National Institute for Health and Care Excellence

Final

Vitamin B12 deficiency in over 16s: diagnosis and management

[E] Evidence review for vitamin B12 replacement

NICE guideline NG239

Evidence reviews underpinning recommendations 1.5.1 to 1.5.17 and recommendations for research in the NICE guideline

March 2024

Final

Developed by NICE

Disclaimer

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

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

Copyright

ISBN: 978-1-4731-5733-0

Contents

1.1 Review question 6
1.1.1 Introduction 6
1.1.2 Summary of the protocol 6
1.1.3 Methods and process 7
1.1.4 Effectiveness evidence 8
1.1.5 Summary of studies included in the effectiveness evidence 8
1.1.6 Summary of the effectiveness evidence 13
1.1.7 Economic evidence 42
1.1.8 Summary of included economic evidence 43
1.1.9 Unit costs 46
1.1.10 Evidence statements 47
1.2 Review question 48
1.2.1 Introduction 48
1.2.2 Summary of the protocol 48
1.2.3 Methods and process 49
1.2.4 Effectiveness evidence 50
1.2.5 Summary of studies included in the effectiveness evidence 50
1.2.6 Summary of the effectiveness evidence 50
1.2.7 Economic evidence 51
1.2.8 Unit costs 51
1.2.9 Evidence statements 52
1.3 The committee's discussion and interpretation of the evidence 52
1.4 References 63
Appendices 65
Appendix A – Review protocols 65
A.1 Vitamin B12 replacement 65
A.2 Self-administration 73
Appendix B – Literature search strategies 84
B.1 Clinical search literature search strategy 84
B.2 Health Economics literature search strategy 92
Appendix C – Effectiveness evidence study selection 97
C.1 Vitamin B12 replacement 97
C.2 Self-administration 98
Appendix D – Effectiveness evidence 100
Appendix E – Forest plots 155
E.1 Vitamin B12 replacement 155
E.2 Self-administration 169
Appendix F – GRADE tables 170

F.2 Self-administration **189**
Appendix G – Economic evidence study selection **190**
Appendix H – Economic evidence tables **191**
H.1 Vitamin B12 replacement **191**
H.2 Self-administration **195**
Appendix I – Excluded studies **196**
I.1 Vitamin B12 replacement **196**
Clinical studies 196
Health Economic studies 207
I.2 Self-administration **208**
Clinical studies 208
Health Economic studies 208
Appendix J – Research recommendations – full details **209**
J.1 Research recommendation **209**

1.1 Review question

What is the clinical and cost effectiveness of vitamin B12 replacement for vitamin B12 deficiency, including the dose, frequency and route of administration?

1.1.1 Introduction

Traditionally the management of vitamin B12 deficiency with vitamin B12 replacement therapy has been carried out to treat and reverse haematological manifestations and treat and prevent progression of neurological problems. The optimal route, dose and frequency of administration of vitamin B12 replacement therapy in different situations has never been clearly established and has often been guided by custom and historical practice.

This review seeks to determine the best way of treating vitamin B12 deficiency. The evidence will be stratified by the different causes of the deficiency because the required intervention is expected to differ depending on the cause.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Inclusion: adults with diagnosed vitamin B12 deficiency Exclusion: metabolic disorders Stratified by: • Cause (dietary/non-dietary/drug-induced)

Interventions	• Hydroxocobalamin
	  ○ Intramuscular injection
	  ○ Subcutaneous injection
	• Cyanocobalamin
	  ○ Oral tablets
	  ○ Intramuscular injection
	  ○ Subcutaneous injection
	• Combinations and sequences of the interventions above
	
	Stratified by:
	• Dosage
	• Frequency
	• Duration

Comparisons	• Each other (any differences in drug, route of administration, dosage, frequency, or duration) • Dietary advice (dietary cause) • Placebo • No treatment

	• Changing drug treatment (drug-induced)

Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical:
	
	• quality of life (such as EQ5D, SF36)
	• patient-reported outcomes (PROM scores including some/all symptoms):
	  ○ fatigue
	  ○ sleep
	  ○ peripheral neuropathy
	  ○ cognition
	  ○ psychiatric symptoms
	  ○ pain
	• haematological values
	• complications and adverse events
	  ○ mortality
	  ○ bleeds
	  ○ self-harm
	  ○ nerve damage
	  ○ frailty/falls
	  ○ severe cognitive effects
	  ○ postural hypotension
	• adherence to treatment
	• education/work absence
	
	• Time points: short-term (up to and including 3 months), long-term (over 3 months)

Study design	• Randomised controlled trials • Systematic reviews of RCTs • Non-randomised studies if insufficient RCT evidence is identified

1.1.3 Methods and process

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

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

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

Seven randomised controlled trials[1, 3-5, 8, 10, 16] and two observational studies[2, 15] were included in the review. These are summarised in Table 2 and Table 3 below. Evidence from these studies is summarised in the clinical evidence summary tables below (Table 4, Table 5, Table 6, Table 7, Table 8, Table 9, Table 10, Table 11, Table 12, Table 13, Table 14, Table 15, and Table 16).

The population characteristics in the included studies were varied, with ages ranging from 18 to >75 years. The definition of B12 deficiency also varied significantly between studies, with B12 concentrations ≤350pg/mL being applied as the highest cut-off for inclusion. Stratification based on vitamin B12 deficiency cause was intended, however in most studies there was not enough information to determine the cause, or the study contained a mixed population that meant this analysis was not possible.

No relevant clinical studies were identified for subcutaneous hydroxocobalamin / cyanocobalamin. Additionally, no relevant clinical studies were identified that used dietary advice, no treatment or changing drug treatment as a comparator.

A range of oral vitamin B12 doses were used in the identified studies, ranging from 100 – 1000mcg. For intramuscular administration the only dose identified was 1000mcg, although there was variation in the frequency of administration, ranging from daily to monthly injections, typically with a declining frequency as studies progressed.

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

1.1.4.2 Excluded studies

Three Cochrane systematic reviews were excluded from this review.[9, 17, 19] These three papers were assessed as full texts but were excluded due to not containing a population relevant to the present review protocol. The populations in these reviews were required to have haematological values that defined vitamin B12 deficiency, whereas the present review accepted any author defined B12 deficiency. Additionally, these reviews contained interventions that were not specified in the present review protocol, including unlicensed forms of vitamin B12 such as liquid solutions. References to the included studies in these Cochrane reviews were screened for eligibility against the review protocol for this review. One study met the inclusion criteria and was included.

See the excluded studies list in Appendix I.

1.1.5 Summary of studies included in the effectiveness evidence

Table 2: Summary of randomised controlled trials included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Castelli 2011 [1]	Oral cyanocobalamin (1000mcg per day for 90 days) n=*24* Vs Intramuscular cyanocobalamin (1000mcg injected on days 1, 3, 7, 10,	Adults (18-60y) with serum cobalamin concentration ≤350 pg/mL and gastrointestinal abnormalities, history of prolonged proton pump inhibitor use or a vegan/vegetarian diet	**≤3 months:** Haematological values: • Total B12 • Holotranscobalamin	Location: USA

Study	Intervention and comparison	Population	Outcomes	Comments
	14, 21, 30, 60 and 90) n=*26*		• Methylmalonic acid • Homocysteine Adverse events	
Dangour 2015 [3]	Oral cyanocobalamin (1000mcg per day for 12 months) *n=99* Vs Placebo *n=102*	Older adults (≥75y) with moderate B12 deficiency (≥107 - ≤210 pmol/L) and haemoglobin concentration ≥110 g/L (female) or ≥120 g/L (male)	**>3 months:** Patient reported outcomes • cognition • general health Haematological values: • Total B12 • Holotranscobalamin • Homocysteine • Haemoglobin	Location: England Excluded participants with pernicious anaemia and very low B12 concentrations (<107pmol/L)
Dhonukshe-Rutten 2005 [4]	Oral cyanocobalamin (1000mcg per day for 12 weeks) *n=19* Vs Placebo *n=24*	Older adults (≥65y) with mild cobalamin deficiency (serum concentrations 100 – 300 pmol/L) and elevated plasma MMA (≥0.30 pmol/L)	**≤3 months:** Haematological values: • Total B12 • Homocysteine • Methylmalonic acid	Location: The Netherlands Excluded participants with self-reported anaemia
Eussen 2005 [5]	Dose comparison study with daily oral cyanocobalamin for 16 weeks: 100mcg *n=24* 250mcg *n=25* 500mcg *n=22* 1000mcg *n=25*	Older adults (>70y) with serum B12 concentration between 100-300 pmol/L, plasma MMA ≥0.26 µmol/L and serum creatinine ≤120 µmol/L	**≤3 and >3 months:** Haematological values: • Total B12 • Holotranscobalamin • Homocysteine • Methylmalonic acid	Location: The Netherlands Excluded participants with self-reported anaemia and very low B12 concentrations (<100pmol/L)
Kuzminski 1998 [8]	Oral cyanocobalamin (2000mcg per day for 4 months) *n=18* Vs Intramuscular cyanocobalamin (1000mcg on days 1, 3, 7, 10, 14, 21, 30, 60 and 90) *n=15*	People with serum cobalamin concentration <160 pg/mL and elevation of serum MMA, homocysteine (compared to normal controls)	**>3 months:** Patient reported outcomes: • general health Haematological values: • Total B12 • Methylmalonic acid • Homocysteine	Location: USA

Study	Intervention and comparison	Population	Outcomes	Comments
			• Mean corpuscular volume	
Metaxas 2017 [10]	Oral cyanocobalamin (1000mcg daily for 28 days) *n=19* Vs Intramuscular hydroxocobalamin (1000mcg weekly for 28 days) *n=18*	Adults (≥18y) with B12 concentration <200 pmol/L	**≤3 months:** Haematological values: • Total B12 • Holotranscobalamin • Homocysteine • Methylmalonic acid	Location: Switzerland
Ubbink 1994 [16]	Oral cyanocobalamin (400mcg daily for 6 weeks) *n=17* Vs Placebo *n=17*	White males aged 20-73 years with confirmed hyperhomocysteinemia (>16.3 µmol/L)	**≤3 months:** Haematological values: • Total B12 • Homocysteine	Location: South Africa

Table 3: Summary of observational studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Couderc 2015 [2]	Oral cyanocobalamin - 5 possible treatment regimens (80% received regimen 2): 1. 1000µg/day for 1 month 2. 1000µg/day for 15 days, then 1000µg/10 days for 1 month, then 1000µg/month for 2 months 3. 1000µg three times per week for a month 4. 1000µg/day for 1 week 5. 1000µg/week for 1 month *n=111*	Geriatric patients attending a geriatric university hospital with confirmed cobalamin deficiency (<200 pg/mL or <160 pg/mL for those who had already received oral or IM cobalamin treatment) **Confounders:** **Cause** Mixed: 12 with pernicious anaemia, 72 with food-cobalamin malabsorption, 15 with nutritional deficiency, 26 undetermined **Severity of deficiency** Inclusion cut-off: 200 pg/mL, mean population value: 144.7 pg/mL **Severity of symptoms**	**>3 months:** Haematological values: • Total B12	Non-randomised trial Location: France

Study	Intervention and comparison	Population	Outcomes	Comments
	Vs Intramuscular cyanocobalamin – 2 possible regimens: 1. 1000µg/day for 1 week, then 1000µg/month 2. 1000µg three times per week for a month then 1000µg/month *n=14*	38 patients had clinical signs of asthenia, oedema on the legs and dyspnea, 6 had signs of neuropathy, 15 had confusion and 53 had dementia **Age/comorbidities/polypharmacy** Median age: 85.5 +/- 7 years, 7 patients had undergone gastric surgery, 5 had alcoholism, 9 had a blood disease, 16 were on long-term metformin for diabetes mellitus, 6 were on ranitidine and 41 were on long-term omeprazole therapy for gastric disease **Renal function** Not reported **Ethnicity** Not reported		
Smelt 2016 [15]	Intramuscular hydroxocobalamin with loading dose (six injections in total, one every two weeks for two months, then one injection after three months (each injection contained 1000µg)) *n=21* Vs Intramuscular hydroxocobalamin with no loading dose (three injections in total, one injection per month for three months (each injection contained 1000µg)) *n=21* Vs No treatment *n=21*	Adults who had undergone a sleeve gastrectomy or Roux-en-Y gastric bypass. Groups were matched for age, gender, pre-operative BMI, current BMI, surgical procedure. **Confounders:** **Cause** Surgical **Severity of deficiency** Baseline mean B12 ranged from 200-226.2 (range 140-300 pmol/L) **Severity of symptoms**	**≤3 months:** Haematological values: • Total B12 • Methylmalonic acid	Non-randomised trial Location: The Netherlands 16 patients (25.4 %) were using high-dose weight loss surgery (WLS) supplements, 43 patients (68.3 %) were using over-the-counter multivitamin supplements, and 4 patients (6.3 %) did not use any supplements

Study	Intervention and comparison	Population	Outcomes	Comments
		Not reported **Age/comorbidities/polypharmacy** Mean age ranged from 39-44.7 years, the majority of participants were 2 years post operation, but ranged from 0 to >5 years, 25.4% were using high-dose weight loss supplements, 68.3% were using multivitamin supplements **Renal function** Patients with renal insufficiency were excluded **Ethnicity** Not reported		

See Appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Table 4: Clinical evidence summary: oral cyanocobalamin vs intramuscular cyanocobalamin

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with intramuscular cyanocobalamin	Risk difference with Oral cyanocobalamin	
Patient reported outcomes at >3 months (general health: marked improvement or clearing of paraesthesias, ataxia or memory loss, final values, higher is better)	33 (1 RCT) follow-up: 4 months	⊕◯◯◯ Very low[a,b,c]	**RR 0.83** (0.25 to 2.78)	267 per 1,000	**45 fewer per 1,000** (200 fewer to 475 more)	MID (precision) = 0.8-1.25 MID (clinical importance) = 100 per 1000
Haematological values at ≤3 months (B12, pg/mL, final values, higher is better)	48 (1 RCT) follow-up: 3 months	⊕◯◯◯ Very low[b,c]	-	The mean B12 was **2057** pg/mL	MD **100 pg/mL lower** (634.25 lower to 434.25 higher)	MID = 91.5 (mean baseline SD x 0.5)
Haematological values at >3 months (B12, pg/mL, final values, higher is better)	32 (1 RCT) follow-up: 4 months	⊕⊕◯◯ Low[b,d]	-	The mean B12 was **325** pg/mL	MD **680 pg/mL higher** (391.86 higher to 968.14 higher)	MID = 34.5 (mean baseline SD x 0.5)
Haematological values at ≤3 months (holoTC, pmol/L, final values, higher is better)	48 (1 RCT) follow-up: 3 months	⊕◯◯◯ Very low[b,c]	-	The mean holoTC was **877** pmol/L	MD **231 pmol/L lower** (469.06 lower to 7.06 higher)	MID = 6 (mean baseline SD x 0.5)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with intramuscular cyanocobalamin	Risk difference with Oral cyanocobalamin	
Haematological values at ≤3 months (MMA, nmol/L, final values, lower is better)	48 (1 RCT) follow-up: 3 months	⊕⊕⊕◯ Moderate[b]	-	The mean MMA was **149** nmol/L	MD **25 nmol/L lower** (56.18 lower to 6.18 higher)	MID = 66.25 (mean baseline SD x 0.5)
Haematological values at >3 months (MMA, nmol/L, final values, lower is better)	33 (1 RCT) follow-up: 4 months	⊕⊕◯◯ Low[b,d]	-	The mean MMA was **265** nmol/L	MD **96 nmol/L lower** (200.76 lower to 8.76 higher)	MID = 3492 (mean baseline SD x 0.5)
Haematological values at ≤3 months (Hcy, µmol/L, final values, lower is better)	48 (1 RCT) follow-up: 3 months	⊕⊕◯◯ Low[b,c]	-	The mean Hcy was **12** µmol/L	MD **1 µmol/L lower** (2.98 lower to 0.98 higher)	MID = 2 (mean baseline SD x 0.5)
Haematological values at >3 months (Hcy, nmol/L, final values, lower is better)	33 (1 RCT) follow-up: 4 months	⊕⊕◯◯ Low[b,d]	-	The mean Hcy was **12.2** µmol/L	MD **1.6 µmol/L lower** (4.5 lower to 1.3 higher)	MID = 17.76 (mean baseline SD x 0.5)
Haematological values at >3 months (MCV, fL, final values, lower is better)	33 (1 RCT) follow-up: 4 months	⊕◯◯◯ Very low[b,c,d]	-	The mean MCV was **91** fL	MD **1 fL lower** (5.8 lower to 3.8 higher)	MID = 5.75 (mean baseline SD x 0.5)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with intramuscular cyanocobalamin	Risk difference with Oral cyanocobalamin	
Adverse events at ≤3 months (general, final values, lower is better)	48 (1 RCT) follow-up: 3 months	⊕◯◯◯ Very low[b,c,e]	**RR 1.02** (0.63 to 1.65)	577 per 1,000	**12 more per 1,000** (213 fewer to 375 more)	MID (precision) = 0.8-1.25 MID (clinical importance) = 100 per 1000
Quality of life at ≤3 and >3 months	No evidence	-	-	-	-	
Patient reported outcomes at ≤3 months	No evidence	-	-	-	-	
Adherence to treatment at ≤3 and >3 months	No evidence	-	-	-	-	
Education/work absence at ≤3 and >3 months	No evidence	-	-	-	-	

a. Downgraded by 2 increments due to bias arising from deviations from the intended intervention and measurement of the outcome

b. Downgraded due to population indirectness (mixed B12 deficiency cause)

c. Downgraded by 1 increment if confidence intervals overlapped one MID and 2 increments if confidence intervals overlapped both MIDs

d. Downgraded by 1 increment due to deviations from the intended intervention

e. Downgraded by 1 increment due to bias due to measurement of the outcome

f. MIDs for continuous outcomes were as follows: B12 at ≤3 months 91.5, B12 at >3 months 34.5, holoTC at ≤3 months 6, MMA at ≤3 months 66.25, MMA at >3 months 3492, Hcy at ≤3 months 2, Hcy at >3 months 17.76, MCV at >3 months 5.75

