as first line testing, for economic reasons	Thank you for your comment. No evidence was identified to show active B12 was more cost effective than total B12. The committee agreed that recommending it over total B12 would be difficult to justify without evidence of cost effectiveness. The committee also noted that recommending active B12 over total B12 (which is more widely available and used) would lead to a significant resource impact. They made a research recommendation in this area.
500	Pernicious Anaemia/B12 2d Support Group	Guideline	029	009	**Rationale** The committee has rightly emphasised the need to take blood samples before starting treatment as well as enquire as to whether supplements are being taken due to recognition that this can elevate B12 concentrations in the blood and affect test results, yet there seems to be no recognition that the same should apply for retesting after oral therapy has been described and have recommended this and a return to normal serum levels as evidence of resolution of deficiency	Thank you for your comment. The recommendation for retesting when people are using oral vitamin B12 replacement at the first follow up appointment has been removed from the guideline following stakeholder comments.
501	Pernicious Anaemia/B12 2d Support Group	Guideline	031	026	**Rationale** Whilst we agree the importance of testing people with an unknown cause of B12 deficiency for autoimmune gastritis we are surprised that given the known poor	Thank you for your comment. The committee agreed the anti-intrinsic factor antibody test is widely available and still the best initial test to use. The rationale has been updated to state 'those who have previously had positive anti-intrinsic

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					accuracy of this test that it has been decided that IF is the best initial option for diagnosing autoimmune gastritis and again economic considerations seem to have been a factor in this decision. We would disagree that the test was not necessary for people who have already had it as the result would be the same. Autoimmune atrophic gastritis is a destructive ongoing process. It is unscientific to assume that time does not change an individual's likelihood of producing intrinsic factor antibodies. This assumption also poses a problem for the elderly, who may have had undiagnosed PA for many years, and no longer produce intrinsic factor antibodies because the destructive process of AIAG is complete, ended. They might not be producing IFAB but that does not mean they do not have PA and do not need b12 injections. The statement that it would be very expensive to test everyone with suspected AIG as the treatment would be the same regardless of known cause and the guideline recommends lifetime IM treatment for autoimmune gastritis or suspected gastritis, the guideline regarding treatment	factor antibody test at any time (because the result would be the same)' to reflect the recommendation. NICE consider cost effectiveness in all its guidelines, so that there is not a significant opportunity cost to other NHS patients. Additional testing can only be justified when it is likely to have a significant effect on management and subsequently on patient outcomes. The recommendation for management of unknown causes has been updated to state 'In people with a vitamin B12 deficiency where the cause is uncertain, and malabsorption is not suspected based on the results of further testing or investigations…..' Considering further investigations are recommended if the test is negative and autoimmune gastritis is still suspected.

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					for unknown causes contradicts this, as a suspicion of AIG is not a "known cause". It is also disappointing that other options for further investigations are not recommended and whilst the recommendation for further research is positive, this does not mean that it will actually happen. It is common amongst our members, particularly when changing GP's to have their lifelong IM treatment stopped because they have a negative IF test on record and no known cause and are thereby deemed to not have Pernicious Anaemia or AIG and therefore not require any further treatment	
502	Pernicious Anaemia/B12 2d Support Group	Guideline	032	007	**Rationale** "The committee agreed that it was important to test anyone who has suspected autoimmune gastritis during pregnancy or during breastfeeding to ensure their health and that of their baby. For this reason, they also agreed that intramuscular treatment should be started without waiting for test results." While not arguing that it is important to test pregnant and breastfeeding individuals, they do not offer a rationale for not testing non pregnant individuals (page 32, line 1). If it is important to test suspected autoimmune atrophic gastritis in pregnant	Thank you for your comment. Testing is recommended for everyone suspected of having autoimmune gastritis. However evidence was not available to show it would be cost effective in all groups so the committee made a weaker consider recommendation. The committee agreed testing everyone suspected of having the condition would be very expensive and people would already be receiving vitamin B12 replacement. However in pregnancy, the committee decided to err on the side of caution because of the risk to the unborn child.

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					individuals to 'ensure their health', why isn't it import to 'ensure the health' of non-pregnant individuals? The NHS constitution applies to all individuals using the service. Selecting only pregnant individuals for IFAB testing goes against the NHS constitution. "1. The NHS provides a comprehensive service, available to all. 2. Access to NHS services is based on clinical need, not an individual's ability to pay, although other aspects of the constitution could also be applied, such as accountable to the public.	
503	Pernicious Anaemia/B12 2d Support Group	Guideline	033	004	**Rationale** We are pleased to see recognition of the fact that evidence has been mainly gathered from studies based on blood test results with little reference to quality of life or other patient reported outcomes yet disappointed that the main aim appears to be to increase levels so whilst we welcome the recommendation that both the cause and symptoms should be taken into account and that further research be carried out we again fear that in practice this will not necessarily happen.	Thank you for your comment. The committee were also disappointed not to find evidence for quality of life or patient reported outcomes.
504	Pernicious Anaemia/B12 2d Support Group	Guideline	033	013	**Rationale** What guidance is going to be given to GP's to help in determining an estimated timeframe for symptom improvement or on	Thank you for your comment. This recommendation has been updated to give more specific information on what to advise people starting vitamin B12 replacement.

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					what are GP's expected to base their advice on?	
505	Pernicious Anaemia/B12 2d Support Group	Guideline	034	001	**Rationale** The inclusion of oral replacement appears to have been included in this group due to no evidence to suggest that it was ineffective as opposed to evidence that proves that it is effective and we feel that this could put patients at risk	Thank you for your comment. We assume you mean the inclusion of oral replacement as an option regardless of the cause of vitamin B12 deficiency. In the absence of evidence, the committee made consensus recommendations. The committee agreed it was important that oral vitamin B12 replacement is an option if it could work. The section on ongoing care and follow up also includes recommendations for switching to vitamin B12 replacement if symptoms do not improve.
506	Pernicious Anaemia/B12 2d Support Group	Guideline	034	011	**Rationale** Terms such as "may not need" or "may have some ability" and "could potentially be reversed" are presumably used here when there is no knowledge as to whether this is possible or not? So, whilst we understand that lack of evidence in this group of people has been the deciding factor in recommending either IM or oral replacement, depending on individual preference, we do feel that it is essential that people are given choice in this matter after being provided with the facts and being made aware of the implications of their choice as well as the fact that if symptoms persist their treatment should be adjusted accordingly.	Thank you for your comment. This section of the rationale relates to vitamin B12 deficiency because of malabsorption that is not caused by autoimmune gastritis or surgery. The recommendation has been updated to consider intramuscular injections over oral vitamin B12 replacement.

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507	Pernicious Anaemia/B12 2d Support Group	Guideline	034	021	**Rationale** Presumably the fact that there is no evidence to suggest which form of replacement was better for medicine-induced deficiency is due to lack of any research regarding this. Again, we do feel that it is essential that people are given choice in this matter after being provided with the facts and being made aware of the implications of their choice as well as the fact that if symptoms persist their treatment should be adjusted accordingly	Thank you for your comment. The recommendation notes that the person's preference should be taken into account.
508	Pernicious Anaemia/B12 2d Support Group	Guideline	035	012	**Rationale** We totally agree with the concept that healthcare professionals discuss suspected deficiency caused by diet as well as the fact that there should be recognition that assuming the cause was dietary is unsafe as there could be other causes. However, we feel in practice that this is unlikely to happen, the experience of our members is that their deficiency is often blamed on diet despite them assuring their doctors that they eat a diet rich in sources of B12.	Thank you for your comment. The committee were aware of this and made the recommendation alerting healthcare professionals to 'be aware that diet (for example, a vegetarian or vegan diet) may not be the cause, or the only cause, of a person's vitamin B12 deficiency'.
509	Pernicious Anaemia/B12 2d Support Group	Guideline	036	007	**Rationale** It is our belief that treatment needs to work quickly for anybody suffering any form of neuro symptom or severe symptoms of B12 deficiency as there is a high risk of rapid	Thank you for your comment. The committee has recommended intramuscular vitamin B12 replacement for people who have another condition that may deteriorate rapidly and have a major effect on their quality of life. There was no evidence to suggest intramuscular injections was

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					deterioration regardless of their age or social situation. Given that the committee have stated here that IM injections are likely to be more effective in managing the B12 deficiency then we feel that this advice should be replicated across all groups	clinically or cost effective as a first line treatment for all people with a dietary vitamin B12 deficiency.
510	Pernicious Anaemia/B12d Support Group	Guideline	036	011	**Rationale** It would again appear that the decision to recommend oral replacement when it is believed that the deficiency is unlikely to be caused by malabsorption in this group of people is based on absence of research and evidence. Despite necessary investigations having been completed it is our opinion that anything other than dietary deficiency will be caused by malabsorption and is therefore unlikely to respond to oral therapy, especially if symptomatic	Thank you for your comment. The section in the rationale to which you refer relates to the recommendation for intramuscular vitamin B12 replacement in older people suspected of a dietary deficiency. There is an assumption that if a dietary deficiency is suspected then in most cases oral vitamin B12 replacement will work. The ongoing care and follow up recommendations also include recommendations for switching to intramuscular injections if oral vitamin B12 replacement does not work.
511	Pernicious Anaemia/B12d Support Group	Guideline	036	030	**Rationale** We are very disappointed that no recommendations have been made for self-administered injections, again this decision appears to have been based on lack of evidence. So, whilst patient preference and cost savings were all considered the decision appears to have been based on lack of data on the effectiveness and safety of self-administration. The effectiveness of self-administered intramuscular injections	Thank you for your comment. The guideline review looked for and found no evidence on the effectiveness of self-medication either by intramuscular or subcutaneous injections. There are also no licenced medications for subcutaneous vitamin B12 injections in the UK. The committee agree that self-administration could be beneficial to people with vitamin B12 deficiency, therefore they made a key research recommendation in this area.

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					would be the same as those administered by a healthcare professional and whilst in the UK Hydroxycobalamin is only licensed for IM use, this is not the case in other countries or with other forms of B12. With regards to the safety of self-administration, patients regularly self-administer injections for other medical issues and provided that the patient is happy to self-administer and has the physical and mental capacity to learn how to safely do so it does not seem reasonable that again a positive route to treatment should not be recommended for consideration. Given that currently many of our members have no option other than to source and self-treat, this would surely be a safer option if they were able to do this under the care and guidance of their healthcare providers. This would also have a positive impact of practice budgets as they will not have to bear the costs of the delivery of IM treatment	
512	Pernicious Anaemia/B12d Support Group	Guideline	037	013	**Rationale** From a patient perspective the fact that IM injections will be cost effective over oral replacement if treatment is continued for longer than 6 months is a positive finding. However, we are concerned that the differences in the way IM injections and oral	Thank you for this comment. Funding arrangements are outside of the scope of this guideline. However, the NICE implementation team are raising this with NHS England.

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					treatment are funded encourages GPs to switch patients to oral tablets instead of IM injections as this moves the cost away from individual practice budgets. This will not only result in poor outcomes for patients due to ineffective oral treatment, but is also more expensive for the NHS overall.	
513	Pernicious Anaemia/B12d Support Group	Guideline	038	028	**Rationale** In the case of a repeated serum test indicating that a person does not have a deficiency and there have been no improvement in symptoms whilst on oral treatment, we believe that the most cost effective method in this scenario would be to trial loading doses of IM treatment to see if there is an improvement in symptoms before exploring other avenues and/or other causes	Thank you for your comment. Repeating the initial test at the first follow up appointment has been removed from the guideline and the rationale updated to reflect this. If oral replacement is not working there is the option to optimise the dose or switch to intramuscular injections.
514	Pernicious Anaemia/B12d Support Group	Guideline	039	011	**Rationale** Whilst the committee have recognised that there is little benefit in repeating the initial diagnostic test to measure serum B12 concentrations in people receiving IM treatment as it will influence the test we would have liked to see the same recognition that higher levels on testing following oral therapy are also not going to be an accurate reflection of how well that is working.	The recommendation to repeat the initial test at the first follow up meeting for people taking oral B12 replacement has now been removed from the guideline.

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515	Pernicious Anaemia/B1 2d Support Group	Guideline	039	014	**Rationale** The agreement of the Committee that if symptoms have not improved or that new symptoms have occurred is likely due to the effects of the treatment wearing off before the next planned injection date and recognition that increasing the frequency of injections may be required is a very positive step. We feel that the return of symptoms before the next planned injection date should also be included and also that this be made clearer in the actual guidelines as many GP's currently flatly refuse to consider increasing the frequency of injections outside of the current 8-12 weeks claiming that "it is not permissible and against the rules", thereby leaving patients to suffer the impact on their daily lives from symptom return often weeks before their next injection. Given that there currently also seems to be a trend of GP's insisting on retesting serum levels at 12 weeks and refusing injections if these are in normal range, this is causing a great deal of stress and having a negative impact of peoples lives	Thank you for your comment. The committee were aware that the licenced doses in the BNF are for injections every 2 to 3 months. A review was carried out on the frequency of injections however no evidence was identified on the specific frequency of injections and the committee made a research recommendation in this area.
516	Pernicious Anaemia/B1	Guideline	040	015	**Rationale** **Again, another decision which appears to be based solely on lack of evidence of**	Thank you for your comment. We searched but did not find evidence to support a recommendation to monitor people with autoimmune gastritis for gastric cancer. Therefore we

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	2d Support Group				**effectiveness and presumably cost effectiveness as opposed to the likely better outcome for patients of early diagnosis**	cross referred to the existing NICE guideline on Suspected cancer: recognition and referral.
517	Pernicious Anaemia/B1 2d Support Group	Evidence Review D	013	001	**Identifying the Cause of B12 Deficiency** We do not believe that the Cobasorb test should be included in the new guidelines at this moment in time. The rationale and impact section indicates that not only is it not currently available but that it is a new test however references to it are seen dating back as far as 2006. We have been unable to find anything other than very small research studies which appear to base the effectiveness of the test on biochemical results with no consideration of symptoms. So, we do not feel that there is sufficient evidence to prove that this is a reliable/accurate test to be suggested for use in the guidelines.	Thank you for your comment. The committee considered the lack of evidence for the CobaSorb test but agreed that it may be useful in some clinical contexts. The aim of the recommendation is for healthcare professionals to be aware of CobaSorb as one option among other possible tests when autoimmune gastritis is still suspected despite a negative anti-intrinsic factor antibody test.
518	Queen Mary University of London, Preventive Neurology Unit	Guideline	009	010 - 014 007	1.3.3 & applies to 1.3.1 We disagree with the use of homocysteine as an initial test. This is impractical (and in most areas it has a very long turn-around time). We would recommend testing serum B12 as a minimum. If the B12 is low then no further testing is necessary as treatment would be initiated. B12 is low in around	Thank you for your comment. The committee do not agree that serum B12 should be used when testing for vitamin B12 deficiency suspected to be caused by recreational nitrous oxide use. This is because nitrous oxide inactivates the B12 molecule. The committee do agree that serum MMA is a suitable test and have recommended using either homocysteine or serum

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					50% of those that develop neurological symptoms due to nitrous oxide use. If the B12 is normal then we would recommend checking methylmalonic acid (MMA) (+/- homocysteine). MMA is practically easier to do in primary care as it does not require transport on ice. MMA is also more specific to functional B12 deficiency, and unlike homocysteine is not affected by folate deficiency. Our case series also shows MMA level is correlated to level of nitrous use (Mair et al. 2023, *JNNP*). Additionally, homocysteine may be useful as it may be related to a possible link between nitrous oxide use and VTE. We would also recommend considering that testing be done in secondary care (e.g. ambulatory care) if there might be a delay in interpretation. Patients with nitrous oxide-induced symptoms often deteriorate more quickly that patients with simple B12 deficiency (sometimes developing severe neurological symptoms over a course of days) and hence testing should in general be expedited with serious consideration of	MMA when testing for vitamin B12 deficiency suspected to be caused by recreational nitrous oxide use. The recommendation has also been updated to state that if homocysteine is the chosen test then the person should be referred to phlebotomy services in secondary care.