Table 5: Clinical evidence summary: oral cyanocobalamin vs placebo

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with Oral cyanocobalamin	
Patient reported outcomes at >3 months (general health: 30-item General Health Questionnaire, scale range unknown, final values, polarity unknown)	168 (1 RCT) follow-up: 12 months	⊕⊕⊕◯ Moderate [a]	-	The mean general health score was **2.7**	MD **0.3 lower** (1.69 lower to 1.09 higher)	MID = 2.35 (CG baseline SD x 0.5)
Patient reported outcomes at >3 months (cognition: California Verbal Learning Test (sum of correct words in first 3 trials), scale range 0-48, final values, higher is better)	184 (1 RCT) follow-up: 12 months	⊕⊕⊕◯ Moderate [a]	-	The mean number of words recalled was **24.6**	MD **0.7 lower** (2.64 lower to 1.24 higher)	MID = 3 (CG baseline SD x 0.5)
Patient reported outcomes at >3 months (cognition: California Verbal Learning Test - words recalled at delayed recall, scale range 0-16, final values, higher is better)	149 (1 RCT) follow-up: 12 months	⊕⊕⊕◯ Moderate [a]	-	The mean number of words recalled was **7.7**	MD **0.2 lower** (0.74 lower to 0.34 higher)	MID = 1.55 (CG baseline SD x 0.5)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with Oral cyanocobalamin	
Haematological values at ≤3 months (B12, pmol/L, final values, higher is better, cyanocobalamin dose: 0.4 mg)	34 (1 RCT) follow up: 6 weeks	⊕◯◯◯ Very low[a,b]	-	The mean B12 was **210.6**	MD **167.9 higher** (71.06 higher to 264.74 higher)	MID = 38.25 (CG baseline SD x 0.5)
Haematological values at ≤3 months (B12, pmol/L, change scores, higher is better, cyanocobalamin dose: 1 mg)	43 (1 RCT) follow up: 12 weeks	⊕◯◯◯ Very low[a,c]	-	The mean change in B12 was **1**	MD 280 higher (217.08 higher to 342.92 higher)	MID = 18.5 (CG follow-up SD x 0.5)
Haematological values at >3 months (B12, pmol/L, final values, higher is better)	144 (1 RCT) follow-up: 12 months	⊕◯◯◯ Very low[a,c]	-	The mean B12 was **235.4**	MD **405.5 higher** (356.6 higher to 454.4 higher)	MID = 30.35 (CG baseline SD x 0.5)
Haematological values at >3 months (holoTC, pmol/L, final values, higher is better)	141 (1 RCT) follow-up: 12 months	⊕◯◯◯ Very low[a,c]	-	The mean holoTC was **54.2**	MD **185.8 higher** (147.28 higher to 224.32 higher)	MID = 8.75 (CG baseline SD x 0.5)
Haematological values at ≤3 months (Hcy, umol/L, final values, lower is better, cyanocobalamin dose: 0.4 mg)	34 (1 RCT) follow up: 6 weeks	⊕◯◯◯ Very low[a,b,e]	-	The mean Hcy was **30.7**	MD **4.7 lower** (16.12 lower to 6.72 higher)	MID = 3.06 (CG follow-up SD x 0.5)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with Oral cyanocobalamin	
Haematological values at ≤3 months (Hcy, umol/L, change scores, lower is better, cyanocobalamin dose: 1 mg)	43 (1 RCT) follow up: 12 weeks	⊕◯◯◯ Very low[a,c,e]	-	The mean change in Hcy was **-0.1**	MD 1.7 lower (8.65 lower to 5.25 higher)	MID = 12.1 (CG baseline SD x 0.5)
Haematological values at >3 months (Hcy, µmol/L, final values, lower is better)	143 (1 RCT) follow-up: 12 months	⊕◯◯◯ Very low[a,c,d]	-	The mean Hcy was **17.4** µmol/L	MD **3.2 µmol/L lower** (4.9 lower to 1.5 lower)	MID = 2.8 (CG baseline SD x 0.5)
Haematological values at ≤3 months (MMA, µmol/L, change scores, lower is better)	43 (1 RCT) follow-up: 12 weeks	⊕◯◯◯ Very low[a,b,d]	-	The mean change in MMA was **0**	MD **0.18 lower** (1.73 lower to 1.37 higher)	MID = 0.13 (CG follow-up SD x 0.5)
Haematological values at >3 months (haemoglobin, g/L, final values, higher is better)	149 (1 RCT) follow-up: 12 months	⊕◯◯◯ Very low[a,c,d]	-	The mean haemoglobin was **137.2** g/L	MD **2.8 g/L higher** (0.97 lower to 6.57 higher)	MID = 6.4 (CG baseline SD x 0.5
Haematological values at ≤3 months (folate, nmol/L, final values, higher is better)	34 (1 RCT) follow-up: 6 weeks	⊕◯◯◯ Very low[b,d]	-	The mean folate was **6.1** nmol/L	MD **2 nmol/L lower** (4.73 lower to 0.73 higher)	MID = 1.8 (CG baseline SD x 0.5)
Haematological values at >3 months (folate, nmol/L, final values, higher is better)	143 (1 RCT) follow-up: 12 months	⊕◯◯◯ Very low[a,c]	-	The mean folate was **20.4** nmol/L	MD **0.2** nmol/L **lower** (4.42 lower to 4.02 higher)	MID = 6.9 (CG baseline SD x 0.5)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with placebo	Risk difference with Oral cyanocobalamin	
Quality of life at ≤3 and >3 months	No evidence	-	-	-	-	
Patient reported outcomes at ≤3 months	No evidence	-	-	-	-	
Complications and adverse events at ≤3 and >3 months	No evidence	-	-	-	-	
Adherence to treatment at ≤3 and >3 months	No evidence	-	-	-	-	
Education/work absence at ≤3 and >3 months	No evidence	-	-	-	-	

a. Downgraded due to population indirectness (mixed cause of B12 deficiency)

b. Downgraded by 2 increments due to bias arising from the randomisation process and missing outcome data

c. Downgraded by 2 increments due to missing outcome data

d. Downgraded by 1 increment if the confidence interval overlapped one MID or 2 increments if the confidence interval overlapped both MIDs

e. MIDs for continuous outcomes were as follows: B12 (0.4mg) at ≤3 months 38.25, B12 (1.0mg) at ≤3 months 18.5, B12 at >3 months 30.35, holoTC at >3 months 8.75, Hcy (0.4mg) at ≤3 months 3.06, Hcy (1.0mg) at ≤3 months 12.1, Hcy at >3 months 2.8, haemoglobin at >3 months 6.4, cognition at >3 months 3, general health at >3 months 2.35, folate at ≤3 months 1.8, folate at >3 months 6.9

Table 6: Clinical evidence summary: oral cyanocobalamin vs intramuscular hydroxocobalamin

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with intramuscular hydroxocobalamin	Risk difference with Oral cyanocobalamin	
Haematological values at ≤3 months (B12, pmol/L, final values, higher is better)	37 (1 RCT) follow-up: 1-month	⊕⊕⊕◯ Moderate[a]	-	The mean B12 was **2796** pmol/L	MD **2442 pmol/L lower** (3854.08 lower to 1029.92 lower)	MID = 12.92 (mean baseline SD x 0.5)
Haematological values at ≤3 months (holoTC, pmol/L, final values, higher is better)	37 (1 RCT) follow-up: 1-month	⊕⊕⊕◯ Moderate[a]	-	The mean holoTC was **1269** pmol/L	MD **1113 pmol/L lower** (2196.83 lower to 29.17 lower)	MID = 10.95 (mean baseline SD x 0.5)
Haematological values at ≤3 months (Hcy, µmol/L, final values, lower is better)	37 (1 RCT) follow-up: 1-month	⊕⊕◯◯ Low[a,b]	-	The mean Hcy was **13.8** µmol/L	MD **5.3 µmol/L higher** (2.13 higher to 8.47 higher)	MID = 2.69 (mean baseline SD x 0.5)
Haematological values at ≤3 months (MMA, nmol/L, final values, lower is better)	37 (1 RCT) follow-up: 1-month	⊕⊕⊕◯ Moderate[a]	-	The mean MMA was **168** nmol/L	MD **12 nmol/L higher** (33.42 lower to 57.42 higher)	MID = 104.72 (mean baseline SD x 0.5)
Adverse events at ≤3 months (final values, lower is better)	37 (1 RCT) follow-up: 1-month	⊕◯◯◯ Very low[a,c,d]	not estimable	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)	MID (precision) = 0.8 – 1.25 MID (clinical importance) = 100 per 1000

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with intramuscular hydroxocobalamin	Risk difference with Oral cyanocobalamin	
Quality of life at ≤3 and >3 months	No evidence	-	-	-	-	
Patient reported outcome measures at ≤3 and >3 months	No evidence	-	-	-	-	
Haematological values at >3 months	No evidence	-	-	-	-	
Complications and adverse events at >3 months	No evidence	-	-	-	-	
Adherence to treatment at ≤3 and >3 months	No evidence	-	-	-	-	
Education/work absence at ≤3 and >3 months	No evidence	-	-	-	-	

a. Downgraded due to population indirectness (mixed B12 deficiency cause)

b. Downgraded by 1 increment if the confidence interval overlapped one MID and 2 increments if the confidence interval overlapped both MIDs

c. Downgraded by 1 increment due to bias arising from measurement of the outcome

d. Downgraded due to zero events and small sample size (no imprecision: sample size >350, serious imprecision: sample size >70 ≤350, very serious imprecision: sample size <70)

e. MIDs for continuous outcomes were as follows: B12 at ≤3 months 12.92, holoTC at ≤3 months 10.95, Hcy at ≤3 months 2.69, MMA at ≤3 months 104.72

Table 7: Clinical evidence summary: oral cyanocobalamin 100mcg vs 250mcg

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with 250mcg	Risk difference with Oral cyanocobalamin 100mcg	
Haematological values at ≤3 months (B12, pmol/L, change scores, higher is better)	49 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean B12 at ≤3 months was **128** pmol/L	MD **20 pmol/L lower** (64.58 lower to 24.58 higher)	MID = 40.24 (mean SD at follow-up x 0.5)
Haematological values at >3 months (B12, pmol/L, change scores, higher is better)	49 (1 RCT) follow-up: 16 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean B12 at >3 months was **153** pmol/L	MD **24 pmol/L lower** (88.87 lower to 40.87 higher)	MID = 59.75 (mean SD at follow-up x 0.5)
Haematological values at ≤3 months (holoTC, pmol/L, change scores, higher is better)	49 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean holoTC at ≤3 months was **40** pmol/L	MD **14 pmol/L lower** (26.76 lower to 1.24 lower)	MID = 12.63 (mean SD at follow-up x 0.5)
Haematological values at >3 months (holoTC, pmol/L, change scores, higher is better)	49 (1 RCT) follow-up: 16 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean holoTC at >3 months was **48** pmol/L	MD **20 pmol/L lower** (34.82 lower to 5.18 lower)	MID = 13.28 (mean SD at follow-up x 0.5)
Haematological values at ≤3 months (Hcy, µmol/L, change scores, lower is better)	49 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean Hcy at ≤3 months was **-1** µmol/L	MD **0.5 µmol/L higher** (0.27 lower to 1.27 higher)	MID = 0.76 (mean SD at follow-up x 0.5)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with 250mcg	Risk difference with Oral cyanocobalamin 100mcg	
Haematological values at >3 months (Hcy, µmol/L, change scores, lower is better)	49 (1 RCT) follow-up: 16 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean Hcy at >3 months was **-1.4** µmol/L	MD **0.7 µmol/L higher** (0.51 lower to 1.91 higher)	MID = 1.11 (mean SD at follow-up x 0.5)
Haematological values at ≤3 months (MMA, µmol/L, change scores, lower is better)	49 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean MMA at ≤3 months was **-0.13** µmol/L	MD **0.04 µmol/L higher** (0.05 lower to 0.13 higher)	MID = 0.082 (mean SD at follow-up x 0.5)
Haematological values at >3 months (MMA, µmol/L, change scores, lower is better)	49 (1 RCT) follow-up: 16 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean MMA at >3 months was **-0.14** µmol/L	MD **0.06 µmol/L higher** (0.04 lower to 0.16 higher)	MID = 0.083 (mean SD at follow-up x 0.5)
Quality of life at ≤3 and >3 months	No evidence	-	-	-	-	
Patient reported outcomes at ≤3 and >3 months	No evidence	-	-	-	-	
Complications and adverse events at ≤3 and >3 months	No evidence	-	-	-	-	
Adherence to treatment at ≤3 and >3 months	No evidence	-	-	-	-	

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with 250mcg	Risk difference with Oral cyanocobalamin 100mcg	
Education/work absence at ≤3 and >3 months	No evidence	-	-	-	-	

a. Downgraded by 1 increment due to bias arising from the randomisation process

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes)

c. Downgraded due to population indirectness (mixed B12 deficiency cause)

d. MIDs for continuous outcomes were as follows: B12 at ≤3 months 40.24, B12 at >3 months 59.75, holoTC at ≤3 months 12.63, holoTC at >3 months 13.28, Hcy at ≤3 months 0.76, Hcy at >3 months 1.11, MMA at ≤3 months 0.082, MMA at >3 months 0.083

Table 8: Clinical evidence summary: oral cyanocobalamin 100mcg vs 500mcg

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with 500mcg	Risk difference with Oral cyanocobalamin 100mcg	
Haematological values at ≤3 months (B12, pmol/L, change scores, higher is better)	46 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean B12 at ≤3 months was **182** pmol/L	MD **74 pmol/L lower** (126.87 lower to 21.13 lower)	MID = 47.64 (mean SD at follow-up x 0.5)
Haematological values at >3 months (B12, pmol/L, change scores, higher is better)	45 (1 RCT) follow-up: 16 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean B12 at >3 months was **212** pmol/L	MD **83 pmol/L lower** (160.55 lower to 5.45 lower)	MID = 70.59 (mean SD at follow-up x 0.5)
Haematological values at ≤3 months (holoTC, pmol/L, change scores, higher is better)	46 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean holoTC at ≤3 months was **49** pmol/L	MD **23 pmol/L lower** (35.71 lower to 10.29 lower)	MID = 11.92 (mean SD at follow-up x 0.5)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with 500mcg	Risk difference with Oral cyanocobalamin 100mcg	
Haematological values at >3 months (holoTC, pmol/L, change scores, higher is better)	45 (1 RCT) follow-up: 16 weeks	⊕⊕◯◯ Low[a,c]	-	The mean holoTC at >3 months was **60** pmol/L	MD **32 pmol/L lower** (46.02 lower to 17.98 lower)	MID = 12.37 (mean SD at follow-up x 0.5)
Haematological values at ≤3 months (Hcy, µmol/L, change scores, lower is better)	46 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean Hcy at ≤3 months was **-1.9** µmol/L	MD **1.4 µmol/L higher** (0.47 higher to 2.33 higher)	MID = 0.88 (mean SD at follow-up x 0.5)
Haematological values at >3 months (Hcy, µmol/L, change scores, lower is better)	45 (1 RCT) follow-up: 16 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean Hcy at >3 months was **-2.4** µmol/L	MD **1.7 µmol/L higher** (0.56 higher to 2.84 higher)	MID = 1.05 (mean SD at follow-up x 0.5)
Haematological values at ≤3 months (MMA, µmol/L, change scores, lower is better)	46 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean MMA at ≤3 months was **-0.22** µmol/L	MD **0.13 µmol/L higher** (0.02 lower to 0.28 higher)	MID = 0.12 (mean SD at follow-up x 0.5)
Haematological values at >3 months (MMA, µmol/L, change scores, lower is better)	45 (1 RCT) follow-up: 16 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean MMA at >3 months was **-0.23** µmol/L	MD **0.15 µmol/L higher** (0 to 0.3 higher)	MID = 0.12 (mean SD at follow-up x 0.5)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with 500mcg	Risk difference with Oral cyanocobalamin 100mcg	
Quality of life at ≤3 and >3 months	No evidence	-	-	-	-	
Patient reported outcomes at ≤3 and >3 months	No evidence	-	-	-	-	
Complications and adverse events at ≤3 and >3 months	No evidence	-	-	-	-	
Adherence to treatment at ≤3 and >3 months	No evidence	-	-	-	-	
Education/work absence at ≤3 and >3 months	No evidence	-	-	-	-	

a. Downgraded by 1 increment due to bias arising from the randomisation process

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes)

c. Downgraded due to population indirectness (mixed B12 deficiency cause)

d. MIDs for continuous outcomes were as follows: B12 at ≤3 months 47.64, B12 at >3 months 70.59, holoTC at ≤3 months 11.92, holoTC at >3 months 12.37, Hcy at ≤3 months 0.88, Hcy at >3 months 1.05, MMA at ≤3 months 0.12, MMA at >3 months 0.12

Table 9: Clinical evidence summary: oral cyanocobalamin 100mcg vs 1000mcg

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with 1000mcg	Risk difference with Oral cyanocobalamin 100mcg	
Haematological values at ≤3 months (B12, pmol/L, change scores, higher is better)	49 (1 RCT) follow-up: 8 weeks	⊕⊕◯◯ Low[a,c]	-	The mean B12 at ≤3 months was **248** pmol/L	MD **140 pmol/L lower** (209.34 lower to 70.66 lower)	MID = 60.06 (mean SD at follow-up x 0.5)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with 1000mcg	Risk difference with Oral cyanocobalamin 100mcg	
Haematological values at ≤3 months (holoTC, pmol/L, change scores, higher is better)	49 (1 RCT) follow-up: 8 weeks	⊕⊕◯◯ Low[a,c]	-	The mean holoTC at ≤3 months was **67** pmol/L	MD **41 pmol/L lower** (55.23 lower to 26.77 lower)	MID = 13.59 (mean SD at follow-up x 0.5)
Haematological values at >3 months (holoTC, pmol/L, change scores, higher is better)	49 (1 RCT) follow-up: 16 weeks	⊕⊕◯◯ Low[a,c]	-	The mean holoTC at >3 months was **73** pmol/L	MD **45 pmol/L lower** (59.82 lower to 30.18 lower)	MID = 13.59 (mean SD at follow-up x 0.5)
Haematological values at ≤3 months (Hcy, µmol/L, change scores, lower is better)	49 (1 RCT) follow-up: 8 weeks	⊕⊕◯◯ Low[a,c]	-	The mean Hcy at ≤3 months was **-5.1** µmol/L	MD **4.6 µmol/L higher** (1.3 lower to 10.5 higher)	MID = 4.27 (mean SD at follow-up x 0.5)
Haematological values at >3 months (Hcy, µmol/L, change scores, lower is better)	49 (1 RCT) follow-up: 16 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean Hcy at >3 months was **-5.7** µmol/L	MD **5 µmol/L higher** (2.07 lower to 12.07 higher)	MID = 5.22 (mean SD at follow-up x 0.5)
Haematological values at ≤3 months (MMA, µmol/L, change scores, lower is better)	49 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean MMA at ≤3 months was **-0.31** µmol/L	MD **0.22 µmol/L higher** (0.14 lower to 0.58 higher)	MID = 0.27 (mean SD at follow-up x 0.5)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with 1000mcg	Risk difference with Oral cyanocobalamin 100mcg	
Haematological values at >3 months (MMA, µmol/L, change scores, lower is better)	49 (1 RCT) follow-up: 16 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean MMA at >3 months was **-0.34** µmol/L	MD **0.26 µmol/L higher** (0.12 lower to 0.64 higher)	MID = 0.29 (mean SD at follow-up x 0.5)
Quality of life at ≤3 and >3 months	No evidence	-	-	-	-	
Patient reported outcomes at ≤3 and >3 months	No evidence	-	-	-	-	
Complications and adverse events at ≤3 and >3 months	No evidence	-	-	-	-	
Adherence to treatment at ≤3 and >3 months	No evidence	-	-	-	-	
Education/work absence at ≤3 and >3 months	No evidence	-	-	-	-	

a. Downgraded by 1 increment due to bias arising from the randomisation process

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes)

c. Downgraded due to population indirectness (mixed B12 deficiency cause)

d. MIDs for continuous outcomes were as follows: B12 at ≤3 months 60.06, holoTC at ≤3 months 13.59, holoTC at >3 months 13.59, Hcy at ≤3 months 4.27, Hcy at >3 months 5.22, MMA at ≤3 months 0.27, MMA at >3 months 0.29

Table 10: Clinical evidence summary: oral cyanocobalamin 250mcg vs 500mcg

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with 500mcg	Risk difference with Oral cyanocobalamin 250mcg	
Haematological values at ≤3 months (B12, pmol/L, change scores, higher is better)	47 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean B12 at ≤3 months was **182** pmol/L	MD **54 pmol/L lower** (102.22 lower to 5.78 lower)	MID = 42.26 (mean SD at follow-up x 0.5)
Haematological values at >3 months (B12, pmol/L, change scores, higher is better)	46 (1 RCT) follow-up: 16 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean B12 at >3 months was **212** pmol/L	MD **59 pmol/L lower** (129.62 lower to 11.62 higher)	MID = 62.22 (mean SD at follow-up x 0.5)
Haematological values at ≤3 months (holoTC, pmol/L, change scores, higher is better)	47 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean holoTC at ≤3 months was **49** pmol/L	MD **9 pmol/L lower** (22.38 lower to 4.38 higher)	MID = 12.68 (mean SD at follow-up x 0.5)
Haematological values at >3 months (holoTC, pmol/L, change scores, higher is better)	46 (1 RCT) follow-up: 16 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean holoTC at >3 months was **60** pmol/L	MD **12 pmol/L lower** (27.39 lower to 3.39 higher)	MID = 13.77 (mean SD at follow-up x 0.5)
Haematological values at ≤3 months (Hcy, µmol/L, change scores, lower is better)	47 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean Hcy at ≤3 months was **-1.9** µmol/L	MD **0.9 µmol/L higher** (0.18 lower to 1.98 higher)	MID = 1.01 (mean SD at follow-up x 0.5)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with 500mcg	Risk difference with Oral cyanocobalamin 250mcg	
Haematological values at >3 months (Hcy, µmol/L, change scores, lower is better)	46 (1 RCT) follow-up: 16 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean Hcy at >3 months was **-2.4** µmol/L	MD **1 µmol/L higher** (0.27 lower to 2.27 higher)	MID = 1.17 (mean SD at follow-up x 0.5)
Haematological values at ≤3 months (MMA, µmol/L, change scores, lower is better)	47 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean MMA at ≤3 months was **-0.22** µmol/L	MD **0.09 µmol/L higher** (0.07 lower to 0.25 higher)	MID = 0.14 (mean SD at follow-up x 0.5)
Haematological values at >3 months (MMA, µmol/L, change scores, lower is better)	46 (1 RCT) follow-up: 16 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean MMA at >3 months was **-0.23** µmol/L	MD **0.09 µmol/L higher** (0.08 lower to 0.26 higher)	MID = 0.14 (mean SD at follow-up x 0.5)
Quality of life at ≤3 and >3 months	No evidence	-	-	-	-	
Patient reported outcomes at ≤3 and >3 months	No evidence	-	-	-	-	
Complications and adverse events at ≤3 and >3 months	No evidence	-	-	-	-	
Adherence to treatment at ≤3 and >3 months	No evidence	-	-	-	-	

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with 500mcg	Risk difference with Oral cyanocobalamin 250mcg	
Education/work absence at ≤3 and >3 months	No evidence	-	-	-	-	

a. Downgraded by 1 increment due to bias arising from the randomisation process

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes)

c. Downgraded due to population indirectness (mixed B12 deficiency cause)

d. MIDs for continuous outcomes were as follows: B12 at ≤3 months 42.26, B12 at >3 months 62.22, holoTC at ≤3 months 12.68, holoTC at >3 months 13.77, Hcy at ≤3 months 1.01, Hcy at >3 months 1.17, MMA at ≤3 months 0.14, MMA at >3 months 0.14

Table 11: Clinical evidence summary: oral cyanocobalamin 250mcg vs 1000mcg

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with 1000mcg	Risk difference with Oral cyanocobalamin 250mcg	
Haematological values at ≤3 months (B12, pmol/L, change scores, higher is better)	50 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean B12 at ≤3 months was **248** pmol/L	MD **120 pmol/L lower** (185.86 lower to 54.14 lower)	MID = 55.72 (mean SD at follow-up x 0.5)
Haematological values at ≤3 months (holoTC, pmol/L, change scores, higher is better)	50 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean holoTC at ≤3 months was **67** pmol/L	MD **27 pmol/L lower** (41.83 lower to 12.17 lower)	MID = 14.35 (mean SD at follow-up x 0.5)
Haematological values at >3 months (holoTC, pmol/L, change scores, higher is better)	50 (1 RCT) follow-up: 16 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean holoTC at >3 months was **73** pmol/L	MD **25 pmol/L lower** (41.12 lower to 8.88 lower)	MID = 14.99 (mean SD at follow-up x 0.5)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with 1000mcg	Risk difference with Oral cyanocobalamin 250mcg	
Haematological values at ≤3 months (Hcy, µmol/L, change scores, lower is better)	50 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean Hcy at ≤3 months was **-5.1** µmol/L	MD **4.1 µmol/L higher** (1.83 lower to 10.03 higher)	MID = 4.4 (mean SD at follow-up x 0.5)
Haematological values at >3 months (Hcy, µmol/L, change scores, lower is better)	50 (1 RCT) follow-up: 16 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean Hcy at >3 months was **-5.7** µmol/L	MD **4.3 µmol/L higher** (2.79 lower to 11.39 higher)	MID = 5.33 (mean SD at follow-up x 0.5)
Haematological values at ≤3 months (MMA, µmol/L, change scores, lower is better)	50 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean MMA at ≤3 months was **-0.31** µmol/L	MD **0.18 µmol/L higher** (0.19 lower to 0.55 higher)	MID = 0.29 (mean SD at follow-up x 0.5)
Haematological values at >3 months (MMA, µmol/L, change scores, lower is better)	50 (1 RCT) follow-up: 16 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean MMA at >3 months was **-0.34** µmol/L	MD **0.2 µmol/L higher** (0.19 lower to 0.59 higher)	MID = 0.31 (mean SD at follow-up x 0.5)
Quality of life at ≤3 and >3 months	No evidence	-	-	-	-	
Patient reported outcomes at ≤3 and >3 months	No evidence	-	-	-	-	
Complications and adverse events at ≤3 and >3 months	No evidence	-	-	-	-	

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with 1000mcg	Risk difference with Oral cyanocobalamin 250mcg	
Adherence to treatment at ≤3 and >3 months	No evidence	-	-	-	-	
Education/work absence at ≤3 and >3 months	No evidence	-	-	-	-	

a. Downgraded by 1 increment due to bias arising from the randomisation process

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes)

c. Downgraded due to population indirectness (mixed B12 deficiency cause)

d. MIDs for continuous outcomes were as follows: B12 at ≤3 months 55.72, holoTC at ≤3 months 14.35, holoTC at >3 months 14.99, Hcy at ≤3 months 4.4, Hcy at >3 months 5.33, MMA at ≤3 months 0.29, MMA at >3 months 0.31

Table 12: Clinical evidence summary: oral cyanocobalamin 500mcg vs 1000mcg

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with 1000mcg	Risk difference with Oral cyanocobalamin 500mcg	
Haematological values at ≤3 months (B12, pmol/L, change scores, higher is better)	47 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean B12 at ≤3 months was **248** pmol/L	MD **66 pmol/L lower** (137.74 lower to 5.74 higher)	MID = 61.84 (mean SD at follow-up x 0.5)
Haematological values at ≤3 months (holoTC, pmol/L, change scores, higher is better)	47 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean holoTC at ≤3 months was **67** pmol/L	MD **18 pmol/L lower** (32.79 lower to 3.21 lower)	MID = 13.63 (mean SD at follow-up x 0.5)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with 1000mcg	Risk difference with Oral cyanocobalamin 500mcg	
Haematological values at >3 months (holoTC, pmol/L, change scores, higher is better)	46 (1 RCT) follow-up: 16 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean holoTC at >3 months was **73** pmol/L	MD **13 pmol/L lower** (28.39 lower to 2.39 higher)	MID = 14.08 (mean SD at follow-up x 0.5)
Haematological values at ≤3 months (Hcy, µmol/L, change scores, lower is better)	47 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean Hcy at ≤3 months was **-5.1** µmol/L	MD **3.2 µmol/L higher** (2.75 lower to 9.15 higher)	MID = 4.52 (mean SD at follow-up x 0.5)
Haematological values at >3 months (Hcy, µmol/L, change scores, lower is better)	46 (1 RCT) follow-up: 16 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean Hcy at >3 months was **-5.7** µmol/L	MD **3.3 µmol/L higher** (3.78 lower to 10.38 higher)	MID = 5.27 (mean SD at follow-up x 0.5)
Haematological values at ≤3 months (MMA, µmol/L, change scores, lower is better)	47 (1 RCT) follow-up: 8 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean MMA at ≤3 months was **-0.31** µmol/L	MD **0.09 µmol/L higher** (0.3 lower to 0.48 higher)	MID = 0.33 (mean SD at follow-up x 0.5)
Haematological values at >3 months (MMA, µmol/L, change scores, lower is better)	46 (1 RCT) follow-up: 16 weeks	⊕◯◯◯ Very low[a,b,c]	-	The mean MMA at >3 months was **-0.34** µmol/L	MD **0.11 µmol/L higher** (0.3 lower to 0.52 higher)	MID = 0.34 (mean SD at follow-up x 0.5)
Quality of life at ≤3 and >3 months	No evidence	-	-	-	-	