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					starting treatment prior to results being available. Please see our recommendations on testing published here: • ABN Clinical Practice Guide To Nitrous Oxide (www.the abn.org). • Paris A, Lake L, Joseph A, et al. Nitrous oxide-induced subacute combined degeneration of the cord: diagnosis and treatment. Practical Neurology 2023;23:222-228.	
519	Queen Mary University of London, Preventive Neurology Unit	Guideline	014	019 - 023	1.5.8 There are often concerns regarding patient adherence (many patients using nitrous oxide are vulnerable and isolated) and the resale of high dose oral vitamin B12. We advise that patients with nitrous oxide-related medical issues are managed in a structured environment (such as hospital ambulatory care). Further, we know of no evidence that outcomes for oral and IM replacement are equal when considering neurological damage. If patients have neurological	Thank you for your comment. These recommendations aim to address how to treat the deficiency and the guideline has not addressed issues related to aspects of managing nitrous oxide-related medical issues. The committee has not made recommendations relating to the acute management of vitamin B12 deficiency caused by recreational nitrous oxide use because they agreed this would be handled by the emergency department. In this situation factors other than vitamin B12 deficiency are likely to be considered first and any vitamin B12 replacement would need to be considered within this context. Other guidance such as the Royal College of Emergency Medicine's best practice guidelines on Suspected nitrous

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					symptoms due to nitrous use we would recommend using I.M. B12 to ensure replacement is occurring (and they do not have a co-existent absorption issue), if the patients are willing.	oxide toxicity in Emergency Departments and guidance from the National Poisons Information Service covers this aspect of care. There is no clear evidence to distinguish which out of oral or intramuscular vitamin B12 replacement was more clinically or cost effective for vitamin B12 deficiency caused by recreational nitrous oxide use. Therefore the committee agreed to recommend either oral or intramuscular vitamin B12 replacement. The committee were aware that the emergency department may prefer to offer intramuscular injections however, they were not in a position to decide for them.
520	Queen Mary University of London, Preventive Neurology Unit	Guideline	014	024 - 025	1.5.9 The point to stop nitrous oxide use is of the greatest importance and should go before 1.5.8.	Thank you for your comment. The committee agreed that the first step would be to treat the deficiency, then advise the person to stop.
521	Queen Mary University of London, Preventive Neurology Unit	Guideline	021	004 - 007	Patients with nitrous oxide use leading to symptoms of B12 deficiency often have other, co-existant pathologies, this should be highlighted.	Thank you for your comment. The aim of this section is to describe how the terms used have been defined in the context of the guideline. Co-existent pathologies were not considered as part of the guideline.
522	Queen Mary University of London,	Guideline	028 - 029	024 - 004	Actually in our large series (Mair et al. 2023 JNNP http://dx.doi.org/10.1136/jnnp-2023-331131) and others (Oussalah et al. 2019 J	Thank you for your comment. The committee agree that serum MMA is a suitable option too and have updated the recommendation and rationale to include both serum MMA

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	Preventive Neurology Unit				Clin Med doi: 10.3390/jcm8040551), approx. 50% have a B12 below the reference range. So B12 is useful for about half, and if within normal range, MMA and homocysteine are useful. We do not think there is good evidence for homocysteine rising prior to MMA and indeed some research has suggested that, at least in certain settings, MMA rises before homocysteine (Lee et al. 2019. *Nutrients* doi: 10.3390/nu11020450) The point about the early rise is not that relevant because most nitrous oxide users are chronic and MMA is more practical in primary and secondary care. It is possible that we should be measuring both (as homocysteine may help stratify and clarify the individuals risk of VTE linked to nitrous oxide use).	and plasma homocysteine. There was not the evidence to support a recommendation for both homocysteine and MMA. The research recommendation for diagnosing vitamin B12 deficiency does include investigating combinations of tests.
523	Queen Mary University of London, Preventive Neurology Unit	Guideline	029	005 – 008	We agree with the need for immediate treatment without the need for waiting for test results to return.	Thank you for your comment.

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524	Queen Mary University of London, Preventive Neurology Unit	Guideline	029	009 – 013	We agree with sampling before treatment if possible. Patients should have tests sent for both B12 and a functional test (MMA or homocysteine) at the initial assessment and prior to starting replacement if possible.	Thank you for your comment. This recommendation applies to all tests used for the initial diagnosis and therefore it is anticipated this would happen before any treatment is given.
525	Queen Mary University of London, Preventive Neurology Unit	Guideline	031	017	We disagree that this would be cost saving. Most patients are chronic users and MMA is more specific than homocysteine. If only one of the tests is to be used in this setting it should be MMA.	Thank you for your comment. The committee has updated the recommendation to offer MMA or homocysteine to people with a deficiency caused by recreational nitrous oxide use. We have removed the statement that this will be cost saving.
526	Queen Mary University of London, Preventive Neurology Unit	Guideline	035	001 - 010	It is unclear how long patients should continue B12 replacement in this context – patients who have had neurological symptoms should have regular reviews and the acute treatment course should stop when clinical improvement plateaus (Paris et al. 2023 *Practical Neurology*). Whether or not long term supplementation is required after an initial course is completed depends on whether or not the patient has a co-existent dietary deficiency of B12, which is relatively common in those that develop neurological symptoms following nitrous oxide use.	Thank you for your comment. A new recommendation has been added which states 'Review the need for vitamin B12 replacement if the person stops using nitrous oxide recreationally and they no longer have symptoms of vitamin B12 deficiency.'

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527	Queen Mary University of London, Preventive Neurology Unit	Evidence review B	018	007 and 014	Nitrous oxide with air should be replaced by "Nitrous oxide with oxygen" as Entonox is actually nitrous oxide with oxygen, not air (this is important as asphyxiation is not a risk). This also applies to other the other documents but is mainly here.	Thank you for your comment. 'Nitrous oxide with air' has now been replaced by 'Nitrous oxide with oxygen' where reference is made to medicinal nitrous oxide throughout the guideline.
528	Queen Mary University of London, Preventive Neurology Unit	Evidence review B	019	005, 008, 009, 013, 016, 019, 023, 024, 027, 033	Nitrous oxide with air should be replaced by "Nitrous oxide with oxygen" as Entonox is actually nitrous oxide with oxygen, not air (this is important as asphyxiation is not a risk). This also applies to other the other documents but is mainly here.	Thank you for your comment. 'Nitrous oxide with air' has now been replaced by 'Nitrous oxide with oxygen' where reference is made to medicinal nitrous oxide throughout the guideline.
529	Queen Mary University of London, Preventive Neurology Unit	Evidence review B	019	028	We would recommend changing this line to being "A functional test of B12 activity, such as homocysteine or MMA should be measured in this context".	Thank you for your comment. This has been updated as suggested. The committee also updated the recommendation for testing when recreational nitrous oxide use is the suspected cause for vitamin B12 deficiency to include homocysteine or MMA as options.
530	Queen Mary University of London, Preventive Neurology Unit	Evidence review C	043 - 044		**Final paragraph / first paragraph.** Nitrous oxide does cause a rise in MMA (Mair et al. 2023 JNNP) which correlates to the degree of nitrous oxide used. We know	Thank you for your comment. We have added the word 'sometimes' to clarify that the tubes are not always required.

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					of no evidence to suggest that this is slower than the rise in homocysteine. Homocysteine is less specific for inactivation of B12 than MMA, and homocysteine can be affected by folate levels. Homocysteine does not always require special tubes (and often does not) but does always require transport on ice, creating a serious barrier to use in primary care as compared to MMA.	
531	Queen Mary University of London, Preventive Neurology Unit	Evidence review E	056	015 – 026	We would recommend that if a patient has neurological symptoms due to nitrous oxide use then they should preferably have I.M. replacement to ensure immediate replacement (any delay in replacement may worsen disability and in this context a co-existent malabsorption cannot be ruled out immediately). There is no evidence to suggest oral replacement is equivalent to IM replacement in this context.	Thank you for your comment. There is no clear evidence to distinguish which out of oral or intramuscular vitamin B12 replacement was more clinically or cost effective for vitamin B12 deficiency caused by recreational nitrous oxide use. The committee has not made recommendations relating to the acute management of vitamin B12 deficiency caused by recreational nitrous oxide use because they agreed this would be handled by the emergency department. In this situation factors other than vitamin B12 deficiency are likely to be considered first and any vitamin B12 replacement would need to be considered within this context. Other guidance such as the Royal College of Emergency Medicine's best practice guidelines on Suspected nitrous

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						oxide toxicity in Emergency Departments and guidance from the National Poisons Information Service covers this aspect of care. Therefore the committee agreed to recommend either oral or intramuscular vitamin B12 replacement. The committee were aware that the emergency department may prefer to offer intramuscular injections however, they were not in a position to decide for them.
532	Royal College of Physicians and Surgeons of Glasgow	Guideline	General	General	The Royal College of Physicians and Surgeons of Glasgow although based in Glasgow represents Fellows and Members throughout the UK. While NICE has a remit for England (where 50% of our UK membership is based), many of the recommendations are applicable to all devolved nations including Scotland. They should be considered by the relevant Ministers of the devolved governments. The College is in general is supportive of the document Vitamin B12 deficiency in over 16s: diagnosis and treatment.	Thank you for your support.
533	Royal College of Physicians and Surgeons of Glasgow	Guideline	008	001	Some drugs can cause macrocytosis without B12 or Folate deficiency eg Methotraxate and Sulfasalazine.	Thank you for your comment. The recommendations are only to highlight the risk factors for vitamin B12 deficiency and not macrocytosis.

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534	Royal College of Physicians and Surgeons of Glasgow	Guideline	012 018	005, 007 018	In the investigation section they do give ranges for vitamin B12 levels but they do not give ranges for the following 1. Anti-intrinsic factor antibodies and in particular if these are +ve what is the chance of having pernicious anaemia and if they are negative what it the chance of not having it (ie negative and positive predictive values). The same applies to anti-parietal cell antibodies where false positives also need to be taken into account. I think this information would be very helpful in allowing the readers to help understand and interpret the results. 2. There are no values given for the MMA results. These would be helpful in allowing readers to interpret results particularly as this is a test which is unfamiliar to many.	Thank you for your comment. The committee agreed it was not possible to provide reference ranges for the anti-intrinsic factor antibody tests. It is a matter of whether antibodies are present or not and the laboratories will advise on this with the test results. The committee were unable to provide values for serum MMA and a recommendation has been added to use the laboratory's reference ranges to decide if vitamin B12 deficiency is likely when interpreting serum MMA.
535	Royal College of Physicians and	Guideline	012	006	Also, within the investigation section there is no comment about looking for other causes of malabsorption and in particular Crohn's disease or pancreatic	Thank you for your comment. Other causes of the vitamin B12 deficiency are recommended in the follow up section of the guideline rather than here. The guideline didn't include a

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	Surgeons of Glasgow				insufficiency (albeit rare). Stool testing for faecal calprotectin as a screen for Crohn's should be considered and if there are symptoms also for faecal elastase to look for pancreatic insufficiency. Consideration should be given to these investigations if the tests for the more comment cause (eg pernicious anaemia or coeliac disease) are negative.	review on testing for all potential other causes because several of the symptoms can apply to many causes. The cross reference to the NICE guideline on Coeliac disease is only included because there is a recommendation on testing for Coeliac disease where the cause of vitamin B12 deficiency is still unknown.
536	Royal College of Physicians and Surgeons of Glasgow	Guideline	017	001	In the treatment section there is no mention of whether patients should be tested for other causes of anaemia (folate or iron deficiency) which often go together. Some advice about treatment of combined deficiencies should be considered and in particular the point that B12 replacement should be started before folate replacement should be included.	Thank you for your comment. Investigating and managing complications related to vitamin B12 deficiency and cofactors were not included as part of the scope of the guideline. Therefore they were not included as part of the guideline reviews and no recommendations have been made related to this.
537	Royal College of Physicians and Surgeons of Glasgow	Guideline	020	006	For the follow up section our reviewer completely agreed with the recommendations on indications for gastroscopy - ie upper GI symptoms or red flag symptoms and B12 deficiency is an indication for OGD but not B12 deficiency alone. It was felt that more clarity could be given about follow up. In the absence of an underlying cause that needs follow up (eg inflammatory bowel disease and, more arguably, coeliac disease) then follow up	Thank you for your comment. We have not included recommendations on managing other conditions as we did not include a section on what else to investigate for people in whom other conditions may be present. The recommendations in this section are there to highlight the increased incidence of gastric adenocarcinoma and gastric neuroendocrine tumours in people with suspected or confirmed autoimmune gastritis. Raising awareness of this may mean people are more likely to report any gastrointestinal symptoms to their healthcare professional.

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					should be in primary care. The wording leaves some ambiguity which may be unhelpful.	
538	Royal Pharmaceutical Society	Guideline	015	012 - 020 and 028	Paragraph 1.5.14 gives a suggested minimum dose of at least 1,000 micrograms a day in pregnancy or during breastfeeding. Paragraph 1.5.12 does not give a suggested minimum dose for all other patient groups and it would support patient counselling if this was included in the guidelines.	Thank you for your comment. NICE does not include dosage in recommendations where they are available in the BNF or SPC. A dosage may be included if this information is not available, or the committee agrees that there needs to be a change to current recommended dosages, for example because of new evidence. The guideline has been updated to recommend at least 1mg a day when oral vitamin B12 replacement is prescribed in cases of malabsorption. This is because all comparisons for oral with intramuscular vitamin B12 replacement used 1mg of oral replacement. The committee also agreed that there was no evidence to suggest a lower dose would be effective in this group and that using this dose is likely to be current practice for this group. The dosage is stated to ensure that these patients receive the appropriate treatment. There wasn't evidence to recommend a 1mg dose for people with medicine or nitrous oxide induced deficiency. Oral vitamin B12 replacement can be prescribed at lower doses for a dietary deficiency.
539	Severnvale PCN	Guideline	General		I am concerned that this guideline will generate an unfeasible amount of work for general practice at a time when the NHS is already under extraordinary pressure. I work as a GP Partner in an NHS practice	Thank you for your comment. The committee discussed all areas carefully before making the recommendations. They agreed to revise the recommendations on who to test so that fewer people are recommended for testing. However, they acknowledge that some investment will be required.

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					and am on the NICE diagnostics advisory committee. Currently I personally see around 4-5 borderline B12 results per week in my practice of 5,500 patients. It is unrealistic and unachievable to provide the care as suggested Fin the NICE guideline and it is outside the scope of what is feasible to achieve within current NHS resources. I appreciate the guidelines may not reflect the standard of care but gap between advice and what is possible is particularly startling in this case.	
540	Severnvale PCN	Guideline	General		It is not clear or easy to understand when oral replacement is acceptable. My interpretation is that oral replacement is generally an acceptable option so long as there is no autoimmune gastritis and no B12 deficiency due to surgery. Given that surgery will generally be obvious, it seems to me that therefore the main concern is to exclude autoimmune gastritis (as well as coeliac, but given that oral replacement is an option here – if I interpret page 14 line 2 correctly - this is arguably less of an issue)	Thank you for your comment. The treatment recommendations and rationale have been updated to make this clearer. Intramuscular injections are recommended for autoimmune gastritis, total gastrectomy and complete terminal ileal resection. Other types of surgery that are a risk factor for vitamin B12 deficiency (partial gastrectomy, partial terminal ileal resection or some forms of bariatric surgery) do not always cause malabsorption and therefore oral replacement could be used. However, there was an absence of evidence for this and the committee agreed that intramuscular injections is likely to be the better option.