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with 1000mcg	Risk difference with Oral cyanocobalamin 500mcg	
Patient reported outcomes at ≤3 and >3 months	No evidence	-	-	-	-	
Complications and adverse events at ≤3 and >3 months	No evidence	-	-	-	-	
Adherence to treatment at ≤3 and >3 months	No evidence	-	-	-	-	
Education/work absence at ≤3 and >3 months	No evidence	-	-	-	-	

a. Downgraded by 1 increment due to bias arising from the randomisation process

b. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes)

c. Downgraded due to population indirectness (mixed B12 deficiency cause)

d. MIDs for continuous outcomes were as follows: B12 at ≤3 months 61.84, holoTC at ≤3 months 13.63, holoTC at >3 months 14.08, Hcy at ≤3 months 4.52, Hcy at >3 months 5.27. MMA at ≤3 months 0.33, MMA at >3 months 0.34

Table 13: Clinical evidence summary: oral cyanocobalamin vs intramuscular cyanocobalamin (observational studies)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with intramuscular cyanocobalamin	Risk difference with Oral cyanocobalamin	
Haematological values - B12 at >3 months (pg/mL, final values, higher is better)	125 (1 observational study) follow up: 3.5 months	⊕◯◯◯ Very low[a,b]	-	The mean haematological values - B12 at >3 months (pg/mL, final values, higher is better) was **730.9** pg/mL	MD **451.5 pg/mL lower** (824.97 lower to 78.03 lower)	MID = 21.03 (baseline population SD x 0.5)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with intramuscular cyanocobalamin	Risk difference with Oral cyanocobalamin	
Quality of life at ≤3 and >3 months	No evidence	-	-	-	-	
Patient reported outcomes at ≤3 and >3 months	No evidence	-	-	-	-	
Complications and adverse events at ≤3 and >3 months	No evidence	-	-	-	-	
Adherence to treatment at ≤3 and >3 months	No evidence	-	-	-	-	
Education/work absence at ≤3 and >3 months	No evidence	-	-	-	-	

a. Downgraded by 2 increments due to risk of bias arising from confounding, selection of participants into the study, classification of the interventions, deviations from the intended interventions, missing data and measurement of the outcome

b. Downgraded by 2 increments due to mixed causes of B12 deficiency

c. MID for hematological values – B12 at >3 months = 21.03

Table 14: Clinical evidence summary: intramuscular hydroxocobalamin (loading dose) vs intramuscular hydroxocobalamin (no loading dose) (observational studies)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with intramuscular hydroxocobalamin (no loading dose)	Risk difference with Intramuscular hydroxocobalamin (loading dose)	
Haematological values - B12 at <3 months (pmol/L, final values, higher is better)	42 (1 observational study) follow up: 3 months	⊕◯◯◯ Very low[a,b]	-	The mean haematological values - B12 at <3 months (pmol/L, final values, higher is better) was **332.9** pmol/L	MD **217.4 pmol/L higher** (13.73 lower to 448.53 higher)	MID = 20.4 (baseline population SD x 0.5)
Haematological values - MMA at <3 months (nmol/L, final values, lower is better)	42 (1 observational study) follow up: 3 months	⊕◯◯◯ Very low[a,b]	-	The mean haematological values - MMA at <3 months (nmol/L, final values, lower is better) was **281.7** nmol/L	MD **100.6 nmol/L lower** (164.48 lower to 36.72 lower)	MID = 107.35 (baseline population SD x 0.5)
Quality of life at ≤3 and >3 months	No evidence	-	-	-	-	
Patient reported outcomes at ≤3 and >3 months	No evidence	-	-	-	-	
Complications and adverse events at ≤3 and >3 months	No evidence	-	-	-	-	
Adherence to treatment at ≤3 and >3 months	No evidence	-	-	-	-	

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with intramuscular hydroxocobalamin (no loading dose)	Risk difference with Intramuscular hydroxocobalamin (loading dose)	
Education/work absence at ≤3 and >3 months	No evidence	-	-	-	-	

a. Downgraded by 2 increments due to risk of bias arising from confounding and selection of participants into the study

b. Downgraded by 1 increment if the confidence interval crossed one MID and 2 increments if the confidence interval cross both MIDs

c. MIDs for hematological values – B12 at <3 months = 20.4 and for hematological values – MMA at <3 months = 107.35

Table 15: Clinical evidence summary: intramuscular hydroxocobalamin (loading dose) vs no treatment (observational studies)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with no treatment	Risk difference with Intramuscular hydroxocobalamin (loading dose)	
Haematological values - B12 at <3 months (pmol/L, final values, higher is better)	42 (1 observational study) follow up: 3 months	⊕⊕◯◯ Low[a]	-	The mean haematological values - B12 at <3 months (pmol/L, final values, higher is better) was **211.4** pmol/L	MD **288.9 pmol/L higher** (95 higher to 482.8 higher)	MID = 17.65 (population baseline SD x 0.5)
Haematological values - MMA at <3 months (nmol/L, final values, lower is better)	42 (1 observational study) follow up: 3 months	⊕⊕◯◯ Low[a]	-	The mean haematological values - MMA at <3 months (nmol/L, final values, lower is better) was **514.3** nmol/L	MD **333.2 nmol/L lower** (437.8 lower to 228.6 lower)	MID = 104.33 (population baseline SD x 0.5)
Quality of life at ≤3 and >3 months	No evidence	-	-	-	-	

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with no treatment	Risk difference with Intramuscular hydroxocobalamin (loading dose)	
Patient reported outcomes at ≤3 and >3 months	No evidence	-	-	-	-	
Complications and adverse events at ≤3 and >3 months	No evidence	-	-	-	-	
Adherence to treatment at ≤3 and >3 months	No evidence	-	-	-	-	
Education/work absence at ≤3 and >3 months	No evidence	-	-	-	-	

a. Downgraded by 2 increments due to risk of bias arising from confounding and selection of participants into the study

b. MIDs for hematological values – B12 at <3 months = 17.65 and for hematological values – MMA at <3 months = 104.33

Table 16: Clinical evidence summary: intramuscular hydroxocobalamin (no loading dose) vs no treatment (observational studies)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with no treatment	Risk difference with Intramuscular hydroxocobalamin (no loading dose)	
Haematological values - B12 at <3 months (pmol/L, final values, higher is better)	42 (1 observational study) follow up: 3 months	⊕◯◯◯ Very low[a,b]	-	The mean haematological values - B12 at <3 months (pmol/L, final values, higher is better) was **211.4** pmol/L	MD **121.5 pmol/L higher** (6.33 lower to 249.33 higher)	MID = 20.05 (population baseline SD x 0.5)
Haematological values - MMA at <3 months (nmol/L, final values, lower is better)	42 (1 observational study) follow up: 3 months	⊕⊕◯◯ Low[a]	-	The mean haematological values - MMA at <3 months (nmol/L, final values, lower is better) was **514.3** nmol/L	MD **232.6 nmol/L lower** (348.78 lower to 116.42 lower)	MID = 81.03 (population baseline SD x 0.5)
Quality of life at ≤3 and >3 months	No evidence	-	-	-	-	
Patient reported outcomes at ≤3 and >3 months	No evidence	-	-	-	-	
Complications and adverse events at ≤3 and >3 months	No evidence	-	-	-	-	
Adherence to treatment at ≤3 and >3 months	No evidence	-	-	-	-	

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Comments
				Risk with no treatment	Risk difference with Intramuscular hydroxocobalamin (no loading dose)	
Education/work absence at ≤3 and >3 months	No evidence	-	-	-	-	

a. Downgraded by 2 increments due to risk of bias arising from confounding and selection of participants into the study

b. Downgraded by 1 increment if the confidence interval crossed one MID and 2 increments if the confidence interval crossed both MIDs

See Appendix F for full GRADE tables

1.1.7 Economic evidence

1.1.7.1 Included studies

Three health economic studies with the relevant comparison were included in this review [6, 11, 18].These are summarised in the health economic evidence profile below (Table 17) and the health economic evidence tables in Appendix H.

1.1.7.2 Excluded studies

One economic study relating to this review question was identified but was excluded due to methodological limitations (Masucci, 2013). This is listed in Appendix I, with reasons for exclusion given.

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

1.1.8 Summary of included economic evidence

Table 17: Health economic evidence profile: oral B12 vs intramuscular B12

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Vidal-Alaball, 2006[18] United Kingdom	Directly applicable [(a)]	Potentially serious limitations[(b)]	• A cost-comparison analysis model based on RCT data assuming no difference in outcomes of treatment strategies. • Population: Patients currently receiving i.m. B12 treatment • Comparators: Continuing i.m. or converting to oral B12 treatment Time horizon: 2 years	£49.12[(c)]	N/A	N/A	Over the two-year time horizon of the study, i.m. treatment was the lowest cost strategy. After the first year which incorporated conversion costs, oral treatment was less costly than i.m. therefore with a longer time horizon oral treatment would be the lower cost strategy. The variable ‘‘home visit’’ had the most significant impact on the results. The authors found that even if there were no home visits required for i.m. treatment, oral treatment from year two was always less costly than i.m. The annual cost from year 2 for oral treatment £35.55 versus £55.99 for i.m. treatment. If home visits are required for the annual cost of i.m. rises to £99.99 Therefore from year 2 onwards the oral cost will be lower than i.m. treatment.
Mnatzaganian, 2015[11], Australia	Partially applicable[(d)]	Potentially serious limitations[(e)]	• Decision tree model comparing five mutually exclusive diagnostic-therapeutic strategies	3-2: -£23[(f)] 5-4: -£94[(f)]	QALYs 3-2: 0 5-4: 0	N/A	Oral treatment was less costly in both cases compared to i.m. when patients undergo a test or if no test is conducted. There

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			using serum cobalamin to test. • Cost-utility analysis (QALYs) • Population: 18 years of age or older, presenting with fatigue • Comparators: 1. No test and no treatment 2. Serum test and treat with i.m. 3. Serum test and treat with oral supplement 4. Do not test and treat all with i.m. 5. Do not test and treat all with oral • Time horizon: 3 months.				were no differences in QALYs thus oral treatment is the lower cost option compared to i.m. treatment. The strategy "do not test but treat all with oral supplements" had a probability of being cost effective (£20/£30K threshold): 100% A pa was performed which included sensitivity and specificity of the diagnostic test, cost, and utility input parameter values. Further deterministic sensitivity analysis was done with varying the prevalence levels of cobalamin deficiency at 1%, 5% 10% and 20%. The results remained robust in all analyses.
Houle 2014 [6] ([Canada])	Partially applicable(g)	Potentially serious limitations(h)	• Cost-comparison analysis • Based on 3 RCTs assuming equivalence in clinical effectiveness for interventions • Population: >65 years, receiving intramuscular B12 treatment • Intervention: B12 tablet (oral) 1000mcg, one tablet once daily • Comparators: B12 10ml vial for injection, 1ml/1000mcg	£-279(i)	N/A	N/A	Sensitivity analysis showed that proportion of people assumed to have an additional physician visit in the i.m. arm had a significant impact on the cost savings.

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
			administered once per month Time horizon: 5 years				

Abbreviations: i.m. = intramuscular, pa = probabilistic sensitivity analysis, QALY= quality-adjusted life years, RCT= randomised controlled trial.

(a) The clinical evidence indicated no difference in effectiveness between oral and i.m. vitamin B12 treatment therefore a cost-comparison economic evaluation was used to compare costs between the interventions. This study has a focus on primary care in the UK, with local costings.

(b) This is not a cost-utility evaluation, the study incorporates costs of converting therapy which may not be directly applicable for example the increased blood test monitoring which doesn't routinely take place since the onset of COVID-19 whereby patients on parenteral have been converted to oral treatment with no increased initial monitoring. There is no account of whether there may be any outcome differences or the direct impact on patients i.e., side effects/acceptability.

(c) 2006 UK pounds. Cost components incorporated: Medication cost, laboratory cost, GP/nursing time, conversion costs from i.m. to oral (assuming three additional physician visits and additional blood testing), syringe and needle (for i.m.)

(d) The UK tariff was not used for EQ-5D; The utility scores were derived using hypothetical state scenarios which may not be comparable to one obtained by using patient data. Study is Australia based.

(e) This study focuses on diagnosis and intervention together using serum cobalamin testing with oral and i.m. treatment. Fatigue is only one symptom which may be related to B12 deficiency, so this study does not capture all potential B12 deficient patients. Only the first consultation was considered; all screening tests that could have been ordered—other than serum cobalamin—were not included in this economic evaluation. The cost of misdiagnosis/referral to specialists was not included which could have a significant impact of the cost-effectiveness. There is uncertainty regarding the baseline prevalence of B12 deficiency. Risk of recurrence of deficiency or symptoms after three months were not explored.

(f) 2013 US dollars converted to UK pounds using purchasing power parities. Cost components incorporated: GP-patient consultation fee, serum cobalamin test, Patient Episode Initiation (specimen) fees, medication costs, service costs for i.m. injections.

(g) Canadian perspective and cost comparison analysis rather than cost-utility analysis. B12 ingredient is not explicitly stated, if the intramuscular version is cyanocobalamin, this is not used in NHS primary care. Limited short term clinical evidence is used to estimate that the interventions are identical in terms of clinical effectiveness.

(h) The price of oral vitamin B12 treatment is much lower than the current NHS drug tariff. For the cost of the oral treatment, this is assumed to be funded 70% by the patient therefore savings. The study incorporates costs of converting therapy which may not be directly applicable for example the increased blood test monitoring which doesn't routinely take place in the NHS. There is no account of whether there may be any outcome differences or the direct impact on patients i.e. side effects/acceptability.

(i) 2012 Canada Canadian Dollars converted to UK pounds[14] Cost components incorporated: Medication cost, dispensing fee of oral, fee for intramuscular administration (in pharmacy and in physician office), blood sampling cost (staff time), cost for laboratory test and laboratory processing cost, physician consultation cos

1.1.9 Unit costs

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

Table 18: Unit costs of B12 treatment

Resource	Unit costs (per tablet/vial)	Source
Oral - cyanocobalamin 50mcg	£0.43	NHS electronic drug tariff[13]
Oral - Orobalin 1mg	£0.33	NHS electronic drug tariff[13]
Parenteral – cyanocobalamin 1mg/ml	£2.90	NHS electronic drug tariff[13]
Parenteral – hydroxocobalamin	£0.89	NHS electronic drug tariff[13]
HCP administration appointment (10 mins) (for parenteral treatment only)	£7.00	Unit costs of health and social care 2021[7]
Injection consumables (2ml syringe, 21g 25mm drawing needle, 25g 35mm needle to inject, 1 litre sharps box) (for parenteral treatment only)	£0.15	NHS electronic drug tariff[13], Committee members' advice

The BNF states "cyanocobalamin injection is less suitable for prescribing". Also, the BNF states that Cytamen (cyanocobalamin) injection cannot be prescribed in NHS primary care. As the unit cost and frequency are higher compared to hydroxocobalamin injection, in addition to the BNF guidance, only hydroxocobalamin injections are considered for the cost analysis below.

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 1mg oral tablet currently and hence this is why this medicine is selected for analysis as other versions of the 1mg tablet would be considered unlicensed.

Table 19 below shows the costs of B12 treatment for people who do not have pernicious anaemia. These treatment doses for parenteral treatment include a loading dose. According to the committee there are usually 6mg (6 injections) given within the first month, but this can vary depending on a person's symptoms. After the loading dose 1mg (one injection) is given every two or three months. Both parenteral treatment schedules are captured in Table 19. For parenteral treatment the administration costs are included which comprise of consumable costs and a 10-minute appointment (see Table 18). The dose for Orobalin is assumed to be 1mg daily.

Table 19: Comparison of treatment costs Orobalin vs Parenteral treatment

Timeline	Orobalin 1mg daily	Parenteral hydroxocobalamin – 6mg in first month then 1mg per two months	Parenteral hydroxocobalamin – 6mg in first month then 1mg per three months
3 months	£30	£56	£48
6 months	£60	£64	£56
1 year	£119	£88	£72
2 years	£233	£134	£103

Table 20 below shows the costs of B12 treatment for people who have pernicious anaemia. The treatment schedule for parenteral treatment is the same for pernicious anaemia and other causes of B12 deficiency. According to the committee there are usually 6mg (6 injections) given within the first month, but this can vary depending on a person's symptoms. After the loading dose 1mg (one injection) is given every two or three months. Both parenteral treatment schedules are captured in Table 19. For parenteral treatment the administration costs are included which comprise consumable costs and a 10-minute appointment (see Table 18). Therefore, it is assumed that the treatment cost for parenteral treatment is the same in pernicious anaemia and other causes of B12 deficiency.

For oral treatment the dose is 4mg a day until remission of symptoms, with the length of time until remission varying depending on the person. It was proposed by the committee that the initial high dose frequency may be needed for a month. After this initial dose then the dose is reduced to 1mg daily.

Table 20: Comparison of treatment costs Orobalin vs Parenteral treatment (dose for pernicious anaemia)

Timeline	Orobalin 4mg daily in first month then 1mg daily	Parenteral hydroxocobalamin – 6mg in first month then 1mg per two months	Parenteral hydroxocobalamin – 6mg in first month then 1mg per three months
3 months	£60	£56	£48
6 months	£90	£64	£56
1 year	£149	£88	£72
2 years	£263	£134	£103

A sensitivity analysis was conducted where 10% of patients (same proportion as the included study by Houle 2014[6]) were administered their intramuscular treatment at home (assumed 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.

1.1.10 Evidence statements

- One cost comparison analysis found that parenteral B12 treatment was less costly than oral B12 treatment for treating B12 deficiency at 2 years. However, from year 2, the annual cost of oral was lower compared to parenteral treatment due to the initial switching costs. This analysis was assessed as directly applicable with potentially serious limitations.
- One cost comparison analysis found that oral B12 treatment was less costly than intramuscular B12 treatment for treating B12 deficiency.
- One cost–utility analysis found that oral B12 treatment was less costly and equally effective (therefore dominant) compared to parenteral B12 treatment for treating B12 deficiency. This analysis was assessed as partially applicable with potentially serious limitations.

All three studies would have found parenteral B12 therapy to be cost saving had they used the current NHS prices of licensed treatments.

1.2 Review question

What is the clinical and cost effectiveness of self-administration compared with healthcare professional administration of parenteral vitamin B12 replacement for vitamin B12 deficiency?

1.2.1 Introduction

Most people receiving parenteral intramuscular injections of vitamin B12 replacement for deficiency are given their treatment in a primary care setting by a healthcare professional. This requires periodic attendance at a primary care location.

Self-administration of vitamin B12 by intramuscular injection is possible and currently undertaken by a minority of patients. However, the relative safety, efficacy, and cost-effectiveness of self- versus healthcare-administration has not been established. It is unclear if self-administration is suitable for all people with vitamin B12 deficiency.

This review seeks to determine whether self-administration of parenteral intramuscular vitamin B12 replacement is a clinically and cost-effective way of treating vitamin B12 deficiency.

1.2.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 21: PICO characteristics of review question

Population	Inclusion: adults with diagnosed vitamin B12 deficiency Exclusion: metabolic disorders Stratify by: • physical/mental barriers to self-administration (people with barriers and people without barriers)
Interventions	• Self-administration (including family/carer administration) of parenteral vitamin B12 replacement ○ Hydroxocobalamin intramuscular injection ○ Hydroxocobalamin subcutaneous injection ○ Cyanocobalamin intramuscular injection ○ Cyanocobalamin subcutaneous injection
Comparisons	• Healthcare professional administration of parenteral vitamin B12 replacement ○ Hydroxocobalamin intramuscular injection ○ Hydroxocobalamin subcutaneous injection ○ Cyanocobalamin intramuscular injection ○ Cyanocobalamin subcutaneous injection
Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • quality of life (such as EQ5D, SF36) • patient-reported outcomes (PROM scores including some/all symptoms): ○ fatigue ○ sleep ○ peripheral neuropathy

	○ cognition ○ psychiatric symptoms ○ pain • haematological values • complications and adverse events ○ mortality ○ bleeds ○ self-harm ○ nerve damage ○ frailty/falls ○ severe cognitive effects ○ postural hypotension • adherence to treatment • education/work absence Time point: short-term (up to 3 months) and long-term (over 3 months)
Study design	• Randomised controlled trials • Systematic reviews of RCTs • Non-randomised comparative studies if no RCTs are identified (priority will be given to inclusion of non-randomised comparative studies that have controlled/adjusted for confounding factors. If insufficient evidence is identified from studies that have controlled/adjusted for confounding factors, non-randomised comparative studies that have not controlled/adjusted for confounding factors will be considered)

1.2.3 Methods and process

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

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

1.2.4 Effectiveness evidence

No relevant clinical studies comparing self-administration with health professional administration of parenteral vitamin B12 replacement were identified.

See also the study selection flow chart in Appendix C.

1.2.5 Summary of studies included in the effectiveness evidence

No studies were included.

1.2.6 Summary of the effectiveness evidence

No evidence was identified.

1.2.7 Economic evidence

1.2.7.1 Included studies

No health economic studies were included.

1.2.7.2 Excluded studies

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

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

1.2.8 Unit costs

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

Table 22: Unit costs for self-administration

Resource	Unit costs (per tablet/vial)	Source
Parenteral – cyanocobalamin 1mg/ml	£2.90	NHS electronic drug tariff[13]
Parenteral – hydroxocobalamin	£0.89	NHS electronic drug tariff[13]
HCP administration appointment (10 mins)	£7.00	Unit costs of health and social care 2021[7]
HCP teaching self-administration appointment (15 mins)	£10.50	Unit costs of health and social care 2021[7]
Injection consumables (2ml syringe, 21g 25mm drawing needle, 25g 35mm needle to inject, 1 litre sharps box)	£0.15 per HCP administration £14.75 for self-administration (one-off cost which will provide consumables for up to 100 injections)	NHS electronic drug tariff[13], Committee members' advice

The BNF states "cyanocobalamin injection is less suitable for prescribing". Also, the BNF states that Cytamen (cyanocobalamin) injection cannot be prescribed in NHS primary care. As the unit cost and frequency are higher compared to hydroxocobalamin injection, in addition to the BNF guidance, only hydroxocobalamin injections are considered for the cost analysis below.

Table 23 below shows the treatment cost differences for people who may be receiving prophylactic treatment. There would be no loading dose required. This would be relevant for consideration if switching people from HCP administered treatment to self-administered treatment.

Table 23: Comparison of treatment/prophylaxis costs self-administration vs HCP administration treatment (no loading doses)

Timeline	Frequency 1mg injection every 2 months		Frequency 1mg injection every 3 months	
	Self-administration	HCP	Self-administration	HCP
3 months	£27	£16	£26	£8

Timeline	Frequency 1mg injection every 2 months		Frequency 1mg injection every 3 months	
6 months	£28	£24	£27	£16
1 year	£31	£48	£29	£32
2 years	£36	£93	£32	£62

Table 24 below shows the treatment cost differences for people who may be receiving prophylactic treatment. There would be a loading dose required and this would be relevant for anyone that needs a treatment dose whether the cause is pernicious anaemia or another cause of B12 deficiency.

Table 24: Comparison of treatment costs self-administration vs HCP administration treatment (loading doses for pernicious anaemia)

Timeline	Frequency 6mg in first month then 1mg per two months		Frequency 6mg in first month then 1mg per three months	
	Self-administration	HCP	Self-administration	HCP
1 month	£31	£48	£31	£48
3 months	£31	£56	£31	£48
6 months	£32	£64	£31	£56
1 year	£35	£88	£33	£72
2 years	£40	£134	£37	£103

1.2.9 Evidence statements

No relevant economic evaluations were identified that compared self-administration with HCP administration for people requiring parenteral B12 treatment.

1.3 The committee's discussion and interpretation of the evidence

The committee discussion of the review of self-administration of parenteral vitamin B12 replacement is included in the discussion of vitamin B12 replacement.

1.3.1. The outcomes that matter most

The committee considered quality of life, patient reported outcomes including symptom scores, haematological values, complications and adverse events, adherence to treatment and education/work absence to be the most important outcomes of vitamin B12 replacement. The possible complications and adverse events listed by the committee were mainly those related to the possible complications and adverse events if a deficiency is insufficiently treated, as there are few complications and adverse events associated with vitamin B12 treatment itself. All outcomes were considered equally important for decision making and were rated as critical.

The majority of the evidence for vitamin B12 replacement identified from randomised controlled trials was for haematological values, with very little evidence identified for patient reported outcomes. No evidence was identified for quality of life, adherence to treatment, or education/work absence. The committee considered that although haematological values

provide useful objective biomarkers, the end purpose of B12 replacement is to improve the patients' quality of life, so the RCT evidence was not considered sufficient upon which to base recommendations. Therefore, a search for observational evidence was carried out. However, the evidence identified from observational studies was for haematological values only.

No evidence was identified for self-administration of parenteral vitamin B12 compared with healthcare professional administration.

1.3.2 The quality of the evidence

Evidence ranged from moderate to very low-quality, with the majority of evidence being assessed as very low-quality. Indirectness was the main reason for downgrading, with almost all evidence being downgraded by one increment due to the inclusion of populations with mixed causes of vitamin B12 deficiency. The most common concern for risk of bias was due to the randomisation process used and deviations from the intended interventions, although concerns arose for multiple domains in most cases. Partly due to the small sample sizes recruited in the identified evidence, a large proportion of the evidence was also downgraded for imprecision.

The committee considered the follow up periods reported in most of the studies to be sufficient. However, they noted that improvements in outcomes may not be clinically important until a person has received three months of replacement, particularly for oral replacement. Therefore, confidence in evidence for the outcomes reported before three months was reduced, especially for the comparison of oral cyanocobalamin versus hydroxocobalamin, where outcomes were reported at one month.

No evidence was identified comparing subcutaneous administration of cyanocobalamin or hydroxocobalamin, or a combination of treatment modalities with any protocol comparators. Additionally, no evidence was identified for any comparison at any time point for quality of life, most of the patient reported outcome measures (fatigue, sleep, peripheral neuropathy, psychiatric symptoms, pain), specific complications and adverse events (mortality, bleeds, self-harm, nerve damage, frailty/falls, severe cognitive effects, postural hypotension), adherence to treatment or education/work absence.

Overall, the committee felt that the evidence identified was of limited use in the decision-making process. The small number of studies identified for each comparator was a particularly limiting factor, with no meta-analyses possible across the review. Compounding the difficulty in interpreting the results was the significant differences in populations and interventions used in the identified studies. Only one study included participants with a single cause of vitamin B12 deficiency, with all others including people with a number of different causes. Furthermore, studies utilised a number of different definitions of deficiency and doses, frequencies and durations of treatment. These factors made it difficult to compare across studies and to draw conclusions from the evidence as a whole.

1.3.3 Benefits and harms

<u>Oral cyanocobalamin vs intramuscular cyanocobalamin</u>

For the comparison between oral and intramuscular cyanocobalamin, low to very low quality RCT evidence showed a benefit of intramuscular cyanocobalamin for total B12 at both ≤3 months and >3 months, and holotranscobalamin at ≤3 months. This finding was supported by the observational evidence, where very low-quality evidence showed a benefit of intramuscular cyanocobalamin for total B12 at >3 months. Moderate to very low-quality

evidence showed no clinically important difference for methylmalonic acid and homocysteine at both ≤3 months and >3 months, patient reported outcome measures (general health) and mean corpuscular volume at >3 months, and adverse events at ≤3 months.

Oral cyanocobalamin vs placebo

For the comparison between oral cyanocobalamin and placebo, very low-quality evidence showed a benefit of oral cyanocobalamin for total B12 at ≤3 months, with both 0.4 and 1 mg doses, total B12, holotranscobalamin and homocysteine at >3 months, methylmalonic acid at ≤3 months and homocysteine at ≤3 months with a 0.4 mg dose only. In contrast, very low quality showed a harm of oral cyanocobalamin for folate at >3 months. Moderate to very low-quality evidence showed no clinically important difference for patient reported outcomes (general health and cognition) at >3 months, homocysteine at ≤3 months with a 0.4 mg dose, haemoglobin and folate at >3 months.

Oral cyanocobalamin vs intramuscular hydroxocobalamin

For the comparison between oral cyanocobalamin and intramuscular hydroxocobalamin, moderate to low-quality evidence showed a benefit of intramuscular hydroxocobalamin for total B12, holotranscobalamin and homocysteine at ≤3 months. Moderate to very low-quality evidence showed no clinically important difference for methylmalonic acid and adverse events at one month. A large effect in favour of intramuscular hydroxocobalamin was seen for this comparison. This was noted by the committee and the results were interpreted with caution given the limitations of the evidence, including the relatively short follow up period.

Oral cyanocobalamin dose comparison

For the comparison between treatment with 100 mcg and 250 mcg of oral cyanocobalamin, very low-quality evidence showed a benefit of 250 mcg for holotranscobalamin at both ≤3 months and >3 months. Very low-quality evidence showed no clinically important difference between doses for total B12, homocysteine or methylmalonic acid at either ≤3 months or >3 months.

For the comparison between treatment with 100 mcg and 500 mcg of oral cyanocobalamin, low to very low-quality evidence showed a benefit of 500 mcg for total B12, holotranscobalamin, homocysteine and methylmalonic at both ≤3 months and >3 months.

For the comparison between treatment with 100 mcg and 1000 mcg of oral cyanocobalamin, low-quality evidence showed a benefit of 1000 mcg for total B12, holotranscobalamin and homocysteine at ≤3 months, and holotranscobalamin at >3 months. Very low-quality evidence showed no clinically important difference between interventions for homocysteine or methylmalonic acid at >3 months, and for methylmalonic acid at ≤3 months.

For the comparison between treatment with 250 mcg and 500 mcg of oral cyanocobalamin, very low-quality evidence showed a benefit of 500 mcg for total B12 at ≤3 months. Very low-quality evidence showed no clinically important difference between treatments for total B12 at ≤3 months, or for holotranscobalamin, homocysteine or methylmalonic acid at both ≤3 months and >3 months.

For the comparison between treatment with 250 mcg and 1000 mcg of oral cyanocobalamin, very low-quality evidence showed a benefit of 1000 mcg for total B12 at ≤3 months, and for holotranscobalamin at both ≤3 months and >3 months. Very low-quality evidence showed no clinically important difference between treatments for homocysteine or methylmalonic acid at both ≤3 months and >3 months.

For the comparison between treatment with 500 mcg and 1000 mcg of oral cyanocobalamin, very low-quality evidence showed a benefit of 1000 mcg for total B12 and holotranscobalamin at ≤3 months. Very low-quality evidence showed no clinically important difference between treatments for holotranscobalamin at >3 months, and homocysteine and methylmalonic acid at both ≤3 months and >3 months.

Intramuscular hydroxocobalamin with loading dose vs intramuscular hydroxocobalamin with no loading dose

For the comparison between IM hydroxocobalamin treatment regimes, very low-quality evidence showed a benefit of IM treatment with a loading dose for total B12 at ≤3 months. Very low-quality evidence showed no clinically important difference between treatments for methylmalonic acid at ≤3 months.

Intramuscular hydroxocobalamin vs no treatment

For the comparisons between IM hydroxocobalamin regimens and no treatment, low-quality evidence showed a benefit of IM hydroxocobalamin with a loading dose for total B12 and methylmalonic acid at ≤3 months. Low to very low-quality evidence showed a benefit of IM hydroxocobalamin with no loading dose compared to no treatment for total B12 and methylmalonic acid at ≤3 months.

Conclusions and committee experiences

It was the experience of the committee that improvements in haematological values do not necessarily translate to improved quality of life for patients. Given the limited evidence identified for outcomes other than haematological values, the committee felt it was difficult to draw conclusions on the preferable treatment option using the clinical evidence alone.

The main comparison of interest for the committee was that made between oral and intramuscular treatments. There was a preference towards intramuscular treatment from the lay members of the committee, due to their own experiences of intramuscular treatment being more effective in managing their conditions. Clinicians on the committee had no strong preference based on their experience and expertise but considered that people may prefer to receive oral treatment where there is a choice due to the discomfort and inconvenience of receiving intramuscular injections.