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					It seems to me it would be more efficient to also check automatically for autoimmune gastritis with anti-intrinsic factor antibody as a cascade test (i.e., requested automatically by lab) when the B12 is low or borderline There are potential logistical issues with bringing patients back for multiple blood tests while waiting to start treatment	Hence the recommendation consider intramuscular injections instead of oral vitamin B12 replacement. Evidence was not identified to test for autoimmune gastritis in everyone with a confirmed vitamin B12 deficiency and there is a large resource impact in recommending everyone is tested. A significant number of people may just have a dietary deficiency that would not require a further test. This would be the same whether the test produced a low or borderline result. Therefore the committee only recommend people suspected of autoimmune gastritis should be considered for an anti-intrinsic factor antibody test.
541	Severnvale PCN	Guideline	007	002	Some of the symptoms listed are extremely common. It would be much more helpful in practice to provide a framework which also includes the duration of the symptom and or the severity. For example, fatigue lasting four weeks or more (see https://bjgp.org/content/59/561/e93) Lowering a threshold for investigation may well have the advantage of identifying people more quickly, but it also increases the risk of false positives, and cascade	Thank you for your comment. Evidence was not available to provide numbers relating to duration of a symptom or prevalence. The citation provided did not meet the protocol criteria because it does not contain information on the diagnostic accuracy of specific signs, symptoms or tests for detecting vitamin B12 deficiency. Therefore, it has not been included as evidence in this guideline. Following stakeholder comments mental health problems have been removed from the symptoms and signs box, and age over 65 removed from the risk factors box. This also

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					testing. Overall, there may be more harm to the population from early investigation than benefit if the risks of waiting are not severe. Other symptoms are common but perhaps rarely associated with b12 deficiency (e.g., anxiety or depression). I could not see any data presented on the prevalence of B12 deficiency in anxiety or depression in the evidence review. It is not clear to me what the evidence is that these conditions are associated specifically with an increased risk of B12 deficiency, rather than an increased risk of blood testing (which then picks up an incidental B12 deficiency). It would be helpful to provide prevalence figures for b12 deficiency for each of the clinical presentations listed so that clinical judgement can inform the relevance and importance of testing. However, I note in the evidence that there is No evidence for any of the symptoms and signs said to be associated with B12 deficiency. I think this severely undermines Box 1 in the guideline. In the absence of evidence why is it not appropriate to simply state:	means there is no longer a statement explicitly recommending testing in these groups. The committee agreed that unexplained fatigue is an important symptom in vitamin B12 deficiency and that this in combination with the risk factors did warrant people being tested for a vitamin B12 deficiency. They agreed that now that age has been removed as a risk factor this would greatly reduce the number of people being tested. The committee agreed that while there is little or no evidence for all of the other entries in the boxes they are commonly accepted as likely symptoms, signs and risk factors for vitamin B12 deficiency. The committee has been careful to only offer a test if the person has at least 1 symptom or sign and 1 risk factor. In the absence of evidence, the committee made a consensus recommendation. They agreed that some guidance was needed for readers and limited recommendations to common symptoms and signs.

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					"use clinical judgement to determine when to test for B12 deficiency. Signs and symptoms may include … and risk factors may include …"	
542	Severnvale PCN	Guideline	011	020	Given the lack of evidence on the signs and symptoms of B12 deficiency it is not clear what this statement is based on. Consideration should be made of why it would not be appropriate, for example for people with intermediate results to be given B12 treatment empirically perhaps over the counter. The proposal as it stands potentially creates a very large number of people who will need a blood test on a six monthly basis (according to the guideline) to ensure that they are not becoming deficient in B12 Given that many intermediate B12 results are identified as incidental findings the requirement to ask about symptoms, which may or may not be attributable to the B12 deficiency – such as fatigue – will add to workload of practices. It is highly likely that in modern general practice many practices would simply issue a prescription and send an email or electronic message to the patient with advice and a link to an advice leaflet; workload levels (and indeed the	Thank you for your comment. This recommendation applies to people who had a total or active B12 test as part of routine testing rather than they were suspected of having a deficiency. In this case the committee agreed they are unlikely to have a deficiency but should seek help if they develop symptoms of a vitamin B12 deficiency. The recommendation has been updated to advise people to seek medical help if they develop symptoms or signs of deficiency.

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					volume of intermediate B12 levels) would make it very hard to do any more than this without seriously impacting on the care available to other patients.	
543	Severnvale PCN	Guideline	017	022	This assumes there is a reasonable basis to attribute the symptom to the B12 deficiency, which there appears to be very little evidence for. If fatigue has not improved with B12 tablets, this is likely to result in many people requiring B12 injections which would significantly add to the work of GP practice nurses when the workforce is already under severe strain	Thank you for your comment. Following stakeholder comments the recommendation for repeating the initial test for people on oral vitamin B12 replacement has been removed from the guideline. The committee were agreed it was important to base response to treatment on the person's symptoms. They were aware that there is increasing pressure on GP practices and had hoped evidence would be available to recommend self-administration of vitamin B12 replacement. However, in the absence of evidence they made a research recommendation in this area. The recommendations have also been updated to advise optimising oral vitamin B12 replacement or switching to intramuscular injections if symptoms have not sufficiently improved, and to consider further testing if they have worsened or new symptoms have developed.
544	The Association for Clinical biochemistry and laboratory	General	General	General	The ACB highlighted the draft consultation to its 1257 full members, and asked for their feedback, this feedback was collated by the scientific and clinical practice committee of the ACB and reviewed for themes and relevance against the draft consultation. It	Thank you for your comment we will respond to these in turn.

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	medicine (ACB)				is summarised below in the following 6 points.	
545	The Association for Clinical biochemistry and laboratory medicine (ACB)	General	General	General	In answer to the Q1 above, hopefully the points above outline that we believe it will be challenging to implement the guidance around diagnosis and the use of the currently not widely available Active B12 and serum/ plasma MMA. With regard to Q2, although the ACB does not have access to all Laboratories costing, as acknowledged by NICE Serum/ plasma MMA is an extra test in this pathway, that in the current market can cost significantly more than Vitamin B12 (One member quotes a test price of £60) so this alongside a substantial increase in workload, is likely to have a large financial impact that would make the recommendation very difficult to implement. We would welcome working with NICE to ensure that Serum/plasma MMA cost were reduced, and availability increased to enable this recommendation to be effective. It should also be noted that the active B12 recommendation will also have financial impact, unless it cost again could be reduced in collaboration with NICE.	Thank you for your comment. The committee thought carefully before making the recommendations and took cost effectiveness into account. Implementing these recommendations will require some reallocation of resources. A resource impact report and tool will be published alongside this guideline. The committee agreed that using active B12 would not require a change in practice for GP surgeries because it can be carried out on the same serum sample as for total B12. They also agreed that in their experience, active B12 is a more accurate test than total B12. However, they recommended either total or active B12 to reflect the lack of evidence demonstrating this and the lack of availability of active B12 at all laboratories. Active B12 is recommended if vitamin B12 deficiency is suspected during pregnancy based on expert witness advice because total B12 may not be an accurate test during pregnancy. Regarding MMA as a first-line test, the committee agreed that total and active B12 are not suitable tests for people with a deficiency caused by nitrous oxide use and therefore recommend more expensive tests. As a second- line test they agreed that serum MMA is expensive and weighed up

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						the benefit of making a diagnosis against the extra cost of serum MMA as a second-line test. Untreated vitamin B12 deficiency could have a harmful impact and the committee agreed that obtaining a diagnosis if possible is important. However, they also agreed that there isn't the evidence to show that MMA will lead to a diagnosis therefore they made a weaker 'consider' recommendation to reflect this.
546	The Association for Clinical biochemistry and laboratory medicine (ACB)	Guideline	009	010	1.3.3 There is evidence that the prevalence of elevated MMA and homocysteine is similar in recreational nitrous oxide users. However, getting an MMA test is operationally simpler, with much lower chances of sample rejection and is more specific in areas with higher prevalence of folate deficiency. (*Reference: Ménétrier T, Denimal D. Vitamin B12 Status in Recreational Users of Nitrous Oxide: A q Review Focusing on the Prevalence of Laboratory Abnormalities. Antioxidants (Basel). 2023 May 31;12(6):1191. Doi: 10.3390/antiox12061191.PMID:37371921)* Therefore, MMA should be considered as the initial test instead of homocysteine, or an option should be provided to test either MMA or homocysteine or both depending on feasibility.	Thank you for your comment. The committee agree and have recommended using either homocysteine or serum MMA when testing for vitamin B12 deficiency suspected to be caused by recreational nitrous oxide use. Thank you for the citation. We checked this to ensure we had not missed evidence. The study did not meet the criteria for the review protocol.

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547	The Association for Clinical biochemistry and laboratory medicine (ACB)	Guideline	009	010	1.3.3 Elevated homocysteine is not specific for B12 deficiency. Another common cause of elevated plasma homocysteine is folate deficiency which is fairly prevalent in the UK population. Whereas elevated methylmalonic acid (MMA) is largely specific for B12 deficiency. The Preanalytical issues, around the measurement of homocysteine should also be outlined, stating that these test would not be routinely available in primary care setting.	Thank you for your comment. Following stakeholder comments the committee have recommended using either homocysteine or serum MMA when testing for vitamin B12 deficiency suspected to be caused by recreational nitrous oxide use. The recommendation has also been updated to state that if homocysteine is the chosen test then the person should be referred to phlebotomy services in secondary care.
548	The Association for Clinical biochemistry and laboratory medicine (ACB)	Guideline	010	018	1.3.10 We strongly recommend that Plasma/ serum MMA is written rather than just MMA, as urine MMA is freely and commonly requested, but would not be useful in this context.	Thank you for your comment. The committee agree and have specified serum MMA in all recommendations.
549	The Association for Clinical biochemistry and laboratory	Guideline	010	018	1.3.10 The ACB understand the rationale for the Vitamin B12 cutoffs- however the ACB are always concerned when numerical target values are assigned in national guidance,	Thank you for your comment. Several stakeholders commented on the thresholds. Some thought they were too low, others thought they were too high and there was also some support that they are about right.

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	medicine (ACB)				due to assay variation seen nationally, in many laboratory medicine tests. It should be noted that Vitamin B12 assays show significant variation and have been shown to have an Bimodal distribution in some cases, when EQA samples are reviewed. With the last 9 samples showing a negative bias (approximately 25%) for one particular supplier. This supplier is shown to be used by 13% of subscribers to the EQA scheme. We suggest that the guidance should state that cut-offs for diagnosis and further testing should be discussed and agreed with provider laboratories.	Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not. Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests. The committee also recommend considering MMA as a further test for people with an indeterminate active or total B12 test result. This is to capture people who may have a vitamin B12 deficiency when their test result doesn't meet the criteria for deficiency. An indeterminate result covers an active B12 of between 25 and 70 pmol per litre, and a total B12 of between 180 and 350 nanograms (133 and 258 pmol) per litre. The committee has also added a recommendation to use the laboratory's reference ranges to decide if vitamin B12 deficiency is likely when interpreting serum MMA and plasma homocysteine test results.
550	The Association for Clinical biochemistry and	Guideline	012	001	1.3.15 The ACB have concerns that no interpretation of Serum/plasma MMA results is discussed, we suggest that reference should be made to local/	Thank you for your comment. The recommendation has been updated to advise investigating other causes as well as

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	laboratory medicine (ACB)				reference laboratory ranges, and it should be mentioned that renal impairment and bacterial overgrowth can affect MMA results.	considering a repeat of the initial test if they are still experiencing symptoms or signs 3 to 6 months later. MMA has been removed because the committee agreed that most laboratories would not allow for an MMA without testing total or active B12 first. However, a recommendation has been added earlier in the guideline advising the use of the laboratory's reference ranges when interpreting serum MMA test results. The factors that affect MMA test results have not been included in the guideline.
551	The Association for Clinical biochemistry and laboratory medicine (ACB)	Guideline	012	001	1.3.15 The ACB have major concerns around the resource, capacity and financial aspect of this recommendation and the measurement of serum/ plasma MMA, as it is not routinely available in most UK laboratories, and will be an extra financial pressure to all laboratories if this recommendation was fulfilled. We could see no mention of how the capacity to do the tests will be generated. As far as we are aware there aren't any rapid methods available, only mass spectrometry for the measurement of plasma/ serum MMA. Some members have attempted to estimate the increase in Serum/plasma MMA	Thank you for your comment. The recommendation has been updated to advise investigating other causes as well as considering a repeat of the initial test if they are still experiencing symptoms or signs 3 to 6 months later. MMA has been removed because the committee agreed that most laboratories would not allow for an MMA without testing total or active B12 first.

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					requests-please see below for direct quotes: "*I work in a health board serving 1.2 million patients. Looking at adult patients, excluding all women under 40 to remove most potentially pregnant patients we perform 3680 B12 analysis / week. Of these 45% or 1660 samples per week are in the indeterminate range 180 – 350 ng/L.* *We have both TMS and HPLC methods evaluated but not in use. With investment in pre-analytics and staffing time we could accommodate up to 10% of this potential workload. Any further analytical demand would require significant capital investment."* And *"My own laboratory measures serum MMA and we certainly would have neither the staffing capacity nor the tandem mass spectrometer capacity to do around 300 samples per day that would fall in the grey zone generated by our local general biochemistry laboratory let alone for our nearest DGH's who have no tandem mass spectrometers at all, and so would be looking for a referral laboratory. No doubt some of these tests would not be indicated, but it is not clear how this would be*	

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					managed, it's hard to envisage vetting the samples with such large numbers, but adding MMA retrospectively by the requesting clinician once the vitamin B12 result has been reviewed would (likely) be unacceptably time consuming for them. The addition of a liquid handler to my laboratory would help alleviate the pressure on staff time, but it would not be possible to free up 15+ hours a day of run time on a TMS; we already have 4 TMS instruments so finding space (along with the venting requirements) for another would not be an option, even if the necessary funding were provided". Although the ACB appreciate the guidance attempts to improve Vitamin B12 deficiency diagnosis, we do not believe that our members laboratories would be able to fulfil this key recommendations, without significant improvement , in capacity, and resources. We have concerns that the full financial cost to laboratories who will likely be impacted has not been fully considered.	
552	The B12 Society	Guideline	General	General	Too many sections of this guideline provide vague or ambiguous statements leaving too	Thank you for your comment. The guideline has been updated to provide more detail and to remove ambiguity

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					much room for confusion, or misinterpretation	where possible. The lack of evidence meant the committee were restricted in what they could recommend.
553	The B12 Society	Guideline	General	General	There is much mention of oral supplementation throughout this guideline, both prescribed and over-the-counter, however no mention of the potential risk of pseudo B12 containing supplements. Because of this risk, only quality certified oral supplements should be recommended.	Thank you for your comment. The recommendation advising people taking oral supplements has been updated to state 'explain that some supplements do not contain enough, or the right type, of vitamin B12 to be effective'. Over-the-counter vitamins, as included in this recommendation are food supplements, which are required to comply with food legislation in terms of their composition, manufacturer and control. It is outside the remit of NICE to cover such legislative issues in recommendations. Advising healthcare professionals on the dose of unlicenced preparations is beyond the remit of NICE. When making decisions about the use of unlicensed medicines, users should follow General Medical Council's prescribing guidance: prescribing unlicensed medicines and the MHRAs drug safety update for off-label or unlicensed use of medicines.
554	The B12 Society	Guideline	General	General	This guideline relies too much of clinicians using their "clinical judgement", covering various aspects of vitamin B12 deficiency: recognising deficiency, testing and diagnosing deficiency, treating and managing deficiency. Although GP's and other clinicians employ this form of decision making on a daily basis, to suggest they do so for a condition they are given what can	Thank you for your comment. The lack of evidence meant the committee were restricted in what they could say. Some recommendations have been updated to define this further. The section on 'Information for the public' on this guideline's web page also provides links to other organisations' websites which provide more detailed advice directly written for people with suspected or confirmed vitamin B12 deficiency. NICE guidelines do not generally link to other medical association

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					only be described as desperately limited education is simply ludicrous and allows too much margin for error, thus putting lives at unnecessary risk. The guideline should, at the least, provide links to appropriate references for the information they require to make such clinical judgements. We suggest adding a link to the British Society for Haematology "Guidelines for the diagnosis and treatment of cobalamin and folate disorders": https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.12959, And/or links to the credible and well researched data available on some B12/PA charity websites: https://www.theb12society.com/treatment and https://pernicious-anaemia-society.org/treatment/	or patient support group guidelines or websites from the recommendations because these may change and NICE has no control over the content.
555	The B12 Society	Guideline	General	General	This guideline refers too often to the person's or individuals' "preference" regarding treatment with either intramuscular injection or oral supplements. Although some people appear to be able to passively absorb enough B12 from oral supplements, (the mechanism of which is	Thank you for your comment. Where there isn't evidence to suggest one treatment is better than the other, both options are given equal weighting. The choice between oral and intramuscular treatment was discussed carefully by the committee. Based on their expert opinion they agreed that oral replacement had worked well for some people during covid and that there was evidence it could be effective. More

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					questionable), this is not the case for the majority of people with B12 deficiency, and further research is required. Therefore, offering oral supplements as an option in any cases of deficiency other than those caused by dietary deficiency, is gambling with people's health, and doing so at low odds! Since the risk of irreversible neurological damage is highly documented, why offer oral supplements as an option to these patients, knowing that, in general, they will be making uninformed decisions, and that most will do so based upon the fact that B12 injections are often painful and unpleasant. It's not about "the person's preference", rather what is best for the person's health and wellbeing. The appropriate treatment is with injections. The rationale notes that "there was no evidence to suggest that oral replacement was ineffective" - until there is clear evidence that it *is* effective, this risk should not be taken.	importantly, there was no evidence to suggest it wasn't effective. The recommendation for people with malabsorption other than autoimmune gastritis and surgery has been updated in light of stakeholder comments. Intramuscular vitamin B12 replacement is considered over oral vitamin B12 replacement instead of them being an equal option.

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556	The B12 Society	Guideline	General	General	It is of great concern to The B12 Society and the members of our online support group (https://www.facebook.com/groups/707933819262618), which has >52,000 members, that throughout this entire draft guideline there is no mention whatsoever of vitamin B12 cofactors. With vitamins B9 (folate) and B6 (pyridoxine) known to be essential to the healthy functioning of vitamin B12, guidance on the necessity of both these cofactors should not be omitted from this guideline. To do so would be to provide an incomplete guide, allowing the diagnosis and management of vitamin B12 deficiency to be less effective, or even ineffective, for significant numbers of people with vitamin B12 deficiency. It is also widely documented that vitamin B12 is an essential cofactor to iron in erythropoiesis, therefore, to avoid macrocytic anaemias, a healthy balance of B12 and iron is a necessity. It should also be noted that during loading doses of parenteral vitamin B12, it is important to monitor potassium levels as they may drop, causing symptoms which	Thank you for your comment. Investigating and managing complications related to vitamin B12 deficiency and cofactors were not included as part of the scope of the guideline. Therefore they were not included as part of the guideline reviews and no recommendations have been made related to this.

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					clinicians often assume are a negative reaction to B12 injections, and stop treatment. Without cofactors B12 cannot work effectively, and we constantly see this with members finding B12 treatment not working due to their cofactor deficiencies/inefficiencies not being addressed by their primary and/or secondary healthcare providers. This causes unnecessary suffering for vitamin B12 deficient people and creates added costs to the NHS for wasted B12 treatment that cannot work effectively due to an individual's lack of B12 cofactors. This is often followed by clinicians assuming that symptoms must be due to other conditions, leading to misdiagnosis/misdiagnoses, thus further unnecessary costs to the NHS. To omit guidance on essential B12 cofactors would be inappropriate and detrimental to the overall success of this guideline.	
557	The B12 Society	Guideline	General	General	It is of great concern to The B12 Society and the members of our online support group (https://www.facebook.com/groups/707933	Thank you for your comment. There was little evidence in relation to paediatrics and unfortunately we were unable to recruit all the expertise necessary to be able to develop

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					819262618), which has >52,000 members, that this guideline does not cover vitamin B12 deficiency in under 16's. We see increasing numbers of parents desperately seeking guidance for their children with either confirmed B12 deficiency or suspected B12 deficiency, so there is clearly a need for such a guideline. Although this guideline recognises the potential threat to unborn babies of pregnant people with vitamin B12 deficiency, it fails to address the risk of B12 deficiency in children from birth until they reach 16 years of age. These are crucial years in human development and have been proven to require efficient levels of vitamin B12 to ensure optimal growth, including neurological development. With increasing mental health needs, and higher occurrence of neurodivergence in this age group, we must not ignore the potential of vitamin B12 deficiency's involvement either in utero, or at other key stages of development.	recommendations in relation to children. Overall, the decision NICE made was that it was better to focus on adults.

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					Sticking our heads in the sand will not make paediatric B12 deficiency disappear, nor will it protect this generation of society. By not addressing paediatric B12 deficiency we are simply shirking our responsibility.	
558	The B12 Society	Guideline	004	003 - 006	If autoimmune gastritis is to be used to describe all autoimmune forms of vitamin B12 deficiency, including Pernicious Anaemia (PA), this should be clearly stated at the start of this document to ensure no ambiguity of its meaning. Generally, most health professionals in the UK are only familiar with the term PA. Although autoimmune gastritis might be a better name to use going forward as it also covers other inflammatory causes of the deficiency, it will take time to familiarise clinicians with this term, during which many people with PA could suffer due to confusion.	Thank you for your comment. The guideline has been updated to acknowledge the difference between autoimmune gastritis and pernicious anaemia and provide a more detailed reason as to why the term 'pernicious anaemia' has not been used. This explains that autoimmune gastritis is sometimes referred to as pernicious anaemia which is a separate condition that can be a consequence of chronic, severe vitamin B12 deficiency, including deficiency caused by autoimmune gastritis. However, pernicious anaemia in its true sense (that is 'a life-threatening anaemia') is now extremely rare because of developments in testing and treatment for, and greater awareness of, vitamin B12 deficiency. For this reason, and to prevent any confusion with autoimmune gastritis, we have not used the term 'pernicious anaemia' in the recommendations.
559	The B12 Society	Guideline	004	020 - 021	"the symptoms and signs associated with vitamin B12 deficiency are also linked to many other conditions"	Thank you for your comment. The intention is to highlight that there is overlap between the symptoms of vitamin B12 deficiency and other conditions. It is not to highlight which

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					This could be misleading as it is known that not only can the symptoms and signs of B12 deficiency present like those of other conditions, but B12 deficiency can also be involved in many other health conditions such as heart attack, stroke, Alzheimer's, multiple sclerosis, mental health disorders, fibromyalgia, functional neurological disorder etc, therefore it is important not to dismiss the symptoms and signs as being some other condition if blood results are not clearcut, as a person could have a B12 deficiency as part of another condition.	symptoms and signs are important for other conditions which would be dealt with in other guidelines. The recommendation has been updated to 'symptoms and signs of vitamin B12 deficiency may also be associated with many other conditions.'
560	The B12 Society	Guideline	005	003 - 004	We suggest a rephrasing: "most people only need 1 blood test to **support** the diagnosis of vitamin B12 deficiency, but some may need further tests **especially in areas with lower reference values set below 200 ng/L. Additional tests may be required to determine the cause of deficiency**". Please be aware that reference ranges can vary drastically from one area of the country to another, with some lower values set as low as 100 ng/L. Analytics from our online support group (https://www.facebook.com/groups/707933	Thank you for your comment. This has been updated to state 'a single blood test can be enough to support a diagnosis of vitamin B12 deficiency but some people may need further tests to diagnose the condition'. The committee noted that there is no universal international threshold with which to define deficiency; it will vary according to how deficiency is diagnosed, the population studied and the assay used for each country.

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					819262618) of >52,000 members, show significantly higher membership from these areas.	
561	The B12 Society	Guideline	005	011	"treatment with vitamin B12 replacement is effective in most people" This is misleading, as it is well established that without sufficient cofactors B12 cannot metabolise effectively. The following should be added to this line: "…even more so when levels of cofactors are optimised, these include iron, folate, and vitamin B6".	Thank you for your comment. Investigating and managing complications related to vitamin B12 deficiency and cofactors were not included as part of the scope of the guideline. Therefore they were not included as part of the guideline reviews and no recommendations have been made related to this. The committee looked at the recommendation again and agree it is still correct.
562	The B12 Society	Guideline	006	007 - 010	Many people do not have a known risk factor, to wait until they develop one, e.g. an autoimmune condition, would be costly to the NHS with a likelihood of countless other appointments, investigations, and treatments, and to the individual with deteriorating health issues, including the potential for irreversible neurological damage.	Thank you for your comment. No evidence was identified to make a strong recommendation that people with one of the symptoms or signs without a risk factor, or one of the risk factors without a symptom or sign, should be tested. The committee agreed that the symptoms and signs associated with vitamin B12 deficiency vary and can also be indicative of other conditions. Without the evidence, making a recommendation to test people with just one of the symptoms or signs or risk factor would hugely increase resource impact without any evidence of benefit. The committee recognise that there may be people in whom there is a suggestion of vitamin B12 deficiency without a risk factor, however this would vary and need to be assessed on

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						a case-by-case basis. Consequently, they recommended that clinical judgement would need to be used to decide if a person should be tested in these circumstances.
563	The B12 Society	Guideline	006	011 – 012	This statement in the guideline should make it clear that anaemia and macrocytosis are usually signs of later stage B12 deficiency, with neurological symptoms and signs generally preceding blood manifestations. It should also be detailed that when both macrocytic anaemia and microcytic anaemia are present, they can cancel each other out on blood screening, effectively masking one another, and returning what appears to be a normalised result. Clinicians who work with our charity confirm that although they see macrocytosis in B12 deficient people, it is not a common finding within this group of people. However, too many clinicians still believe that a B12 deficiency cannot exist without anaemia or macrocytosis. Better clarity could help reduce this issue.	Thank you for your comment. The committee agree that macrocytic and microcytic anaemia can cancel each other out. They also agree that there is a common misconception that you cannot have a deficiency without either, or both, of these signs being present. This recommendation is to help ensure vitamin B12 deficiency is not missed in people who do not have anaemia or macrocytosis. The committee agreed to keep the detail as simple as possible in the recommendation and rationale and did not put all detail around anaemia and macrocytosis in. The point about anaemia and macrocytosis are usually signs of a later stage of vitamin B12 deficiency could be interpreted that they will be present and detract from the main point of the recommendation.
564	The B12 Society	Guideline	006 - 007	018 - 019	And including box 1	Thank you for your comment. The recommendations and box have been updated to make it clear that these are common symptoms and signs. NICE guidelines do not generally link

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					"Recognise that the symptoms and signs listed in box 1 can suggest a vitamin B12 deficiency." This statement is misleading, as the list it refers to offers only limited information of the possible symptoms and signs of vitamin B12 deficiency. Please make it clear that Box 1 lists "some" of the potential symptoms and signs. We understand that a comprehensive list would be too long and require too much explanation for it to be included in this guideline, therefore we suggest providing links to external resources such as B12/PA charity websites, e.g. https://www.theb12society.com/signs-and-symptoms, or https://pernicious-anaemia-society.org/symptoms/	to other organisation guidelines or websites because these may change and NICE has no control over the content. The section on 'Information for the public' on this guideline's web page also provides links to other organisations' websites which provide more detailed advice directly written for people with suspected or confirmed vitamin B12 deficiency.
565	The B12 Society	Guideline	007		Box 1 "Neurological or mobility problems related to peripheral neuropathy, or to central nervous system disease including myelopathy (spinal cord disease):"	Thank you for your comment. No evidence was identified to suggest autonomic nervous systems should be listed here and the committee agreed it should not be included. The box and recommendations related to symptoms and signs have been edited to make them clear that this refers to 'common' symptoms and signs.

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					This statement in Box 1 should also include the autonomic nervous system so that it is clear to both clinicians and people with B12 deficiency that central, peripheral, and autonomic nervous systems can all be affected by B12 deficiency. Pain (neuro/musculoskeletal) should also be listed in Box 1, as this is a common symptom of vitamin B12 deficiency.	
566	The B12 Society	Guideline	007	006 - 008	People with a total gastrectomy should be receiving injections as they will not be able to absorb oral B12.	Thank you for your comment. The committee agreed there was no evidence to suggest oral treatment would not work in this group. However following stakeholder comments the recommendation has been updated to state 'Consider intramuscular instead of oral vitamin B12 replacement'.
567	The B12 Society	Guideline	008	001	Including Box 2 It is concerning that medicines such as the contraceptive pill are not being included even though "there are plausible mechanisms by which these medicines cause or may cause a deficiency of vitamin B12" (https://www.nice.org.uk/guidance/gid-ng10176/documents/evidence-review-2). The evidenc" review document notes that they should not be included until evidence is available; however, it would be safer to	Thank you for your comment. The committee agreed to limit the risk factors to only the common risk factors. Evidence was not identified to suggest it was a risk factor and therefore the oral contraceptive pill was not included. The research recommendation for risk factors has been updated to reflect there are two types of contraceptive pill to investigate.

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					include these medicines for consideration until any causation is confirmed or ruled out. Also, if research is being recommended for the contraceptive pill, a distinction should be made between the combined pill (oestrogen and progesterone) and the "mini-pill" (progesterone only), as we need to understand which of these is an issue. And whether it's only oral contraceptives or other hormonal contraception methods such as implants/injections and IUDs	
568	The B12 Society	Guideline	009	008 - 009	This would be challenging for primary care clinicians to implement as active B12 (holotranscobalamin) test is not readily available in most primary care settings, and referral to secondary care could cause potentially harmful delays. We suggest that a SYMPTOMS NOT SERUM approach with an empirical trial of B12 injections to look for a positive clinical response would offer the best possible outcome for pregnant and breastfeeding people and would be cost saving at the same time.	Thank you for your comment. The committee agreed that using active B12 would not require a change in practice for GP surgeries because it can be carried out on the same serum sample as for total B12. They agreed that in their experience, active B12 is a more accurate test than total B12. However, they recommended either total or active B12 to reflect the lack of evidence demonstrating this and the lack of availability of active B12 at all laboratories. A trial of vitamin B12 deficiency without testing was not one of the options considered in the review. Therefore, no recommendations have been made advising healthcare professionals whether or not to trial vitamin B12 replacement in this scenario.