However, the committee considered circumstances where intramuscular vitamin B12 replacement may be preferable to oral replacement to ensure that the treatment works quickly and prevent the long-term symptoms and complications. Examples of these circumstances include: if there are concerns about adherence to oral treatment, such as those with delirium or a health inequality that affects access to care such as homelessness. 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. To reduce the risk of diversion parenteral treatment may be the preferred route of treatment. Intramuscular injections may also be more appropriate in hospitalised older people with complex co-morbidity requiring multidisciplinary management including interacting polypharmacy. For example, undernutrition, disease associated anorexia, dementia, decompensated frailty, where long-term adherence with oral replacement is deemed to be compromised, and those at risk of rapid deterioration which could have a major effect on quality of life, such as those with neurological or haematological conditions. The committee agreed that in these circumstances, intramuscular replacement

should be considered over oral replacement, regardless of the cause of vitamin B12 deficiency.

The committee noted that giving people an estimated timeframe for when they can expect to see an improvement in their symptoms will empower them to return to their healthcare professional sooner if symptoms are not improving as expected. Therefore, the committee made a recommendation to give people information about how long it takes for treatment to take effect and when they are likely to see an improvement in their symptoms.

The committee agreed there was no reason why treatment should be stopped during pregnancy or breastfeeding if the person is already receiving vitamin B12 replacement. To stop treatment may lead to a return or increase in symptoms and put the person and their baby at risk. Therefore, the committee made a recommendation to continue treatment in this group.

Deficiency caused by malabsorption

In people with vitamin B12 deficiency due to autoimmune gastritis, the committee agreed that intramuscular vitamin B12 replacement is the appropriate treatment. This is because this group are unable to absorb adequate vitamin B12 from oral replacement or their diet, meaning intramuscular treatment is the only option and should be given as a life-long treatment. In most cases, replacement should be given with an initial loading dose to rapidly increase vitamin B12 levels and stop the progression of neurological damage. This is current practice and should remain this way. The committee noted the difficulties in diagnosing this condition and agreed that those who are strongly suspected of having autoimmune gastritis should be offered the same treatment as if they had a confirmed diagnosis. The committee agreed that this treatment should not be discontinued unless another reversible cause of vitamin B12 deficiency is identified, at which point treatment should be reviewed to see if intramuscular treatment is still the best option or whether they will need long-term treatment.

In people with vitamin B12 deficiency due to surgery such as major gastric resection, bypass (including bariatric procedures) or terminal ileal resection, the committee agreed that lifelong vitamin B12 replacement is usually required to prevent deficiency. This is because in all cases, ability to absorb enough vitamin B12 from the diet is irreversibly impaired. In the absence of any evidence that either treatment route is more effective than another in this population, the committee debated whether oral or intramuscular vitamin B12 replacement would be preferable. The committee considered that current practice in the UK is most commonly to offer intramuscular replacement, although experience in other countries suggests that oral 1000 mcg cyanocobalamin is at least as effective for some forms of surgery. Therefore, the committee decided to split recommendations in two. People who have had a total gastrectomy, or a complete terminal ileal resection need lifelong intramuscular injections because these types of surgery cause permanent malabsorption. People who have had a partial gastrectomy, partial terminal ileal resection or some forms of bariatric surgery may be able to absorb vitamin B12. In these cases the committee agreed that the preference would be for intramuscular replacement, as it is often difficult to know how much of an oral dose will be absorbed and by giving it intramuscularly, there is more certainty that the person has received enough of the vitamin. Therefore, they recommended intramuscular injections over oral vitamin B12 replacement.

In people with vitamin B12 deficiency due to malabsorption that is not caused by autoimmune gastritis, gastric or bariatric surgery, such as those with coeliac disease, no evidence was identified on the most effective route of administration. Intramuscular treatment was found to be more cost effective than oral replacement when used for 6 months or more. In the committee's experience, injections could be the better option for these groups of

people because it can be difficult to judge how much of an oral dose will be absorbed by the body, so injections will help ensure they are getting enough of the vitamin. However, the committee did not rule out the use of oral vitamin B12 replacement, because there was no evidence on its use in these groups of people and therefore there was nothing to suggest it would be ineffective. Therefore, the committee recommended that intramuscular is considered instead of oral vitamin B12 replacement. The treatment may be lifelong, or for as long as is necessary, depending on the cause. For example, people with coeliac disease may be able to manage their deficiency effectively through a gluten free diet. In these people, symptoms and medicines should be regularly reviewed and discontinuation of replacement considered if the cause is successfully reversed.

In all cases the committee noted that intramuscular injections are also cheaper when vitamin B12 replacement is needed for more than six months. The committee agreed that for all malabsorption conditions where oral replacement has been recommended, a dose of 1 mg per day should be prescribed as a minimum.

Medicine induced deficiency

The committee agreed that in people who have vitamin B12 deficiency caused by a medicine such as metformin, a H2 receptor antagonist, a proton pump inhibitor, or an antiseizure medicine, they should remain on vitamin B12 replacement as long as they are receiving the causative medicine. No evidence was identified on the most effective route of administration in people with medicine induced deficiency, therefore the committee recommended that either intramuscular or oral replacement should be offered, based on clinical judgement and patient preference. If possible, medicine that can cause vitamin B12 deficiency should be stopped or changed to an alternative medicine, although the committee noted that there are many cases where this would not be possible or preferable. The committee agreed that if the medicine is stopped and the person no longer has symptoms of vitamin B12 deficiency, the need for vitamin B12 replacement should be reviewed.

Recreational nitrous oxide induced deficiency

No evidence was identified on the most effective route of administration in people with nitrous oxide induced deficiency, therefore the committee recommended that either intramuscular or oral replacement should be offered, and this should depend on patient preference. Nitrous oxide affects B12 concentrations by inactivating either the vitamin B12 molecule or the enzyme methionine synthase and therefore can cause vitamin B12 deficiency. Its longer-term effects on the body are unknown. Where nitrous oxide is being used recreationally, the committee agreed that there is probably a lack of awareness of the possible adverse effects by people using it. Therefore, the committee agreed that advising the person to stop using the drug, and the reasons why, is important and made a recommendation to reflect this. The committee agreed that if the person stops using nitrous oxide recreationally and they no longer have symptoms of vitamin B12 deficiency, the need for vitamin B12 replacement should be reviewed.

Dietary vitamin B12 deficiency

The committee agreed that anybody with a suspected or confirmed vitamin B12 deficiency due to a lack of the vitamin in their diet should be given information on how to improve their intake of vitamin B12, regardless of any other replacement that may be offered in addition. As low dietary intake is a potentially reversible cause of deficiency, the committee considered that people should be given the opportunity to manage their deficiency though changes to their diet.

However, the healthcare professional may recommend that the person receives B12 replacement, depending on the clinical presentation and individual circumstances. The committee recommended that for those with confirmed deficiency, oral replacement should be considered. This is the licensed treatment for vitamin B12 deficiency.

The committee considered making recommendations regarding dose for oral vitamin B12 replacement. Licensed doses of cyanocobalamin vary from 50 mcg to 1000 mcg. The committee noted that most of the studies included in the evidence review used 1000 mcg, however there was no strong evidence comparing different doses. The committee noted that dose may depend on the cause of the deficiency and the clinical presentation. For example, 1000 mcg may be considered a more appropriate dose for a person with malabsorption that is not caused by autoimmune gastritis or surgery, to ensure that enough of the vitamin is absorbed. For a person with a dietary deficiency, 50-150 mcg may be suitable. The committee considered that there would be the opportunity to increase the dose to at least 1000 mcg during follow up appointments if a lower dose did not adequately improve symptoms and vitamin B12 concentrations. However, in the absence of evidence, the committee agreed that dose should be a clinical decision.

The committee also agreed that during pregnancy or breastfeeding, oral replacement at a dose of at least 1000 mcg should be considered. This was because the demand for vitamin B12 increases during pregnancy, so setting a minimum dose of 1000 mcg per day would ensure that enough vitamin B12 is absorbed to meet this demand.

The committee agreed that people who follow restrictive diets should not be assumed to be deficient as a result of their diet. Due to the difficulty in identifying cause, other causes should be considered throughout the treatment pathway. The committee agreed that whilst restrictive diets can cause vitamin B12 deficiency, people who follow them may be aware of this and ensure they consume adequate vitamin B12. Assuming the diet is the cause of the deficiency can lead to under-investigation of other potential causes, for example autoimmune gastritis, which can have serious long-term implications if left undiagnosed. Therefore, the committee made recommendations to raise awareness that diet may not be the cause or the only cause of deficiency and to have a full discussion with the person suspected of having a dietary deficiency regarding sources of vitamin B12 in their diet, use of supplements, and signs, symptoms or risk factors that could suggest another reason for the deficiency. If the discussion suggests that diet may not be linked to the deficiency, the committee agreed that this would raise suspicion of other possible causes such as autoimmune gastritis and further investigations should be considered. See the recommendations on identifying the cause of vitamin B12 deficiency.

The committee noted that some people purchase over-the-counter supplements online, from pharmacies or health food shops. Vitamin B12 injections are also available from some beauty clinics and over the counter in other countries and some people import these products for personal use. The committee considered that there is wide variation in the forms and doses of vitamin B12 used in purchasable oral vitamin B12 containing products and while some can effectively treat deficiency, others do not contain enough of the vitamin. Some products contain B12 analogues, which are not used by the body in the same way as the cyanocobalamin, methylcobalamin and adenosylcobalamin forms of vitamin B12. The committee agreed that this should be explained to the person to give them the best chance of selecting an effective supplement if that is what they choose to do.

The committee also agreed that intramuscular vitamin B12 replacement could be the best option for some people with confirmed deficiency if there are concerns about adherence to oral treatment. This would include hospitalised older adults with multimorbidity; those with delirium or cognitive impairment; or those who have difficulties accessing care due to health

inequalities, such as homelessness. This would ensure they get the treatment they need, prevent the long-term symptoms and complications caused by deficiency, resulting in fewer hospitalisations in the future. 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 intramuscular injections 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. Intramuscular replacement could also be considered for older people in hospital with complex comorbidities, who are often taking multiple medicines and whose care is usually overseen by a multidisciplinary team. This is because there may be issues with long-term adherence to oral replacement in this group of people, which can include those with undernutrition, dementia or decompensation linked to frailty. The committee also agreed intramuscular replacement may be preferable when a person is at risk of rapid deterioration that could have a major effect on their quality of life, because the treatment works quickly. This includes people with neurological or haematological conditions.

Unknown causes of vitamin B12 deficiency

The committee agreed that people presenting with vitamin B12 deficiency where the cause is unknown should be treated with oral replacement initially. The committee made this recommendation on the basis that if malabsorption conditions are not suspected, then oral vitamin B12 replacement should be suitable for correcting the deficiency. If symptoms do not improve, or worsen, then the treatment can be changed to intramuscular (see ongoing care and follow up recommendations) and further investigations can be made into the presence of autoimmune gastritis or other malabsorption issues as the possible cause of vitamin B12 deficiency (see identifying the cause recommendations). The committee agreed that this was a suitable approach as the inefficacy of oral vitamin B12 replacement is indicative that an underlying malabsorption condition may be present and further investigations into the underlying cause are more difficult after intramuscular injections have been received.

Self-administration of parenteral vitamin B12 replacement

The committee considered that during the COVID-19 pandemic, many people self-administered their vitamin B12 replacement due to the inability to receive their injections from clinicians as usual. The committee were also aware of patient surveys indicating a preference for the option to self-administer vitamin B12 injections, which the lay members on the committee agreed with. The committee discussed the potential benefits of self-administration for people with vitamin B12 deficiency. These included being able to receive their injections at times convenient for them, in environments where they feel comfortable, not having to rely on the availability of GP appointments to receive their treatment when it is due and saving time and costs to attend GP appointments. The committee also noted other health conditions for which self-administration of injectable treatments were common practice, including rheumatoid arthritis, fertility issues, rhesus disease and anaphylaxis.

The committee considered the possible safety issues associated with injections, such as anaphylaxis and bleeds. The committee also considered groups of people in whom self-administration may not be suitable due to reduced physical or mental capacity. The committee concluded that without data on the effectiveness or safety of self-administration, a recommendation for further research was the most appropriate action.

1.3.4 Cost effectiveness and resource use

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 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. Evidence was not available to suggest everyone with a suspected or confirmed dietary vitamin B12 deficiency should be offered oral vitamin B12 replacement and the committee agreed for a lot of people dietary advice alone may be enough to correct the deficiency. However recognised that some people would need additional treatment and recommended that oral vitamin B12 replacement should be considered for people who have a suspected or confirmed dietary deficiency. The committee agreed that 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.

Oral cyanocobalamin vs intramuscular hydroxocobalamin

Published cost effectiveness evidence

Three economic evaluations were identified for this review comparing oral and parenteral vitamin B12 treatment. The three published economic evaluations had conflicting results. All three studies deemed both treatments as equally effective. In two papers the oral treatment was a lower cost strategy, however in the other economic evaluation parenteral treatment was the lower cost.

In the economic evaluation that deemed parenteral treatment as the lower cost strategy, the study found that from year two of treatment oral cost would always be lower than parenteral treatment cost. This was due to the high costs of switching people from parenteral treatment to oral treatment in year one, which would not be relevant if people were started on oral treatment rather than parenteral treatment. If the study time horizon had been longer than two years or if the additional monitoring costs were not required, then oral treatment would

have been the lower cost strategy compared to parenteral treatment. However, imporantly, none of the studies used current NHS prices.

Consideration of cost effectiveness

A simple cost comparison was presented to aid the committee with the consideration of cost effectiveness.

For people who are newly diagnosed with B12 deficiency, oral treatment with Orobalin 1000mcg daily dose is lower cost than parenteral treatment over short time horizons due to the initial loading dosing with parenteral treatment. After the initial loading dose, if the parenteral maintenance dose is hydroxocobalamin 1000mcg every three months, then parenteral treatment will be the lower cost by six months. If the maintenance parenteral dose is hydroxocobalamin 1000mcg every two months, then parenteral treatment will be the lower cost strategy within eight months. For people who are newly diagnosed with autoimmune gastritis (also known as pernicious anaemia), or any other B12 deficiency that requires long-term treatment, parenteral treatment is the lower cost strategy. The cost of parenteral treatment is considerably more expensive for people who cannot travel to their general practice. When home visits for 10% of patients were accounted for, it took up to one year for parenteral treatment to be cost saving.

Despite the lack of evidence identified relating to quality of life, the committee expressed the view that quality of life will be improved more quickly with parenteral treatment for people with symptomatic B12 deficiency. Timely parenteral treatment can also reduce hospitalisations due to the complications of B12 deficiency, which is expected to improve patient outcomes and QALY gains, and this, in turn, is likely to improve the cost effectiveness of parenteral treatment compared to oral treatment. However, the committee noted that some people may prefer oral administration for ease of treatment rather than booking an appointment for parenteral administration. This may contribute to treatment adherence and improve patient outcomes for oral administration of B12. Furthermore, in some places, shortages of practice nursing staff might make the use of oral treatment more practical even if it is more costly.

The committee agreed that for people with malabsorption or autoimmune gastritis (also known as pernicious anaemia), the parenteral route is preferred over oral. The committee noted that some people may have been switched to oral administration of vitamin B12 during the Covid-19 pandemic and may have not resumed parenteral treatment. Parenteral treatment for autoimmune gastritis would be the preferred cost-effective option over oral treatment.

Self-administration of parenteral treatment vs healthcare professional (HCP) administration

Published cost effectiveness evidence

There was no economic evidence identified for this question.

Consideration of cost effectiveness

A simple cost analysis using unit costs was presented to aid the committee with the consideration of cost effectiveness.

From these calculations, if a person needed three or more injections, then treatment via self-administration would be cost saving. This is due to the initial one-off cost of the consumables that would be required to be prescribed to enable self-administration.

The most significant cost for HCP administration is the cost of the healthcare professional's time; the cost of consumables and the cost of the medicine is low in comparison. For newly diagnosed autoimmune gastritis patients or people that required a loading dose, the total costs of the consumables required for self-administration would be offset within the first month, making self-administration the least costly option.