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						Implementing these recommendations will require some reallocation of resources, including investment in pathology services, so that testing can become more widely available. A resource impact report and tool will be published alongside this guideline.
569	The B12 Society	Guideline	009	012	The rationale behind this recommendation states "based on their experience, the committee agreed homocysteine was more reliable because elevated homocysteine in the body is seen before a rise in MMA", however we see cases within our support group where MMA is raised before homocysteine and vice versa, therefore perhaps both MMA and homocysteine need to be considered for the nitrous oxide group of people?	Thank you for your comment. The committee agree and have recommended using either homocysteine or serum MMA when testing for vitamin B12 deficiency suspected to be caused by recreational nitrous oxide use.
571	The B12 Society	Guideline	009	020 - 022	If there is no information provided in this guideline for the clinician regarding what action to take when dosage is established, then what is the point of this statement? Furthermore, dosage of vitamin B12 is irrelevant, as it can take many months for blood levels to normalise after taking supplements, whether parenteral, oral, dietary fortification, etc, due to enterohepatic circulation and the reuptake of B12, and especially so when there is a	Thank you for your comment. This recommendation is to ensure clinicians get the information about supplementation because some people buy supplements over the counter if they think they will help before going to the doctor. It is also linked to the following recommendation advising healthcare

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					B12 deficiency as the body attempts to scavenge as much as possible. It is also the case that if any supplements that have been taken include vitamin B9 (folate), e.g. multi vitamins, or B complex, this could mask the haematological signs of a B12 deficiency.	professionals that this could affect test results and that they take this into account when making a diagnosis. The committee agreed it is important to get all the information about any supplements that may be used and therefore it is important to ask about dosage. The recommendation is written so that it covers any supplement that contains B12. This could include multivitamins. It has also been updated to include all forms of vitamin B12 supplementation including vitamin B12 tablets, injections or transdermal patches. Dietary factors are included in the risk factors box as part of risk assessment and are therefore not repeated here. Foods and drinks fortified with vitamin B12 have been added to this.
571	The B12 Society	Guideline	009 - 012		Section 1.3 Whole Section It is essential that information is provided at the start of this section that details the fact that there is currently NO gold standard tests available for vitamin B12 deficiency diagnosis. The tests that are available: total serum B12, active B12 (holoTC), Methylmalonic Acid (MMA), total homocysteine (tHcy), are to be used for guidance only and should not be used alone as either diagnostic or exclusionary tools.	Thank you for your comment. A statement has been added to the start of the rationale making it clear there is no gold standard test for diagnosing vitamin B12 deficiency. A trial of vitamin B12 replacement without testing was not one of the options considered in the review. Therefore, no recommendations have been made advising healthcare professionals whether or not to trial vitamin B12 replacement in this scenario.

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					In cases of uncertainty, a SYMPTOMS NOT SERUM approach with an empirical trial of B12 injections to look for a positive clinical response offers the best potential for accurate diagnosis, patient outcome, and cost saving.	
572	The B12 Society	Guideline	009 - 012		Section 1.3 whole section The lower values of reference intervals being recommended in this section are too low and will allow too many B12 deficient people to fall through the diagnostic net. It is also the case that reference ranges can vary drastically from one area of the country to another, with some lower values set as low as 100 ng/L. Analytics from our online support group (https://www.facebook.com/groups/707933819262618) of >52,000 members, show significantly higher membership from these areas With rising levels of Alzheimer's and other dementia's, mental health issues, heart disease and stroke, and all the other biggest killers in the UK today, we should be using our knowledge of the role vitamin B12 deficiency can play in each of these conditions to minimise the impact. For the	Thank you for your comment. Several stakeholders commented on the thresholds. Some thought they were too low, others thought they were too high and there was also some support that they are about right. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not. Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests. The committee also recommend considering MMA as a further test for people with an indeterminate active or total B12 test result. This is to capture people who may have a vitamin B12 deficiency when their test result doesn't meet the criteria for deficiency. An indeterminate result covers an active B12 of between 25 and 70 pmol per litre, and a total

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					sake of disease prevention, we should be aiming for optimal levels of B12 and not settling for being "in range", especially so when the bottom of range is set below 200ng/L. The cost savings that could be made by raising reference ranges, thus preventing B12 related health conditions could contribute enormously to the revival of the NHS, both from a financial perspective and by creating reductions in demand for service. This could be achieved in a relatively short space of time with a capital investment that is minimal to the forecasted payback, and at a fraction of the cost that could be predicted for the consequences of untreated/undertreated B12 deficiency. What is the point of having common sense and insight if it is not used?	B12 of between 180 and 350 nanograms (133 and 258 pmol) per litre. The committee has also added a recommendation to use the laboratory's reference ranges to decide if vitamin B12 deficiency is likely when interpreting serum MMA and plasma homocysteine test results.
573	The B12 Society	Guideline	010	002	Other interfering factors that should be added to this section are: • Regularly taking highly fortified foods (incl. marmite, cereals, energy type drinks, etc) – as such	Thank you for your comment. This recommendation is to highlight areas that a GP can find out about that a laboratory will not know or be able to advise about.

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					fortification can be no different to taking oral/dietary supplements. This should also include pseudo B12 foods such as spirulina and some nori seaweeds. • Kidney disease – as the reduced ability to filter spent B12 can force it back into the bloodstream cause falsely elevated levels. • Liver disease which may cause higher levels to remain in the blood. • Macro B12/antibody interference. • Functional B12 deficiency	Oral vitamin B12 supplements are highlighted because the healthcare professional may not be aware that this could affect test results. It has been updated to include all forms of vitamin B12 supplementation including vitamin B12 tablets, injections or transdermal patches. Assessing the person's dietary intake is included as part of the risk factors in the section on 'When to recognise vitamin B12 deficiency'. This includes the section on recognising vitamin B12 deficiency and has been updated to include food or drinks fortified with vitamin B12.
574	The B12 Society	Guideline	010	002	Although "caution" is suggested no information is given to what that caution should look like. There needs to be clearer guidance as to how to interpret such results. Ambiguity such as this will only lead	Thank you for your comment. This recommendation is to highlight factors the healthcare professional may not be aware of when assessing a person for vitamin B12 deficiency. Evidence was not available to be more specific. However, further testing with MMA is also recommended for

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					to a lack of continuity of care from one clinician to another.	people with an indeterminate test result and that could include testing people with one of these factors.
575	The B12 Society	Guideline	010	010	"nanogram" should read "nanograms". This change should also be made elsewhere where applicable.	Thank you for your comment. We have updated this as suggested.
576	The B12 Society	Guideline	010	013	Although it is good to advise that active B12 is the preferred measurement for pregnant and breastfeeding people, an appropriate total B12 measurement for this group of people should also be included in the guideline, as active B12 testing is not widely available in the primary care setting, and referral to secondary care could cause potentially harmful delays.	Thank you for your comment. The committee thought carefully before making the recommendations. Implementing these recommendations will require some reallocation of resources, including investment in pathology services, so that testing can become more widely available in primary care. A resource impact report and tool will be published alongside this guideline.
577	The B12 Society	Guideline	010	015 - 016	This statement is far too open to individual interpretation, and since homocysteine tests are not widely available, clinicians are not accustomed to using this test. A clear guide as to what measurement is likely to show a B12 deficiency is necessary here.	Thank you for your comment. We have updated this to make it more specific. The recommendation now states 'Use laboratory reference ranges to interpret plasma homocysteine test results when deciding if vitamin B12 deficiency is likely, but take into account additional factors that may increase plasma homocysteine levels (such as folate deficiency).'
578	The B12 Society	Guideline	010	017	This is a positive inclusion in the guidelines. However anecdotal evidence from our online support group (https://www.facebook.com/groups/707933	Thank you for your comment. Several stakeholders commented on the thresholds. Some thought they were too low, others thought they were too high and there was also some support that they are about right.

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					819262618), which has >52,000 members, is highly indicative of the upper limit of this needing to be higher than 350ng/L. This is a good start though and we hope that further research will give cause to raise this level in future.	Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not. Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests. The committee also recommend considering MMA as a further test for people with an indeterminate active or total B12 test result. This is to capture people who may have a vitamin B12 deficiency when their test result doesn't meet the criteria for deficiency. An indeterminate result covers an active B12 of between 25 and 70 pmol per litre, and a total B12 of between 180 and 350 nanograms (133 and 258 pmol) per litre. The committee has also added a recommendation to use the laboratory's reference ranges to decide if vitamin B12 deficiency is likely when interpreting serum MMA and plasma homocysteine test results.
579	The B12 Society	Guideline	010	018 - 020	Since there is no gold standard test for B12 deficiency, to rely on MMA as the only 2nd line test leaves too many holes in the diagnostic net. Homocysteine should also	Thank you for your comment. The committee agreed that there are several practical issues with the homocysteine test. These included the requirement for stabilising tubes if samples cannot be transported immediately to the laboratory

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					be considered where MMA is found to be within range. We see cases within our support group where MMA is raised before homocysteine and vice versa, therefore perhaps both MMA and homocysteine need to be considered for this group of people? In cases of uncertainty, a SYMPTOMS NOT SERUM approach with an empirical trial of B12 injections to look for a positive clinical response offers the best potential for accurate diagnosis, patient outcome, and cost saving.	on ice, which not all hospitals have, and the requirement of a second blood sample. Results of the homocysteine test are more difficult to interpret in people with folate, B6 or B2 deficiency and in people with renal impairment because these conditions also affect homocysteine levels. In addition, the committee considered the additional cost of the homocysteine test. MMA does not require stabilising tubes and can be performed on the original blood sample taken for the first-line test. Avoiding the need for a second blood sample would speed up the diagnostic process and would involve less burden on the person being tested. Therefore, without evidence to support the use of a more costly test the committee recommend MMA as the test for indeterminate test results. A trial of vitamin B12 replacement without testing was not one of the options considered in the review. Therefore, no recommendations have been made advising healthcare professionals whether or not to trial vitamin B12 replacement in this scenario.
580	The B12 Society	Guideline	011	024 - 025	Because there is no gold standard test for B12 deficiency, it would be foolish to rule out such a diagnosis based purely on the blood results. Our support group members have provided many examples of blood results being well within range, and even high, despite a B12 deficiency. This can be	Thank you for your comment. Several stakeholders commented on the thresholds. Some thought they were too low, others thought they were too high and there was also some support that they are about right. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted

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					explained by any functional B12 issues that occur post ileal absorption, e.g. B12 transportation, pseudo B12, macro B12, low cofactors, kidney disease, liver disease, bile insufficiency, and other reuptake difficulties. In such cases, a SYMPTOMS NOT SERUM approach with an empirical trial of B12 injections to look for a positive clinical response offers the best potential for accurate diagnosis, best patient outcome, and would be cost saving.	that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not. Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests. The committee also recommend considering MMA as a further test for people with an indeterminate active or total B12 test result. This is to capture people who may have a vitamin B12 deficiency when their test result doesn't meet the criteria for deficiency. An indeterminate result covers an active B12 of between 25 and 70 pmol per litre, and a total B12 of between 180 and 350 nanograms (133 and 258 pmol) per litre. The committee has also added a recommendation to use the laboratory's reference ranges to decide if vitamin B12 deficiency is likely when interpreting serum MMA and plasma homocysteine test results. A trial of vitamin B12 deficiency without testing was not one of the options considered in the review. Therefore, no recommendations have been made advising healthcare professionals whether or not to trial vitamin B12 replacement in this scenario.

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581	The B12 Society	Guideline	012	001 – 005	Add bullet point: • Check cofactor levels to see if they are at sufficient/efficient levels for B12 to be functional.	Thank you for your comment. The recommendation has been updated to advise investigating other causes as well as considering a repeat of the initial test if they are still experiencing symptoms or signs 3 to 6 months later. MMA has been removed because the committee agreed that most laboratories would not allow for an MMA without testing total or active B12 first.
582	The B12 Society	Guideline	012	007	It is important to note that the IFAb test, although specific, is not sensitive - approx 50 % of people with pernicious anaemia (PA) will have a negative result, so this test does not rule out PA. Furthermore, less experienced clinicians are known to exclude pernicious anaemia and/or B12 deficiency on the results of this ineffectual test.	Thank you for your comment. The rationale in the guideline does state that the evidence 'showed that, while a positive anti-intrinsic factor antibody test strongly suggests autoimmune gastritis, a negative test is less reliable so cannot be used to rule out the condition.' This is why the committee recommended further tests. The committee also recommend lifelong intramuscular vitamin B12 replacement is offered to people if autoimmune gastritis is the suspected cause. This is the same as the recommendation for those with a confirmed diagnosis to take account of the lack of certainty in the outcome of a negative test result.
583	The B12 Society	Guideline	012 - 013		Section 1.4 whole section Testing for Helicobactor Pylori/other parasitic infestations, and/or Small Intestinal Bacterial Overgrowth (SIBO) should be added into this section. In cases where these are the cause, antibiotic or antibacterial treatment should	Thank you for your comment. Testing for Helicobacter Pylori/other parasitic infestations, and/or Small Intestinal Bacterial Overgrowth (SIBO) were not included as part of the review and therefore no recommendations have been made relating to them. However, the recommendation does recommend considering further investigations 'such as' and lists the tests looked at. This doesn't prevent healthcare professionals from ordering other investigations should they need to.

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					be able to reverse the B12 deficiency, correcting B12 related health issues for these people, and saving ongoing costs to NHS.	
584	The B12 Society	Guideline	013	001	It should also be highlighted that the CobaSorb test is not able to answer the question of causes of B12 malabsorption, especially those related to food cobalamin malabsorption (e.g. in the elderly). CobaSorb tests rely on biochemical response rather than a person's symptomatic response. Therefore, a SYMPTOMS NOT SERUM approach with an empirical trial of B12 injections to look for a positive clinical response offers the best potential for accurate diagnosis, patient outcome, and cost saving.	Thank you for your comment. The list of tests are further investigations that may help with the diagnosis. The committee agreed that it was important to suggest which further investigations may help. These recommendations apply to people diagnosed with a deficiency and therefore it is anticipated that treatment will be given regardless of the outcome of these investigations. Whether this is intramuscular or oral vitamin B12 replacement will depend on the suspected cause.
585	The B12 Society	Guideline	013	009 - 010	What information can clinicians' reference in order to provide people with B12 deficiency with this information?	Thank you for your comment. Following stakeholders' comments this recommendation has been updated to provide more detail. It now states:

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					From anecdotal evidence within our online support group (https://www.facebook.com/groups/707933819262618), with >52,000 members, it is clear that, just like each person with a B12 deficiency experiences a different combination of symptoms, recovery times and recovery experiences are also different for each individual person. Some feel better at the outset of treatment, others find it takes weeks/months before the see improvements. Some feel worse before they get better (the positive negative effect). Depending on the variants involved in an individual's B12 deficiency, e.g. duration of untreated B12 deficiency, if irreversible neurological damage has occurred, administration route of treatment (oral vs IM), cofactor involvement, other comorbidities, etc, optimal recovery can take anything from weeks to several years.	Explain to people starting treatment with vitamin B12 replacement: • that response to treatment can vary and depends on the cause of the vitamin B12 deficiency • that their symptoms could start to improve within 2 weeks, but this may take up to 3 months • that it can take much longer for symptoms to disappear altogether, and that although their symptoms could get worse initially during treatment, this should improve • when to seek medical help (without waiting for any scheduled appointments) if their symptoms have not improved, get worse or return, or they get new symptoms, after starting treatment.
586	The B12 Society	Guideline	013	017 - 021	For B12 deficiency as a result of such surgery, oral B12 won't be absorbed	Thank you for your comment. The committee recommend that intramuscular is considered instead of oral vitamin B12

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					properly - the appropriate treatment is with injections. The rationale notes that "there was no evidence to suggest that oral replacement was ineffective" - until there is clear evidence that it *is* effective, this risk should not be taken.	replacement. The weaker 'consider' recommendation reflects that there is no evidence to demonstrate that oral vitamin B12 replacement does not work.
587	The B12 Society	Guideline	013 - 016		Section 1.5 whole section This provides no clear guidance on the dose or frequency of intramuscular B12, or even a cross-reference to the British National Formulary (BNF). Given that many clinicians currently ignore the BNF guidance to prescribe alternate day injections for people with neurological symptoms until there is no further improvement, it would be beneficial to include this information in the document: https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.12959,	Thank you for your comment. NICE does not include dosages in recommendations where they are available in the BNF or SPC. A dosage may be included if this information is not available, or the committee agrees that there needs to be a change to current recommended dosages, for example because of new evidence. The guideline has been updated to recommend at least 1mg a day when oral vitamin B12 replacement is prescribed in cases of malabsorption. This is because all comparisons for oral with intramuscular vitamin B12 replacement used 1mg of oral replacement. The committee also agreed that there was no evidence to suggest a lower dose would be effective in this group and that using this dose is likely to be current practice for this group. The dosage is stated to ensure that these patients receive the appropriate treatment. There wasn't evidence to recommend a 1mg dose for people with medicine or nitrous oxide induced deficiency. Oral vitamin B12 replacement can be prescribed at lower doses for a dietary deficiency.
588	The B12 Society	Guideline	014	001 - 004	Although some people appear to be able to passively absorb enough B12 from oral	Thank you for your comment. Following stakeholder comments the recommendations have been updated.

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					supplements, (the mechanism of which is questionable), this is not the case for a majority of people with B12 deficiency, and further research is required. Therefore, offering oral supplements as an option in cases of malabsorption is gambling with people's health, and doing so at low odds! Since the risk of irreversible neurological damage is highly documented, why offer oral supplements as an option to these patients, knowing that, in general, they will be making uninformed decisions, and that most will do so based upon the fact that B12 injections are often painful and unpleasant. It's not about "the person's preference", rather what is best for the person's health and wellbeing. The appropriate treatment is with injections. The rationale notes that "there was no evidence to suggest that oral replacement was ineffective" - until there is clear evidence that it *is* effective, this risk should not be taken.	Intramuscular injections are offered to people with autoimmune gastritis or who have had a total gastrectomy or complete terminal ileal resection. For all other people with vitamin B12 deficiency because of malabsorption intramuscular injections are considered over oral replacement.

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589	The B12 Society	Guideline	015	006 - 007	Good to see this included in the guideline, as this point can often be overlooked.	Thank you for your support for the recommendation.
590	The B12 Society	Guideline	016	018 - 021	If the cause of deficiency is unknown, then it would be safer to give injections. Even if there is no cause of malabsorption found, it is still the most likely explanation if other causes such as dietary deficiency, medication-induced deficiency, parasitic infestation, bacterial overgrowth, etc. have been ruled out. Therefore, a SYMPTOMS NOT SERUM approach with an empirical trial of B12 injections to look for a positive clinical response offers the best potential for accurate diagnosis, patient outcome, and cost saving.	Thank you for your comment. The recommendation has been updated to make clear that it applies to people where malabsorption is not suspected. It has also been updated to make it clear this is a trial of oral vitamin B12 replacement and the response to treatment should be reviewed at the first follow up appointment. The committee agreed that there was no evidence that oral treatment would not work in this group. The expectation is that healthcare professionals will take symptoms into account when making a diagnosis. The recommendations for ongoing care and follow up have been updated to make it clearer that symptoms need to be taken into account when assessing a person's response to treatment.
591	The B12 Society	Guideline	017	003	This statement is too reliant on both the clinician and patient having a good enough understanding of symptoms and signs of B12 deficiency. However, the symptoms and signs of this deficiency are so wide, and the education for clinicians desperately limited, which often leads to misdiagnosis/mistreatment of some	Thank you for your comment. The committee agreed it was important to ask about symptoms as a change in these gives the healthcare professional an idea of whether or not treatment is working. The recommendation has been rephrased to state 'At each follow-up appointment, ask the person if their symptoms have improved or worsened, or if they are experiencing new symptoms that could be linked to vitamin B12 deficiency.'

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					symptoms, as they are not being recognised as B12 related. Many members of our online support group (https://www.facebook.com/groups/707933819262618), which has >52,000 members, report this happening, e.g. chronic pain being treated with opioids, but when more frequent IM B12 plus appropriate cofactors are administered pain symptoms can reduce/resolve, thus saving NHS costs and the persons health. Can a link to credible, more comprehensive lists/explanations of signs and symptoms be provided with this guideline, e.g. from B12/PA charity websites such as: https://www.theb12society.com/signs-and-symptoms and https://pernicious-anaemia-society.org/symptoms/	The section on 'Information for the public' on this guideline's web page also provides links to other organisations' websites which provide more detailed advice directly written for people with suspected or confirmed vitamin B12 deficiency.
592	The B12 Society	Guideline	017	017 - 018	Retesting B12 whilst receiving treatment will likely give falsely normal results for many months. Therefore, it is unhelpful to test B12 during treatment. The Rationale notes that "The committee emphasised the need to take blood samples from people before they start	Thank you for your comment. Following stakeholder comments the recommendation for repeating the initial test for people on oral vitamin B12 replacement has been removed from the guideline.

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					vitamin B12 replacement treatment, because this could affect their test results. They also highlighted the need to ask people which vitamin B12 supplements they are taking (if any) and at what dosage, because higher doses can elevate vitamin B12 concentrations in the blood and affect test results." To do so would be a waste of time and money	
593	The B12 Society	Guideline	017	017 - 023	Since the risk of irreversible neurological damage is highly documented, why offer oral supplements as an option to these patients, knowing that, in general, they will be making uninformed decisions, and that most will do so based on the fact that B12 injections can be unpleasant and often painful. The appropriate treatment is with injections. The rationale notes that "there was no evidence to suggest that oral replacement was ineffective" - until there is clear evidence that it *is* effective, this risk should not be taken.	Thank you for your comment. Where evidence was available intramuscular injections were recommended over oral vitamin B12 replacement. However, the committee also agreed that where evidence was not available the choice should be given to the person. No evidence was identified to suggest either oral or intramuscular treatment is better for vitamin B12 deficiency caused by medicines or recreational nitrous oxide use. However, the committee also recommend either increasing the oral dosage or switching to intramuscular injections if the person's symptoms do not improve. Investigating and managing complications related to vitamin B12 deficiency and cofactors were not included as part of the scope of the guideline. Therefore they were not included as part of the guideline reviews and no recommendations have been made related to this.

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					It's not about "the person's preference", rather what is best for the person's health and wellbeing. This bullet point should also be added to this section: • Check cofactors: folate, vitamin B6, and iron. Along with contraindicative factor: potassium	
594	The B12 Society	Guideline	017	025 - 027	This statement is too reliant on both the clinician and patient having a good enough understanding of symptoms and signs of B12 deficiency. However, the symptoms and signs of this deficiency are so wide, and the education for clinicians desperately limited, which often leads to misdiagnosis/mistreatment of some symptoms, as they are not being recognised as B12 related. Many members of our online support group (https://www.facebook.com/groups/707933819262618), which has >52,000 members, report this happening, e.g. chronic pain being treated with opioids, but when more frequent IM B12 plus appropriate cofactors are administered, pain symptoms can	Thank you for your comment. The committee agreed it was important to ask about symptoms as a change in these gives the healthcare professional an idea of whether or not treatment is working. The recommendation has been rephrased to state 'At each follow-up appointment, ask the person if their symptoms have improved or worsened, or if they are experiencing new symptoms that could be linked to vitamin B12 deficiency.' The section on 'Information for the public' on this guideline's web page also provides links to other organisations' websites which provide more detailed advice directly written for people with suspected or confirmed vitamin B12 deficiency.

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					reduce/resolve, thus saving NHS costs and the persons health. Can a link to credible, more comprehensive lists/explanations of signs and symptoms be provided with this guideline, e.g. from B12/PA charity websites such as: https://www.theb12society.com/signs-and-symptoms and https://pernicious-anaemia-society.org/symptoms/ ?	
595	The B12 Society	Guideline	017-020		Section 1.6 whole section This bullet point should be added to this section: • Monitor cofactors: folate, vitamin B6, and iron. Along with contraindication of: low potassium	Thank you for your comment. Investigating and managing complications related to vitamin B12 deficiency and cofactors were not included as part of the scope of the guideline. Therefore they were not included as part of the guideline reviews and no recommendations have been made related to this. The committee agreed that everyone will still test folate and vitamin B12 together despite there being no mention of folate in this guideline.
596	The B12 Society	Guideline	018	011 - 017	Check B12 cofactors: iron, folate, vitamin B6, and monitor potassium levels during early stages of B12 treatment. Without an appropriate balance of essential cofactors, B12 cannot work effectively; the chemistry must be correct.	Thank you for your comment. Investigating and managing complications related to vitamin B12 deficiency and cofactors were not included as part of the scope of the guideline. Therefore they were not included as part of the guideline reviews and no recommendations have been made related to this.

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					Retesting B12 whilst receiving treatment will likely give falsely normal results for many months. Therefore, it is unhelpful to test B12 during treatment. The Rationale notes that "The committee emphasised the need to take blood samples from people before they start vitamin B12 replacement treatment, because this could affect their test results. They also highlighted the need to ask people which vitamin B12 supplements they are taking (if any) and at what dosage, because higher doses can elevate vitamin B12 concentrations in the blood and affect test results." Therefore, a SYMPTOMS NOT SERUM approach with an empirical trial of B12 injections to look for a positive clinical response offers the best potential for accurate diagnosis, patient outcome, and cost saving.	Following stakeholder comments the recommendation for repeating the initial test for people on oral vitamin B12 replacement has been removed from the guideline. The ongoing care and follow up recommendations have also been updated to make it clearer that response to treatment should be made by assessing symptoms.
597	The B12 Society	Guideline	018	019 - 022	Check B12 cofactors: iron, folate, vitamin B6, and monitor potassium levels during early stages of B12 treatment. Without an	Thank you for your comment. Investigating and managing complications related to vitamin B12 deficiency and cofactors were not included as part of the scope of the guideline.

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					appropriate balance of essential cofactors, B12 cannot work effectively; the chemistry must be correct. Retesting B12 whilst receiving treatment will likely give falsely normal results for many months. Therefore, it is unhelpful to test B12 during treatment. The Rationale notes that "The committee emphasised the need to take blood samples from people before they start vitamin B12 replacement treatment, because this could affect their test results. They also highlighted the need to ask people which vitamin B12 supplements they are taking (if any) and at what dosage, because higher doses can elevate vitamin B12 concentrations in the blood and affect test results." Therefore, a SYMPTOMS NOT SERUM approach with an empirical trial of B12 injections to look for a positive clinical response offers the best potential for accurate diagnosis, patient outcome, and cost saving.	Therefore they were not included as part of the guideline reviews and no recommendations have been made related to this. Following stakeholder comments the recommendation for repeating the initial test for people on oral vitamin B12 replacement has been removed from the guideline. The ongoing care and follow up recommendations have also been updated to make it clearer that response to treatment should be made by assessing symptoms.

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598	The B12 Society	Guideline	019	001 - 002	Check B12 cofactors: iron, folate, vitamin B6, and monitor potassium levels during early stages of B12 treatment. Without an appropriate balance of essential cofactors, B12 cannot work effectively; the chemistry must be correct. Retesting B12 whilst receiving treatment will likely give falsely normal results for many months. Therefore, it is unhelpful to test B12 during treatment. The Rationale notes that "The committee emphasised the need to take blood samples from people before they start vitamin B12 replacement treatment, because this could affect their test results. They also highlighted the need to ask people which vitamin B12 supplements they are taking (if any) and at what dosage, because higher doses can elevate vitamin B12 concentrations in the blood and affect test results." Therefore, a SYMPTOMS NOT SERUM approach with an empirical trial of B12 injections to look for a positive clinical	Thank you for your comment. Investigating and managing complications related to vitamin B12 deficiency and cofactors were not included as part of the scope of the guideline. Therefore they were not included as part of the guideline reviews and no recommendations have been made related to this. Following stakeholder comments the recommendation for repeating the initial test for people on oral vitamin B12 replacement has been removed from the guideline. The ongoing care and follow up recommendations have also been updated to make it clearer that response to treatment should be made by assessing symptoms.

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					response offers the best potential for accurate diagnosis, patient outcome, and cost saving.	
599	The B12 Society	Guideline	019	006	Add: check B12 cofactors: iron, folate, vitamin B6, and monitor potassium levels during early stages of B12 treatment. Without an appropriate balance of essential cofactors, B12 cannot work effectively; the chemistry must be correct.	Thank you for your comment. Investigating and managing complications related to vitamin B12 deficiency and cofactors were not included as part of the scope of the guideline. Therefore they were not included as part of the guideline reviews and no recommendations have been made related to this.
600	The B12 Society	Guideline	019	008	Statement is ambiguous. The word "frequency" should be quantified and the word "optimised", in terms of dosage, should be explained so as to provide appropriate guidance. We suggest adding a link to the British Society for Haematology flow chart for this: https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.12959, And/or links to the credible and well researched data available on some B12/PA charity websites: https://www.theb12society.com/treatment	Thank you for your comment. No evidence was identified for the frequency of intramuscular injections and the committee made a research recommendation for this. The committee were aware that people could be started on a dose at 3 monthly intervals and the BNF suggests these could be reduced to 2 monthly intervals. The recommendation is meant to reflect this. The recommendation has been updated to recommend increasing the frequency of injections if needed, in line with the summary of product characteristics.