For people that are already receiving parenteral treatment who are switched to self-administration, it would take six months for self-administration to be cheaper than healthcare professional administration if dose frequency is two months, whilst it would take one year for self-administration to be cheaper if the dose frequency was every three months. This would be under the assumption that no loading dose would be required.

There is uncertainty whether self-administration will be as equally effective as healthcare professional administered treatment due to the possible risk of injuries with self-administration which would also incur treatment costs. There is also concern that people starting parenteral treatment may be at risk of anaphylaxis and, if not undertaken under healthcare professional supervision, this may delay management and affect outcomes.

Recommendation

Self-administration of parenteral B12 treatment was not recommended due to a lack of clinical evidence and concerns regarding the safety of recommending self-administration.

Hydroxocobalamin is not licensed for subcutaneous administration, but it is for intramuscular. For self-administration, the subcutaneous route is considered easier compared to intramuscular, however this would be considered off-label.

Despite self-administration being likely to be cost saving versus healthcare professional administration there was a concern regarding the risk of injuries with intramuscular administration as well as the risk of anaphylaxis. The committee discussed offsetting the risk of anaphylaxis by having the first injection with a healthcare professional and the following could be self-administered. However, there would still be risks of injury. With this uncertainty the committee thought it would be prudent to continue usual practice and to investigate self-administration as a research recommendation.

1.3.5 Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.1 to 1.5.17 and the research recommendations on what is the clinical and cost effectiveness of vitamin B12 replacement for vitamin B12 deficiency, including the dose, frequency and route of administration; and what is the clinical and cost effectiveness of self-administration of parenteral vitamin B12 replacement for deficiency compared with administration by a healthcare professional.

1.4 References

1. Castelli MC, Friedman K, Sherry J, Brazzillo K, Genoble L, Bhargava P et al. Comparing the efficacy and tolerability of a new daily oral vitamin B12 formulation and intermittent intramuscular vitamin B12 in normalizing low cobalamin levels: a randomized, open-label, parallel-group study. Clinical Therapeutics. 2011; 33(3):358-371.e352

2. Couderc AL, Camalet J, Schneider S, Turpin JM, Bereder I, Boulahssass R et al. Cobalamin deficiency in the elderly: aetiology and management: a study of 125 patients in a geriatric hospital. Journal of nutrition, health & aging. 2015; 19(2):234-239

3. Dangour AD, Allen E, Clarke R, Elbourne D, Fletcher AE, Letley L et al. Effects of vitamin B-12 supplementation on neurologic and cognitive function in older people: a randomized controlled trial. American Journal of Clinical Nutrition. 2015; 102(3):639-647

4. Dhonukshe-Rutten RA, van Zutphen M, de Groot LC, Eussen SJ, Blom HJ, van Staveren WA. Effect of supplementation with cobalamin carried either by a milk product or a capsule in mildly cobalamin-deficient elderly Dutch persons. American Journal of Clinical Nutrition. 2005; 82(3):568-574

5. Eussen SJ, de Groot LC, Clarke R, Schneede J, Ueland PM, Hoefnagels WH et al. Oral cyanocobalamin supplementation in older people with vitamin B12 deficiency: a dose-finding trial. Archives of Internal Medicine. 2005; 165(10):1167-1172

6. Houle SK, Kolber MR, Chuck AW. Should vitamin B12 tablets be included in more Canadian drug formularies? An economic model of the cost-saving potential from increased utilisation of oral versus intramuscular vitamin B12 maintenance therapy for Alberta seniors. BMJ Open. 2014; 4(5):e004501

7. Jones K, Burns A. Unit costs of health and social care 2021. Canterbury. Personal Social Services Research Unit University of Kent, 2021. Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-of-health-and-social-care-2021/

8. Kuzminski AM, Del Giacco EJ, Allen RH, Stabler SP, Lindenbaum J. Effective treatment of cobalamin deficiency with oral cobalamin. Blood. 1998; 92(4):1191-1198

9. Malouf R, Areosa SA. Vitamin B12 for cognition. Cochrane Database of Systematic Reviews 2003, Issue 3. Art. No.: CD004394. DOI: 10.1002/14651858.cd004394.

10. Metaxas C, Mathis D, Jeger C, Hersberger KE, Arnet I, Walter P. Early biomarker response and patient preferences to oral and intramuscular vitamin B12 substitution in primary care: a randomised parallel-group trial. Swiss Medical Weekly. 2017; 147:w14421

11. Mnatzaganian G, Karnon J, Moss JR, Elshaug AG, Metz M, Frank OR et al. Informing disinvestment with limited evidence: cobalamin deficiency in the fatigued. International Journal of Technology Assessment in Health Care. 2015; 31(3):188-196

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

13. NHS Business Services Authority. NHS electronic drug tariff December 2022. 2022. Available from: https://www.nhsbsa.nhs.uk/pharmacies-gp-practices-and-appliance-contractors/drug-tariff Last accessed: 09/12/2022.

14. Organisation for Economic Co-operation and Development (OECD). Purchasing power parities (PPP). 2021. Available from: https://data.oecd.org/conversion/purchasing-power-parities-ppp.htm Last accessed: 01/06/2022.

15. Smelt HJ, Pouwels S, Said M, Berghuis KA, Boer AK, Smulders JF. Comparison between different intramuscular vitamin B12 supplementation regimes: a retrospective matched cohort study. Obesity Surgery. 2016; 26(12):2873-2879

16. Ubbink JB, Vermaak WJ, van der Merwe A, Becker PJ, Delport R, Potgieter HC. Vitamin requirements for the treatment of hyperhomocysteinemia in humans. Journal of Nutrition. 1994; 124(10):1927-1933

17. Vidal-Alaball J, Butler CC, Cannings-John R, Goringe A, Hood K, McCaddon A et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. Cochrane Database of Systematic Reviews 2005, Issue 3. Art. No.: CD004655. DOI: doi: 10.1002/14651858.CD004655.pub2.

18. Vidal-Alaball J, Butler CC, Potter CC. Comparing costs of intramuscular and oral vitamin B12 administration in primary care: a cost-minimization analysis. The European journal of general practice. 2006; 12(4):169-173

19. Wang H, Li L, Qin L, Song Y, Vidal?Alaball J, Liu T. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. Cochrane Database of Systematic Reviews 2018, Issue 3. Art. No.: CD004655. DOI: 10.1002/14651858.cd004655.pub3.

Appendices

Appendix A – Review protocols

A.1 Vitamin B12 replacement

Review protocol for vitamin B12 replacement

ID	Field	Content
0.	PROSPERO registration number	Not registered
1.	Review title	What is the clinical and cost effectiveness of vitamin B12 replacement for vitamin B12 deficiency, including the dose, frequency and route of administration?
2.	Review question	What is the clinical and cost effectiveness of vitamin B12 replacement for vitamin B12 deficiency, including the dose, frequency and route of administration?
3.	Objective	To evaluate the most clinically and cost-effective strategy for vitamin B12 replacement in vitamin B12 deficiency.
4.	Searches	List key papers if known. The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by:

		• English language studies • Human studies The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Vitamin B12 deficiency
6.	Population	Inclusion: adults with diagnosed vitamin B12 deficiency Exclusion: metabolic disorders Stratify by: • Cause (dietary/non-dietary/drug-induced)

7.	Intervention	• Hydroxocobalamin
		  ○ Intramuscular injection
		  ○ Subcutaneous injection
		• Cyanocobalamin
		  ○ Oral tablets
		  ○ Intramuscular injection
		  ○ Subcutaneous injection
		• Combinations and sequences of the interventions above
		Stratify by:
		• Dosage (all licenced)

		• Frequency • Duration
8.	Comparator	• Each other (any differences in drug, route of administration, dosage, frequency, or duration) • Dietary advice (dietary cause) • Placebo • No treatment • Changing drug treatment (drug-induced)
9.	Types of study to be included	• Randomised controlled trials • Systematic reviews of RCTs • Non-randomised studies if insufficient RCT evidence is identified (priority will be given to inclusion of non-randomised comparative studies that have controlled/adjusted for confounding factors. If insufficient evidence is identified from studies that have controlled/adjusted for confounding factors, non-randomised comparative studies that have not controlled/adjusted for confounding factors will be considered) Key confounders (most important/highest priority): • Cause (PA/not/diet/surgical) • Severity of deficiency • Severity of symptoms at baseline Key confounders (lower importance/priority): • Age/Comorbidity/Polypharmacy • Renal function • Ethnicity
10.	Other exclusion criteria	• Non-comparative studies • Before and after studies

		• Non-English language studies • Conference abstracts
11.	Context	NA

12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical:
		• quality of life (such as EQ5D, SF36)
		• patient-reported outcomes (PROM scores including some/all symptoms):
		  ○ fatigue
		  ○ sleep
		  ○ peripheral neuropathy
		  ○ cognition
		  ○ psychiatric symptoms
		  ○ pain
		• haematological values
		• complications and adverse events
		  ○ mortality
		  ○ bleeds
		  ○ self-harm
		  ○ nerve damage
		  ○ frailty/falls
		  ○ severe cognitive effects
		  ○ postural hypotension
		• adherence to treatment
		• education/work absence
		Time point: short term (up to 3 months), long term (over 3 months)

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

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

		explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.	
16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • age (older adults >65 years vs. younger adults) • pregnancy/breastfeeding (pregnant/breastfeeding vs. not pregnant/breastfeeding) • religion/belief (e.g., religious fasting vs. no religious fasting) • veganism (vegan vs. not vegan)	
17.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)

18.	Language	English		
19.	Country	England		
20.	Anticipated or actual start date	13/06/2022		
21.	Anticipated completion date	01/11/2023		
22.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
23.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail PerniciousAnaemia@nice.nhs.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre		

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

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

A.2 Self-administration

Review protocol for self-administration versus healthcare professional administration

ID	Field	Content
0.	PROSPERO registration number	Not registered
1.	Review title	What is the clinical and cost effectiveness of self-administration compared with healthcare professional administration of parenteral vitamin B12 replacement for vitamin B12 deficiency?

2.	Review question	What is the clinical and cost effectiveness of self-administration compared with healthcare professional administration of parenteral vitamin B12 replacement for vitamin B12 deficiency?
3.	Objective	To evaluate the clinical and cost-effectiveness of self-administration of vitamin B12 replacement for vitamin B12 deficiency.
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos • CINAHL Searches will be restricted by: • English language studies • Human studies The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Vitamin B12 deficiency
6.	Population	Inclusion: adults with diagnosed vitamin B12 deficiency Exclusion: metabolic disorders

		Stratify by: • physical/mental barriers to self-administration (people with barriers and people without barriers)
7.	Intervention	• Self-administration (including family/carer administration) of parenteral vitamin B12 replacement ○ Hydroxocobalamin intramuscular injection ○ Hydroxocobalamin subcutaneous injection ○ Cyanocobalamin intramuscular injection ○ Cyanocobalamin subcutaneous injection
8.	Comparator	• Healthcare professional administration of parenteral vitamin B12 replacement ○ Hydroxocobalamin intramuscular injection ○ Hydroxocobalamin subcutaneous injection ○ Cyanocobalamin intramuscular injection ○ Cyanocobalamin subcutaneous injection
9.	Types of study to be included	• Randomised controlled trials • Systematic reviews of RCTs • Non-randomised comparative studies if no RCTs are identified (priority will be given to inclusion of non-randomised comparative studies that have controlled/adjusted for confounding factors. If insufficient evidence is identified from studies that have controlled/adjusted for confounding factors, non-randomised comparative studies that have not controlled/adjusted for confounding factors will be considered)
10.	Other exclusion criteria	• Non-comparative studies • Non-English language studies • Conference abstracts
11.	Context	NA
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical:

		• quality of life (such as EQ5D, SF36)
		• patient-reported outcomes (PROM scores including some/all symptoms):
		  ○ fatigue
		  ○ sleep
		  ○ peripheral neuropathy
		  ○ cognition
		  ○ psychiatric symptoms
		  ○ pain
		• haematological values
		• complications and adverse events
		  ○ mortality
		  ○ bleeds
		  ○ self-harm
		  ○ nerve damage
		  ○ frailty/falls
		  ○ severe cognitive effects
		  ○ postural hypotension
		• adherence to treatment
		• education/work absence
		
		Time point: short-term (up to 3 months) and long-term (over 3 months)

13.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4).

		10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
14.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: Randomised Controlled Trial: Cochrane RoB (2.0) Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS)
15.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome.

		The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.	
16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • bleeding disorders (people with bleeding disorders vs. those without bleeding disorders) • age (older adults >65 years vs. younger adults) • pregnancy/breastfeeding (pregnant/breastfeeding vs. not pregnant/breastfeeding) • religion/belief (e.g., religious fasting vs. no religious fasting)	
17.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
18.	Language	English	
19.	Country	England	
20.	Anticipated or actual start date	06/05/2022	
21.	Anticipated completion date	01/11/2023	

22.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
23.	Named contact	5a. Named contact National Guideline Centre 5b Named contact e-mail PerniciousAnaemia@nice.nhs.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and National Guideline Centre		
24.	Review team members	From the National Guideline Centre: Carlos Sharpin [Guideline lead] Maria Smyth [Senior systematic reviewer]		

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

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

Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2006, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[12] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:*

	• UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2006 or later but that depend on unit costs and resource data entirely or predominantly from before 2006 will be rated as 'Not applicable'. • Studies published before 2006 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B – Literature search strategies

These literature search strategies were used for the following reviews:

- What is the clinical and cost effectiveness of vitamin B12 replacement for vitamin B12 deficiency, including the dose, frequency and route of administration?
- What is the clinical and cost effectiveness of self-administration compared with healthcare professional administration of parenteral vitamin B12 replacement for vitamin B12 deficiency?

The literature searches for these reviews are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[12]

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

B.1 Clinical search literature search strategy

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

Table 25: Database parameters, filters and limits applied

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

Database	Dates searched	Search filter used
	Cochrane Central Register of Controlled Trials to Issue 12 of 12, 15 December 2022	
Epistemonikos (The Epistemonikos Foundation)	Inception to 15 December 2022	Systematic review Exclusions (Cochrane reviews)
Current Nursing and Allied Health Literature (CINAHL) (EBSCO)	Inception to 15 December 2022	Human Exclusions (Medline records) English Language

Medline (Ovid) search terms

1.	exp Vitamin B 12 Deficiency/
2.	((b12 or b 12 or cobalamin* or c?anocobalamin* or transcobalamin*) adj4 (deficien* or malabsor* or absor* or lack* or diminish* or low* or level* or abnormal* or deficit or disorder* or inadequa* or hypovitaminosis or hypo vitaminosis or avitaminosis)).ti,ab.
3.	exp Macrocytic Anemia/
4.	((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) adj3 (anemia* or anaemia*)).ti,ab.
5.	Intrinsic Factor/
6.	intrinsic factor.ti,ab.
7.	or/1-6
8.	letter/
9.	editorial/
10.	news/
11.	exp historical article/
12.	Anecdotes as Topic/
13.	comment/
14.	case report/
15.	(letter or comment*).ti.
16.	or/8-15
17.	randomized controlled trial/ or random*.ti,ab.
18.	16 not 17
19.	animals/ not humans/
20.	exp Animals, Laboratory/
21.	exp Animal Experimentation/
22.	exp Models, Animal/
23.	exp Rodentia/
24.	(rat or rats or mouse or mice or rodent*).ti.
25.	or/18-24
26.	7 not 25
27.	limit 26 to English language

28.	exp Vitamin B 12/
29.	(b12 or b 12 or cobalamin* or c?anocobalamin* or hydrox?cobalamin* or methylcobalamin* or MeCbl or adenosylcobalamin* or AdoCbl or cobamamide* or dibencozide*).ti,ab,kf.
30.	or/28-29
31.	exp Administration, Oral/
32.	Self Administration/
33.	Injections, Intramuscular/
34.	Injections, Subcutaneous/
35.	(replace* or inject* or tablet* or spray* or dose* or dosing or dosage or therap* or treatment* or administ*).ti,ab,kf.
36.	(enteral* or oral* or sublingual* or buccal* or parenteral* or subcutaneous or intramuscular).ti,ab,kf.
37.	(interval* or frequen* or time* or timing* or regular* or periodic* or recurr* or repeat* or optimal or optimum).ti,ab,kf.
38.	or/31-37
39.	27 and 30 and 38
40.	Meta-Analysis/
41.	Meta-Analysis as Topic/
42.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
43.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
44.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
45.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
46.	(search* adj4 literature).ab.
47.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
48.	cochrane.jw.
49.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
50.	or/40-49
51.	randomized controlled trial.pt.
52.	controlled clinical trial.pt.
53.	randomi#ed.ab.
54.	placebo.ab.
55.	randomly.ab.
56.	clinical trials as topic.sh.
57.	trial.ti.
58.	or/51-57
59.	Epidemiologic studies/
60.	Observational study/
61.	exp Cohort studies/
62.	(cohort adj (study or studies or analys* or data)).ti,ab.
63.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.