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					and https://pernicious-anaemia-society.org/treatment/	
601	The B12 Society	Guideline	019	016 - 018	If a person's B12 deficiency is reversible, why would that not be addressed? If this is simply a compliance issue, then ensure the person and/or carers are provided with accurate information to assist the reversal. Offer them links to credible B12/PA charities website: https://www.theb12society.com/treatment and https://pernicious-anaemia-society.org/treatment/	Thank you for your comment. The person could be taking a medicine that may be stopped in the future but is still currently needed, or they may have coeliac disease that has not yet been effectively managed. The committee agreed that both these causes could be managed in a way that they no longer cause a vitamin B12 deficiency. However, it is not down to adherence.
602	The B12 Society	Guideline	020	001 - 002	Because the diagnosis of autoimmune gastritis, including pernicious anaemia, is so inaccurate with the anti-intrinsic factor antibodies test and anti-parietal cell antibodies test, being around 50% sensitive, and 50% specific respectively, therefore around 50% of people with autoimmune gastritis not receiving the appropriate diagnosis. This leaves a huge sector of B12 deficient people at higher risk of gastric cancers but not being monitored.	Thank you for your comment. We have amended our recommendation so it includes 'suspected or confirmed' autoimmune gastritis. The recommendation for unknown causes is limited to people in whom malabsorption is not suspected. There is not the evidence to suggest that people with an unknown cause will be at increased risk of gastric cancer. The recommendations on upper gastrointestinal tract cancers in NICE's guideline on suspected cancer advise that anyone with upper gastrointestinal symptoms should be considered for referral regardless of whether they have autoimmune gastritis or vitamin B12 deficiency. The recommendations in this section are there to highlight the increased incidence of gastric adenocarcinoma and gastric neuroendocrine tumours in people with suspected or

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					Section 1.7 should include people with B12 deficiency of no known cause.	confirmed autoimmune gastritis. Raising awareness of this may mean people are more likely to report any gastrointestinal symptoms to their healthcare professional.
603	The B12 Society	Guideline	020	008	"consider referral for a gastrointestinal endoscopy" should state "**prioritise** referral for a gastrointestinal endoscopy"	Thank you for your comment. We did not have the evidence to make a recommendation that all people should be referred for gastrointestinal endoscopy. Therefore, the strength of the recommendation in this guideline matches the strength of the recommendations on upper gastrointestinal tract cancers in NICE's guideline on suspected cancer.
604	The B12 Society	Guideline	021	007	Add: clinical nitrous oxide exposure	Thank you for your comment. This section is used to describe how specific terms have been used in the guideline recommendations. No recommendations have been made in relation to clinical nitrous oxide use and therefore it has not been mentioned as part of this definition.
605	The B12 Society	Guideline	021	019 - 020	We agree that this research is vital. However, until such time as this is available, we should be using the currently known scientific and anecdotal evidence to provide the best possible treatment for B12 deficient people at this point in time. We know what works, that it is proven to be safe, and that when applied effectively, it will improve vitamin B12 deficiency and be preventative of other conditions. The potential cost savings to the NHS and government of effective B12 deficiency treatment, which must include balancing essential cofactors, is hugely significant.	Thank you for your comment and support for the research recommendation.

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					Likewise, the savings in human cost would be massive and admirable. The effectiveness of this treatment is evidence based, so we should be using what we already know whilst waiting for the science of new studies to catch up.	
606	The B12 Society	Guideline	022	002 - 004	With >52,000 members of our online support group (https://www.facebook.com/groups/707933819262618), >26,000 of which are in the UK, we have a ready-made study group, as do other charities and patient advocate groups. However, until such research can be carried out, we should be making decisions based on the present knowledge that there is no gold standard tests currently available for vitamin B12 deficiency. Therefore, it is only right that when a clearcut picture is not given by blood test results, that symptoms and signs are used as the best predictor of a B12 deficiency. The consequences of overtreating are negligible since B12 is both nontoxic and cheap (ref: Page 29, lines 25-28	Thank you for your comment. The committee agree that symptoms need to be taken into account when making a diagnosis of vitamin B12 deficiency. The opportunity cost of over-treating is not insignificant, when potentially it could be lifelong for some patients. Therefore, the committee have made recommendations about management that take into account both symptoms and test results. They also hope the research recommendations will be undertaken and help improve diagnosis of vitamin B12 deficiency.

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					"Diagnosing vitamin B12 deficiency, Why the committee made the recommendations, Thresholds for initial test results"), as opposed to the consequences of undertreating/mistreating which causes unnecessary NHS (financial) and human costs.	
607	The B12 Society	Guideline	025	001 - 002	Change wording "the use of over-counter-supplements" to "prior supplementation with B12 containing products, including highly fortified foods and drinks". This will cover all supplemental bases and help both clinicians and their patients have a clearer understanding of this point.	Thank you for your comment. Reference to over-the-counter supplements have been removed as an example from the rationale here and therefore fortified foods have not been added.
608	The B12 Society	Guideline	025	021 - 024	Significant numbers of B12 deficient people present without known risk factors at initial consultation. Therefore, this guide will not improve the diagnostic process, it will in fact cause increasing numbers of people to fall through the diagnostic net. We agree that risk factors can be an important and helpful element for	Thank you for your comment. No evidence was identified to make a strong recommendation that people with one of the symptoms or signs without a risk factor, or one of the risk factors without a symptom or sign, should be tested. The committee agreed that the symptoms and signs associated with vitamin B12 deficiency vary and can also be indicative of other conditions. Without the evidence, making a recommendation to test people with just one of the symptoms or signs or risk factor would hugely increase resource impact without any evidence of benefit. The committee recognise that there may be people in whom there is a suggestion of vitamin B12 deficiency without a risk

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					diagnosing but should never be a critical diagnostic criterion.	factor, however this would vary and need to be assessed on a case-by-case basis. Consequently, they recommended that clinical judgement would need to be used to decide if a person should be tested in these circumstances.
609	The B12 Society	Guideline	028	013v - 018	We agree that there is an "absence of high-quality evidence" regarding the efficacy of total B12 versus active B12 tests and recognise the committee's experience of active B12 proving more effective in practice. However, we see evidence of our support group members with active B12 showing "in range", and total b12 below range, then when B12 treatment is established, they experience clinically significant improvements in their symptoms. Therefore, for the time being, we must not ignore the utility of the total B12 test until better tests become available.	Thank you for your comment. The committee agree that total B12 is still a useful test which is why they recommend either total or active B12. Thank you for the information from your support group which supports the research recommendation for tests.
610	The B12 Society	Guideline	028	016 - 017	The wording "This is because it measures the form of B12 that is taken up and used by the body" should be changed to " This is because it measures the form of B12 that **can be** taken up and used by the body ". Just because B12 is available for cellular uptake, this does not mean cellular uptake is effectively happening in a person.	Thank you for your comment. The committee agree and have updated this statement to 'can be'.

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611	The B12 Society	Guideline	029	009-013	This statement should include heavily fortified foods and drinks as they can have the same effect of elevating vitamin B12 concentrations in the blood and affect test results.	Thank you for your comment. This statement is just to highlight that oral vitamin B12 supplements may affect test results. It has been updated to include all forms of vitamin B12 supplementation including vitamin B12 tablets, injections or transdermal patches. Assessing the person's dietary intake is included as part of the risk factors in the section on 'When to recognise vitamin B12 deficiency'. This includes the section on recognising vitamin B12 deficiency and has been updated to include food or drinks fortified with vitamin B12.
612	The B12 Society	Guideline	032	003 - 004	In the text "the test was not necessary for people who have already had it", "had it" should be "had a positive result" - even if someone previously had a negative IFAb test result, they could still have a positive result in the future.	Thank you for your comment. The rationale has been updated to state 'those who have previously had positive anti-intrinsic factor antibody test at any time (because the result would be the same)'.
613	The B12 Society	Guideline	033	013 - 016	We see significant variations in recovery times and levels of recovery. Where does the committee recommend this information should be found for clinicians and patients to be guided by. We suggest links are provided to B12/PA charity and patient advocate websites where such data is available. https://www.theb12society.com/ and https://pernicious-anaemia-society.org/	Thank you for your comment. This recommendation has been updated to give more specific information on what to advise people starting vitamin B12 replacement. The section on 'Information for the public' on this guideline's web page also provides links to other organisations' websites which provide more detailed advice directly written for people with suspected or confirmed vitamin B12 deficiency.

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614	The B12 Society	Guideline	036	024 - 028	Currently the only malabsorption tests carried out are the anti-intrinsic factor antibodies test and anti-parietal cell antibodies test, which are only around 50% sensitive, and 50% specific respectively. Tests for achlorhydria, haptocorrin deficiency, pancreatic protease issues, parasitic infestation, bacterial overgrowth, IBD, and cubilin dysfunction are only rarely or never tested. Endocytosis at terminal ileum is only the first stage of absorption, there is also a secondary absorption required at cellular level. Thus, malabsorption cannot be ruled out in these groups.	Thank you for your comment. The recommendation and rationale have been updated to make it clear that this applies when malabsorption is not suspected. The follow up recommendations also provide guidance on switching treatment should oral replacement not be working.
615	The B12 Society	Guideline	036 037	029 - 031 001 - 005	Even if there are no data on safety of B12 injections done at home by patients, data from other types of self-administered injections could be used to assess safety. In terms of efficacy, there doesn't seem to be any reason to think that injections administered by patients would be any less effective than those administered by healthcare professionals. Self-administered injections could save considerable time and money and be convenient for patients, especially when frequent injections are	Thank you for your comment. The guideline review looked for and found no evidence on the effectiveness of self-medication either by intramuscular or subcutaneous injections. There are also no licenced medications for subcutaneous vitamin B12 injections in the UK. The committee agree that self-administration could be beneficial to people with vitamin B12 deficiency, therefore they made a key research recommendation in this area.

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					needed. We urge the committee to reconsider.	
616	The B12 Society	Guideline	037	012 - 013	The correct terminology is "loading doses", not "a loading dose". Also, it should be defined that loading doses consist of 6 doses given over 2 weeks.	Thank you for your comment. We have updated the text to state 'loading doses'. NICE does not generally include dosages in recommendations where they are available in the BNF or SPC. A dosage may be included if this information is not available, or the committee agrees that there needs to be a change to current recommended dosages, for example because of new evidence. Loading doses are covered in the BNF and therefore not included in the guideline. The guideline did look for clinical evidence relating to the frequency of intramuscular injections however no evidence was identified and the committee made a research recommendation. Loading doses are only mentioned in this section to illustrate the cost of treatment and when intramuscular injections are likely to be cost effective.
617	The B12 Society	Guideline	038	012 - 021	This contradicts previous statements made by the committee: The Rationale notes that "The committee emphasised the need to take blood samples from people before they start vitamin B12 replacement treatment,	Thank you for your comment. Repeating the initial test at the first follow up appointment has been removed from the guideline and therefore this paragraph has been deleted.

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					because this could affect their test results. They also highlighted the need to ask people which vitamin B12 supplements they are taking (if any) and at what dosage, because higher doses can elevate vitamin B12 concentrations in the blood and affect test results." Retesting B12 whilst receiving treatment will likely give falsely normal results for many months. Therefore, it is unhelpful to test B12 during treatment. To do so would be a waste of time and money. Instead, we suggest checking essential B12 cofactors: iron, folate, vitamin B6, and monitor potassium levels during early stages of B12 treatment. Without an appropriate balance of essential cofactors, B12 cannot work effectively; the chemistry must be correct. Also, taking a SYMPTOMS NOT SERUM approach with an empirical trial of B12 injections to look for a positive clinical response offers the best potential for accurate diagnosis, patient outcome, and cost saving in the long run.	

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618	The B12 Society	Guideline	039	006 - 009	This contradicts previous statements made by the committee: The Rationale notes that "The committee emphasised the need to take blood samples from people before they start vitamin B12 replacement treatment, because this could affect their test results. They also highlighted the need to ask people which vitamin B12 supplements they are taking (if any) and at what dosage, because higher doses can elevate vitamin B12 concentrations in the blood and affect test results." Retesting B12 whilst receiving treatment will likely give falsely normal results for many months. Therefore, it is unhelpful to test B12 during treatment. To do so would be a waste of time and money. Instead, we suggest checking essential B12 cofactors: iron, folate, vitamin B6, and monitor potassium levels during early stages of B12 treatment. Without an appropriate balance of essential cofactors,	Thank you for your comment. The committee agreed that for ongoing care and follow up, further testing with MMA is meaningful because it reveals whether B12 replacement is influencing B12 status at a metabolic level. In other words, a decrease in MMA concentration is a sensitive and specific way of demonstrating a positive impact on the function of one of the two B12-dependent enzymes. Investigating and managing complications related to vitamin B12 deficiency and cofactors were not included as part of the scope of the guideline. Therefore they were not included as part of the guideline reviews and no recommendations have been made related to this.

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					B12 cannot work effectively; the chemistry must be correct. Also, taking a SYMPTOMS NOT SERUM approach with an empirical trial of B12 injections to look for a positive clinical response offers the best potential for accurate diagnosis, patient outcome, and cost saving in the long run.	
619	The B12 Society	Guideline	041	002 - 004	Other causes of B12 deficiency such as drug or surgically induced deficiency, clinical nitrous oxide use, parasitic infestation, bacterial overgrowth, and inborn metabolic errors, should be included in this section.	Thank you for your comment. Surgery has been added to this section. This section is only a brief introduction to the context of the guideline. It doesn't cover all aspects of vitamin B12 deficiency and only the causes mentioned in the guideline have been covered in the context.
620	The B12 Society	Guideline	041	005 - 007	Our knowledge of this evidence should be sufficient reason to avoid the use of clinical nitrous oxide, except in emergencies. With increasing levels of mental health disorders, including post-natal depression, we should be actively eliminating clinical nitrous oxide use during surgery, labour and breastfeeding.	Thank you for your comment. The effects of medicinal nitrous oxide use is covered in MHRA guidance https://www.gov.uk/drug-safety-update/nitrous-oxide-neurological-and-haematological-toxic-effects and therefore has not been included in this guideline.
621	The B12 Society	Evidence review E	050 051	016 - 021 001 - 006	The data given in this document regarding self-administration vs HCP, shows clear and substantial cost savings year on year in favour of self-administration of parenteral vitamin B12 treatment. We understand that	Thank you for your comment. The committee considered that although self-administration would be cost saving, a recommendation could not be made without sufficient safety data and data from other conditions should not be extrapolated to this population. It is hoped that by making a

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					the committee are bound to evidence-based decision making, however, for the sake of cost savings for the NHS and better health care for B12 deficient people who require regular B12 injections for life, we must allow room for common sense when making these types of recommendations. Even if there are no data on safety of B12 injections done at home by patients, data from other types of self-administered injections could be used to assess safety. In terms of efficacy, there doesn't seem to be any reason to think that injections administered by patients would be any less effective than those administered by healthcare professionals. Self-administered injections could save considerable time and money and be convenient for patients, especially when frequent injections are needed. We should be doing what we already know works, whilst waiting for the science of new studies to catch up. We urge the committee to reconsider.	research recommendation in the area, studies will be conducted to inform future guideline updates.

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622	Vitamin B12 deficiency 406lub406se group	Guideline	007		Box 1 symptoms: No mention of Heart palpitations and abnormal rhythms with no obvious cause Loss of gastric / digestive motility due to nerve damage reducing peristalsis Crohn's disease Shooting pains (Lhermette's sign) and twitches/ palsies Mood swings, irritability IBS Fish tapeworm Within the section on undexplained fatigue, should include ME (Myalgic Encephalomyelitis)/ Cfs (Chronic Fatigue Syndrome) / FM (Fibromyalgia) Within the section on neurological or mobility problems should include MS-like presentation, Subacute Combined degeneration of the spinal cord (see "Vitamin B12 deficiency in clinical practice" (available from www.b12d.org/book and Amazon.co.uk by Dr Chandy and myself) pp40-41)	Thank you for your comment. Only the most common symptoms and signs were included in the guideline review therefore the recommendations have been restricted to these. The recommendations and box have been updated to make it clear that these are common symptoms and signs.
623	Vitamin B12 deficiency 406lub406se group	Guideline	009	003	blood serum B12 test is only useful in about 30% of cases – blood test is not a reliable test Consider a diagnosis similar to that proposed in Appendix A of "Vitamin B12	Thank you for your comment. As well as recommending total or active B12 tests for the initial diagnosis the committee recommends serum MMA if the results are indeterminate. The committee also anticipate that healthcare professionals

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					deficiency in clinical practice" (available from www.b12d.org/book and Amazon.co.uk by Dr Chandy and myself) , based on the presence and severity of symptoms in a number of different body systems. If all of the symptoms are in a single body system (eg nervous system), then it is more likely to be a disease of that system. If symptoms are present – *and severe* – across a number of different body systems (eg nervous system, gastrointestinal system, neuropsychiatric, connective tissue) then the likelihood of a number of simultaneous diseases becomes small and the likelihood of a common cause such as B12 deficiency becomes the most likely cause.	will also consider symptoms when determining if someone has a vitamin B12 deficiency.
624	Vitamin B12 deficiency 407lub407se group	Guideline	010	010	Diagnose the likelihood of B12 deficiency according to the number of body systems simultaneously expressing symptoms – see Appendix A of "Vitamin B12 deficiency in clinical practice" (available from www.b12d.org/book and Amazon.co.uk by Dr Chandy and myself) . B12 levels and active B12 levels in the blood are not reliable diagnostic tools This applies to "Confirmed deficiency" and "intermediate test results".	Thank you for your comment. Several stakeholders commented on the thresholds. Some thought they were too low, others thought they were too high and there was also some support that they are about right. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not. Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set

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						by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests. The committee also recommend considering MMA as a further test for people with an indeterminate active or total B12 test result. This is to capture people who may have a vitamin B12 deficiency when their test result doesn't meet the criteria for deficiency. An indeterminate result covers an active B12 of between 25 and 70 pmol per litre, and a total B12 of between 180 and 350 nanograms (133 and 258 pmol) per litre. The committee has also added a recommendation to use the laboratory's reference ranges to decide if vitamin B12 deficiency is likely when interpreting serum MMA and plasma homocysteine test results.
625	Vitamin B12 deficiency support group	Guideline	004	005	"the consequence of this is vitamin B12 deficiency…**although vitamin B12 deficiency can also occur from other causes, and vitamin B12 deficiency ..** can lead to pernicious anaemia	Thank you for your comment. The guideline has been updated to acknowledge the difference between autoimmune gastritis and pernicious anaemia and provide a more detailed reason as to why the term 'pernicious anaemia' has not been used. This explains that autoimmune gastritis is sometimes referred to as pernicious anaemia which is a separate condition that can be a consequence of chronic, severe vitamin B12 deficiency, including deficiency caused by autoimmune gastritis. However, pernicious anaemia in its true sense (that is 'a life-threatening anaemia') is now extremely rare because of developments in testing and treatment for, and greater awareness of, vitamin B12

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						deficiency. For this reason, and to prevent any confusion with autoimmune gastritis, we have not used the term 'pernicious anaemia' in the recommendations.
626	Vitamin B12 deficiency support group	Guideline	005	003	lines 4 & 5 "most people only need 1 blood test" is not correct. B12 deficiency should be diagnosed from presenting symptoms, and whilst low blood serum B12 can be used to confirm B12 deficiency, it is not possible to exclude B12 deficiency on the basis of a higher reading of blood serum B12 (since it might be cobalamin analogues which are not biologically active). A combination of blood tests (blood serum B12, holotranscobalamin, MMA, homocysteine) is thought to diagnose 70% of cases. The 1 minute assessment in Appendix A of the book "Vitamin B12 deficiency in clinical practice" (available from www.b12d.org/book and Amazon.co.uk by Dr Chandy and myself) lists a reliable process and forms for making a diagnosis.	Thank you for your comment. The aim of this bullet point is just to highlight how many tests a person may need rather than go into all the details about testing. Further testing is also recommended if the test result is indeterminate, or a person tries treatment and it becomes apparent that their symptoms have not improved. The bullet point has been updated to state 'a single blood test can be enough to support a diagnosis of vitamin B12 deficiency but some people may need further tests to diagnose the condition'.
627	Vitamin B12 deficiency support group	Guideline	005	018	lines 18-20 one of the causes of the recent rise vitamin B12 deficiency and neurological symptoms arising (although often not diagnosed as B12 deficiency because of the problems with the blood test giving a high reading when the cobalamin is not useable by the body) is the recreational use	Thank you for your comment. Several stakeholders commented on this suggesting that without evidence to support this the statement should not be made. The committee agreed and the recommendation relating to this has been removed from the guideline.

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					of nitrous oxide. Women using gas and air during labour should have their vitamin B12 replaced after labour as soon as possible, and neonatal babies should be observed and if necessary supplemented as well. It is relatively easy to replace B12 lost due to a medical intervention, and this should be a matter of routine	Recommendations related to pregnant patients on gas and air are covered by MHRA guidance on Nitrous oxide: neurological and haematological toxic effects. The guideline did not look at the evidence for routinely replacing vitamin B12 following labour and therefore no recommendation has been made in this area.
628	Vitamin B12 deficiency support group	Guideline	010	018	"consider the changes to symptoms when a series of loading doses have been given. One or other symptoms might change and improve, and at the same time other symptoms might deteriorate as a result of the administration of Vitamin B12. Changes in symptoms confirm B12 deficiency, and different symptoms might improve at different points throughout treatment. Note that during administration of Vitamin B12, symptoms such as nerve pains and spastic movement might occur due to nerves starting to conduct a signal again after a period of no conduction. Patients should be counselled that this occurs in around 1 in 10 patients and is a sign that healing is underway and the uncomfortable symptoms will pass. Nerve conduction can include very rapid heartbeat.	Thank you for your comment. This recommendation is to advise healthcare professionals when to consider further testing if an indeterminate test result is obtained during the initial testing. The wording of the recommendation has been updated and the word 'follow up' removed. It now states 'Consider a further test to measure serum MMA….' Using symptoms to guide a response to treatment is part of the recommendations on ongoing care and follow up. NICE does not generally include dosages in recommendations where they are available in the BNF or SPC. A dosage may be included if this information is not available, or the committee agrees that there needs to be a change to current recommended dosages, for example because of new evidence. Loading doses are covered in the BNF and therefore not included in the guideline. The guideline did look for clinical evidence relating to the frequency of intramuscular injections however no evidence was identified and the committee made a research recommendation.

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629	Vitamin B12 deficiency support group	Guideline	011	026	550ng/l is a figure used in some Japanese hospitals. 350ng/L is from McBride and was a diagnostic threshold that still missed some people who responded well to Vitamin B12 treatment. **B12 Deficiency May Be More Widespread Than Thought,** Series Title: Agricultural Research Service Published by: USDA Last Updated: 2 Aug 2000 Judy McBride http://www.ars.usda.gov/is/pr/2000/000802.htm	Thank you for your comment. Several stakeholders commented on the thresholds. Some thought they were too low, others thought they were too high and there was also some support that they are about right. Following stakeholder comments the committee discussed these again and updated the recommendations. They noted that there are 4 main manufacturers of the tests. Three out of the 4 have thresholds for total B12 similar to those recommended in the guideline, however 1 does not. Therefore, they have added the caveat that where there is substantial local variation in validated thresholds, those set by the laboratory doing the testing should be used. The committee also noted that either active or total B12 are recommended as tests. The committee also recommend considering MMA as a further test for people with an indeterminate active or total B12 test result. This is to capture people who may have a vitamin B12 deficiency when their test result doesn't meet the criteria for deficiency. An indeterminate result covers an active B12 of between 25 and 70 pmol per litre, and a total B12 of between 180 and 350 nanograms (133 and 258 pmol) per litre. The committee has also added a recommendation to use the laboratory's reference ranges to decide if vitamin B12 deficiency is likely when interpreting serum MMA and plasma homocysteine test results.

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						The committee noted that there is no universal international threshold with which to define deficiency; it will vary according to how deficiency is diagnosed, the population studied and assay used for each country.
630	Vitamin B12 deficiency support group	Guideline	012	001	If a person's initial diagnosis suggested…	Thank you for your comment. The recommendation is directly related to the test result rather than a diagnosis. Therefore, the recommendation has been left as 'If the person's initial test result suggests…'
631	Vitamin B12 deficiency support group	Guideline	012	022	A test to measure gastrin levels - my GP had never heard about it - so is it available	Thank you for your comment. The committee confirmed that a test to measure gastrin levels is available to GPs.
632	Vitamin B12 deficiency support group	Guideline	013	010	is there a table of when they are likely to see an improvement in their symptoms? See "Vitamin B12 deficiency in clinical practice" (available from www.b12d.org/book and Amazon.co.uk by Dr Chandy and myself) page 81, table 3-2 "how long does it take for symptoms to heal"	Thank you for your comment. Following stakeholders' comments this recommendation has been updated to provide more detail. It now states: Explain to people starting treatment with vitamin B12 replacement: • that response to treatment can vary and depends on the cause of the vitamin B12 deficiency • that their symptoms could start to improve within 2 weeks, but this may take up to 3 months • that it can take much longer for symptoms to disappear altogether, and that although their symptoms could get worse initially during treatment, this should improve

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						• when to seek medical help (without waiting for any scheduled appointments) if their symptoms have not improved, get worse or return, or they get new symptoms, after starting treatment.
633	Vitamin B12 deficiency support group	Guideline	013	012	Frequency of injections is an issue for many people. The current NICE guidelines say every 3 months without neurological symptoms, every 2 months with neurological symptoms (and who doesn't have neurological symptoms), but also alternate days for a loading does and until no further improvement. These new guidelines should say "alternate days until no further improvement (different symptoms might improve at different rates and the clinician should consider all potential symptoms not just the ones the patient reported initially), and then as a minimum injections every 3 months without neurological symptoms and every 2 months with neurological symptoms, at a frequency to minimise the recurrence of symptoms"	Thank you for your comment. No evidence was identified on the frequency of injections therefore the committee made a research recommendation relating to this. Loading doses and stratification of treatment by severity were not considered as part of the guideline review therefore no recommendations have been made relating to this. The ongoing care and follow up recommendations cover optimising treatment if symptoms are not improving.
634	Vitamin B12 deficiency support group	Guideline	014	004	"based on effectiveness at reducing symptoms"	Thank you for your comment. No evidence on the effectiveness of vitamin B12 deficiency on improving a person's symptoms was identified in the guideline reviews therefore this has not been added into the guideline.
635	Vitamin B12 deficiency	Guideline	015	006	yes this is good	Thank you for your support for the recommendation.

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	support group					
636	Vitamin B12 deficiency support group	Guideline	015	017	Cyanocobalamin does not stay in the blood or body long, because it is selectively excreted by kidneys. We also observed that some people are unable to use it (unable to split the cyano group from the cobalamin and replace it with other biologically active R groups), and others get headaches which suggests an over-sensitivity to cyanide. Cyanocobalamin should not be in this guidance except as a warning NOT to take it in either oral or injectable form. Yes it does work for about 2/3 of patients, but there are issues.	Thank you for your comment. The committee decided that cyanocobalamin is a suitable source of vitamin B12 as it is the drug used when prescribing oral vitamin B12 replacement.
637	Vitamin B12 deficiency support group	Guideline	017	023	"repeated diagnostic test result suggests"	Thank you for your comment. Following stakeholder comments the recommendation for repeating the initial test for people on oral vitamin B12 replacement has been removed from the guideline. The ongoing care and follow up recommendations have also been updated to make it clearer that response to treatment should be made by assessing symptoms.
638	Vitamin B12 deficiency support group	Guideline	021	019	see http://www.b12d.org/misdiagnosis written in 2009 - the numbers will be different but probably not radically different	Thank you for the information. The research recommendations here are written as broad questions giving an indication of what area and interventions are considered for further research. More detail is provided in the appendix of the evidence report linked to just below the research recommendation.

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639	Vitamin B12 deficiency support group	Guideline	022	001	"diagnosing" Compare methods of diagnosis, whether by signs and symptoms or by blood test, with those people who respond to parenteral B12 treatment (since B12 is harmless and can be administered to people without a diagnosis of B12 deficiency)	Thank you for your comment. The research recommendations here are written as broad questions giving an indication of what area and interventions are considered for further research. More detail is provided in the appendix of the evidence report linked to just below the research recommendation.
640	Vitamin B12 deficiency support group	Guideline	022	009	"identifying the cause" What are the psychological and cost-effectiveness advantages (if any) of trying to find the cause, as opposed to treating regardless of cause?	Thank you for your comment. This has not been included as part of the research recommendation. The recommendations within the guideline assume that a person would be treated for their deficiency regardless of whether the cause is identified. Should their treatment not be effective then the guideline includes recommendations for changing treatment.
641	Vitamin B12 deficiency support group	Guideline	025	005	lines 5 – 9 Patients assurance that treatment will not be stopped. This section should be more prominent - and there should be more freedom given for GP s to prescribe a greater frequency of injections. If they don't patients will continue to take treatment into their own hands in unmonitored ways.	Thank you for your comment. The recommendations in the ongoing care and follow up section advise optimising treatment if symptoms do not improve or they have new symptoms.
642	Vitamin B12 deficiency support group	Guideline	026	001	in many cases where the symptoms are shared, eg alcoholism, smoking, eczma medication, heavy metal poisoning, the symptoms are shared BECAUSE the external factor causes B12 deficiency as the B12 is used up removing toxins from the blood	Thank you for your comment. This point in the rationale was just to highlight that symptoms are shared with other conditions and not specify all of those or their possible associations with vitamin B12 deficiency.

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643	Vitamin B12 deficiency support group	Guideline	029	028	More prominence should be given to saying that B12 is not harmful.	Thank you for your comment. A safety review of the use of vitamin B12 replacement was not conducted for this guideline. Without evidence to state it is safe the statement has been kept as "…treatment with vitamin B12 replacement is not expensive, nor is it known to be harmful".
644	Vitamin B12 deficiency support group	Guideline	030	014	I see reference to ethnic differences being a risk factor but no reference to Celtic background. For example, the prevalence of MS is higher amongst those with Scottish surnames suggesting a Celtic predisposition. **High incidence and prevalence of multiple sclerosis in south east Scotland: evidence of a genetic predisposition,** P. M. Rothwell and D. Charlton, J Neurol Neurosurg Psychiatry 1998 Vol. 64 Issue 6 Pages 730-5, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=9647300; http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=2170112&blobtype=pdf. My own opinion, for what it's worth, is that genetic pressure to recycle B12 efficiency applied to people on diets more likely to include plants. The genetic pressure on Celts (who ate a lot of meat) was for strength and speed to catch the meat. You	Thank you for your comment. The recommendation and rationale for higher thresholds in people with Black ethnicity is based on evidence from laboratory testing. Details of the studies behind this are included in the diagnosis report, Evidence review C. Ethnicity as a factor was included as a strata in the review however, no evidence was identified to suggest a similar association for people from a Celtic background.

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					can't have genetic pressure for everything, so B12 recycling lost out.	
645	Vitamin B12 deficiency support group	Guideline	040	014	It is shocking that patients have to wait for gastric cancer symptoms before following up. Other countries offer 3 yearly surveillance. Maybe at least offer the patient with autoimmune gastritis the choice of screening - as they do for breast screening in the over 70s. We also note that blood serum B12 is often high er in people with early onset cancer, and the level of B12 in the blood might be an early indicator. My own opinion for what it's worth is that B12 is a natural protector against cancer, so when our bodies detect pre-cancer and cancer, we raise the B12 if we are able to (have enough in stores) in order to fight the cancer; therefore if B12 is not raised when pre-cancer or cancer is present this should be taken as a sign that the person has exhausted their stores of B12	Thank you for your comment. We searched but did not find evidence to support a recommendation to monitor people with autoimmune gastritis for gastric cancer. Therefore we cross referred to the existing NICE guideline on Suspected cancer: recognition and referral.

**None of the stakeholders who comments on this clinical guideline have declared any links to the tobacco industry.*