64.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
65.	Controlled Before-After Studies/
66.	Historically Controlled Study/
67.	Interrupted Time Series Analysis/
68.	(before adj2 after adj2 (study or studies or data)).ti,ab.
69.	exp case control study/
70.	case control*.ti,ab.
71.	Cross-sectional studies/
72.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
73.	or/59-72
74.	39 and (50 or 58 or 73)

Embase (Ovid) search terms

1.	exp B12 deficiency/
2.	((b12 or b 12 or cobalamin* or c?anocobalamin* or transcobalamin*) adj4 (deficien* or malabsor* or absor* or lack* or diminish* or low* or level* or abnormal* or deficit or disorder* or inadequa* or hypovitaminosis or hypo vitaminosis or avitaminosis)).ti,ab.
3.	exp macrocytic anemia/
4.	((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) adj3 (anemia* or anaemia*)).ti,ab.
5.	intrinsic factor/
6.	intrinsic factor.ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	case report/ or case study/
12.	(letter or comment*).ti.
13.	(conference abstract or conference paper).pt.
14.	or/8-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/16-23
25.	7 not 24
26.	limit 25 to English language
27.	cyanocobalamin/
28.	cobalamin/

29.	hydroxocobalamin/
30.	(b12 or b 12 or cobalamin* or c?anocobalamin* or hydrox?cobalamin* or methylcobalamin* or MeCbl or adenosylcobalamin* or AdoCbl or cobamamide* or dibencozide*).ti,ab,kf.
31.	or/27-30
32.	parenteral drug administration/
33.	intramuscular drug administration/
34.	subcutaneous drug administration/
35.	enteral drug administration/
36.	oral drug administration/
37.	drug self administration/
38.	(replac* or inject* or tablet* or spray* or dose* or dosing or dosage or therap* or treatment* or administ*).ti,ab,kf.
39.	(enteral* or oral* or sublingual* or buccal* or parenteral* or subcutaneous or intramuscular).ti,ab,kf.
40.	(interval* or frequen* or time* or timing* or regular* or periodic* or recurr* or repeat* or optimal or optimum).ti,ab,kf.
41.	or/32-40
42.	26 and 31 and 41
43.	random*.ti,ab.
44.	factorial*.ti,ab.
45.	(crossover* or cross over*).ti,ab.
46.	((doubl* or singl*) adj blind*).ti,ab.
47.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
48.	crossover procedure/
49.	single blind procedure/
50.	randomized controlled trial/
51.	double blind procedure/
52.	or/43-51
53.	Systematic Review/
54.	Meta-Analysis/
55.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
56.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
57.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
58.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
59.	(search* adj4 literature).ab.
60.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
61.	cochrane.jw.
62.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
63.	or/53-62
64.	Clinical study/
65.	Observational study/
66.	Family study/

67.	Longitudinal study/
68.	Retrospective study/
69.	Prospective study/
70.	Cohort analysis/
71.	Follow-up/
72.	cohort*.ti,ab.
73.	71 and 72
74.	(cohort adj (study or studies or analys* or data)).ti,ab.
75.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
76.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
77.	(before adj2 after adj2 (study or studies or data)).ti,ab.
78.	exp case control study/
79.	case control*.ti,ab.
80.	cross-sectional study/
81.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
82.	or/64-70,73-81
83.	42 and (52 or 63 or 82)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Vitamin B 12 Deficiency] explode all trees
#2.	((b12 or b 12 or cobalamin* or c?anocobalamin* or transcobalamin*) near/4 (deficien* or malabsor* or absor* or lack* or diminish* or low* or level* or abnormal* or deficit or disorder* or inadequa* or hypovitaminosis or hypo vitaminosis or avitaminosis)):ti,ab
#3.	MeSH descriptor: [Anemia, Macrocytic] explode all trees
#4.	((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) near/3 (anemia* or anaemia*)):ti,ab
#5.	MeSH descriptor: [Intrinsic Factor] this term only
#6.	intrinsic factor:ti,ab
#7.	(or #1-#6)
#8.	conference:pt or (clinicaltrials or trialsearch):so
#9.	#7 not #8
#10.	MeSH descriptor: [Vitamin B 12] explode all trees
#11.	(b12 or b 12 or cobalamin* or c?anocobalamin* or hydrox?cobalamin* or methylcobalamin* or MeCbl or adenosylcobalamin* or AdoCbl or cobamamide* or dibencozide*):ti,ab,kw
#12.	(or #10-#11)
#13.	MeSH descriptor: [Administration, Oral] explode all trees
#14.	MeSH descriptor: [Self Administration] this term only
#15.	MeSH descriptor: [Injections, Intramuscular] this term only
#16.	MeSH descriptor: [Injections, Subcutaneous] this term only
#17.	(replac* or inject* or tablet* or spray* or dose* or dosing or dosage or therap* or treatment* or administ*):ti,ab,kw
#18.	(enteral* or oral* or sublingual* or buccal* or parenteral* or subcutaneous* or intramuscular*):ti,ab,kw

#19.	(interval* or frequen* or time* or timing* or regular* or periodic* or recurr* or repeat* or optimal or optimum):ti,ab,kw
#20.	(or #13-#19)
#21.	#9 and #12 and #20

Epistemonikos search terms

1.	(title:((title:(b12 deficien* OR "B 12 deficien*" OR "cobalamin* deficien*" OR "c?anocobalamin* deficien*" OR "transcobalamin* deficien*" OR "b12 malabsor*" OR "b 12 malabsor*" OR "cobalamin* malabsor*" OR "c?anocobalamin* malabsor*" OR "transcobalamin* malabsor*" OR "b12 anemia*" OR "b 12 anemia*" OR "macrocytic anemia*" OR "megaloblastic anemia*" OR "pernicious anemia*" OR "addison* anemia*" OR "b12 anaemia*" OR "b 12 anaemia*" OR "macrocytic anaemia*" OR "megaloblastic anaemia*" OR "pernicious anaemia*" OR "addison* anaemia*" OR "intrinsic factor") OR abstract:(b12 deficien* OR "B 12 deficien*" OR "cobalamin* deficien*" OR "c?anocobalamin* deficien*" OR "transcobalamin* deficien*" OR "b12 malabsor*" OR "b 12 malabsor*" OR "cobalamin* malabsor*" OR "c?anocobalamin* malabsor*" OR "transcobalamin* malabsor*" OR "b12 anemia*" OR "b 12 anemia*" OR "macrocytic anemia*" OR "megaloblastic anemia*" OR "pernicious anemia*" OR "addison* anemia*" OR "b12 anaemia*" OR "b 12 anaemia*" OR "macrocytic anaemia*" OR "megaloblastic anaemia*" OR "pernicious anaemia*" OR "addison* anaemia*" OR "intrinsic factor")) AND (title:(b12 OR b 12 OR cobalamin* OR c?anocobalamin* OR hydrox?cobalamin* OR methylcobalamin* OR MeCbl OR adenosylcobalamin* OR AdoCbl OR cobamamide* OR dibencozide*) OR abstract:(b12 OR b 12 OR cobalamin* OR c?anocobalamin* OR hydrox?cobalamin* OR methylcobalamin* OR MeCbl OR adenosylcobalamin* OR AdoCbl OR cobamamide* OR dibencozide*)) AND (title:(replac* OR inject* OR tablet* OR spray* OR dose* OR dosing OR dosage OR therap* OR treatment* OR administ* OR enteral* OR oral* OR sublingual* OR buccal* OR parenteral* OR subcutaneous* OR intramuscular* OR interval* OR frequen* OR time* OR timing* OR regular* OR periodic* OR recurr* OR repeat* OR optimal OR optimum) OR abstract:(replac* OR inject* OR tablet* OR spray* OR dose* OR dosing OR dosage OR therap* OR treatment* OR administ* OR enteral* OR oral* OR sublingual* OR buccal* OR parenteral* OR subcutaneous* OR intramuscular* OR interval* OR frequen* OR time* OR timing* OR regular* OR periodic* OR recurr* OR repeat* OR optimal OR optimum))) OR abstract:((title:(b12 deficien* OR "B 12 deficien*" OR "cobalamin* deficien*" OR "c?anocobalamin* deficien*" OR "transcobalamin* deficien*" OR "b12 malabsor*" OR "b 12 malabsor*" OR "cobalamin* malabsor*" OR "c?anocobalamin* malabsor*" OR "transcobalamin* malabsor*" OR "b12 anemia*" OR "b 12 anemia*" OR "macrocytic anemia*" OR "megaloblastic anemia*" OR "pernicious anemia*" OR "addison* anemia*" OR "b12 anaemia*" OR "b 12 anaemia*" OR "macrocytic anaemia*" OR "megaloblastic anaemia*" OR "pernicious anaemia*" OR "addison* anaemia*" OR "intrinsic factor") OR abstract:(b12 deficien* OR "B 12 deficien*" OR "cobalamin* deficien*" OR "c?anocobalamin* deficien*" OR "transcobalamin* deficien*" OR "b12 malabsor*" OR "b 12 malabsor*" OR "cobalamin* malabsor*" OR "c?anocobalamin* malabsor*" OR "transcobalamin* malabsor*" OR "b12 anemia*" OR "b 12 anemia*" OR "macrocytic anemia*" OR "megaloblastic anemia*" OR "pernicious anemia*" OR "addison* anemia*" OR "b12 anaemia*" OR "b 12 anaemia*" OR "macrocytic anaemia*" OR "megaloblastic anaemia*" OR "pernicious anaemia*" OR "addison* anaemia*" OR "intrinsic factor")) AND (title:(b12 OR b 12 OR cobalamin* OR c?anocobalamin* OR hydrox?cobalamin* OR methylcobalamin* OR MeCbl OR adenosylcobalamin* OR AdoCbl OR cobamamide* OR dibencozide*) OR abstract:(b12 OR b 12 OR cobalamin* OR c?anocobalamin* OR hydrox?cobalamin* OR methylcobalamin* OR MeCbl OR adenosylcobalamin* OR AdoCbl OR cobamamide* OR dibencozide*)) AND (title:(replac* OR inject* OR tablet* OR spray* OR dose* OR dosing OR dosage OR therap* OR treatment* OR administ* OR enteral* OR oral* OR sublingual* OR buccal* OR parenteral* OR subcutaneous* OR intramuscular* OR interval* OR frequen* OR

	time* OR timing* OR regular* OR periodic* OR recurr* OR repeat* OR optimal OR optimum) OR abstract:(replac* OR inject* OR tablet* OR spray* OR dose* OR dosing OR dosage OR therap* OR treatment* OR administ* OR enteral* OR oral* OR sublingual* OR buccal* OR parenteral* OR subcutaneous* OR intramuscular* OR interval* OR frequen* OR time* OR timing* OR regular* OR periodic* OR recurr* OR repeat* OR optimal OR optimum))))

CINAHL (EBSCO) search terms

S1.	(MH "Vitamin B12 Deficiency+")
S2.	(((TI b12 OR AB b12) OR (TI "b 12" OR AB "b 12") OR (TI cobalamin* OR AB cobalamin*) OR (TI c#anocobalamin* OR AB c#anocobalamin*) OR (TI transcobalamin* OR AB transcobalamin*)) AND ((TI deficien* OR AB deficien*) OR (TI malabsor* OR AB malabsor*) OR (TI absor* OR AB absor*) OR (TI lack* OR AB lack*) OR (TI diminish* OR AB diminish*) OR (TI low* OR AB low*) OR (TI level* OR AB level*) OR (TI abnormal* OR AB abnormal*) OR (TI deficit OR AB deficit) OR (TI disorder* OR AB disorder*) OR (TI inadequa* OR AB inadequa*) OR (TI hypovitaminosis OR hypovitaminosis) OR (TI hypo vitaminosis OR AB hypo vitaminosis) OR (TI avitaminosis OR AB avitaminosis)))
S3.	(MH "Anemia, Macrocytic+")
S4.	(((TI b12 OR AB b12) OR (TI "b 12" OR AB "b 12") OR (TI macrocytic OR AB macrocytic) OR (TI megaloblastic OR AB megaloblastic) OR (TI pernicious OR AB pernicious) OR (TI addison* OR AB addison*)) AND ((TI anemia* OR AB anemia*) OR (TI anaemia* OR AB anaemia*)))
S5.	(TI "intrinsic factor" OR AB "intrinsic factor")
S6.	S1 OR S2 OR S3 OR S4 OR S5
S7.	(MH "Vitamin B12")
S8.	((TI b12 OR AB b12 OR SU b12) OR (TI "b 12" OR AB "b 12" OR SU "b 12") OR (TI cobalamin* OR AB cobalamin* OR SU cobalamin*) OR (TI c#anocobalamin* OR AB c#anocobalamin* OR SU c#anocobalamin*) OR (TI hydrox#cobalamin* OR AB hydrox#cobalamin* OR SU hydrox#cobalamin*))
S9.	S7 OR S8
S10.	(MH "Administration, Oral+")
S11.	(MH "Self Administration+")
S12.	(MH "Injections, Intramuscular+")
S13.	(MH "Injections, Subcutaneous+")
S14.	((TI replace* OR AB replace* OR SU replace*) OR (TI inject* OR AB inject* OR SU inject*) OR (TI tablet* OR AB tablet* OR SU tablet*) OR (TI dose* OR AB dose* OR SU dose*) OR (TI dosing OR AB dosing OR SU dosing) OR (TI dosage OR AB dosage OR SU dosage) OR (TI therap* OR AB therap* OR SU therap*) OR (TI treatment* OR AB treatment* OR SU treatment*) OR (TI administ* OR AB administ* OR SU administ*))
S15.	((TI enteral* OR AB enteral* OR SU enteral*) OR (TI oral* OR AB oral* OR SU oral*) OR (TI sublingual* OR AB sublingual* OR SU sublingual*) OR (TI buccal* OR AB buccal* OR SU buccal*) OR (TI parenteral* OR AB parenteral* OR SU parenteral*) OR (TI subcutaneous OR AB subcutaneous OR SU subcutaneous) OR (TI intramuscular OR AB intramuscular OR SU intramuscular))
S16.	((TI interval* OR AB interval* OR SU interval*) OR (TI frequen* OR AB frequen* OR SU frequen*) OR (TI time* OR AB time* OR SU time*) OR (TI timing* OR AB timing* OR SU timing*) OR (TI regular* OR AB regular* OR SU regular*) OR (TI periodic* OR AB periodic* OR SU periodic*) OR (TI recurr* OR AB recurr* OR SU recurr*) OR (TI

	repeat* OR AB repeat* OR SU repeat*) OR (TI optimal OR AB optimal OR SU optimal) OR (TI optimum OR AB optimum OR SU optimum))
S17.	S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16
S18.	S6 AND S9 AND S17

B.2 Health Economics literature search strategy

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

Table 26: Database parameters, filters and limits applied

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

Medline (Ovid) search terms

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

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

Embase (Ovid) search terms

1.	exp B12 deficiency/
2.	((b12 or b 12 or cobalamin* or c?anocobalamin* or transcobalamin*) adj4 (deficien* or malabsor* or absor* or lack* or diminish* or low* or level* or abnormal* or deficit or disorder* or inadequa* or hypovitaminosis or hypo vitaminosis or avitaminosis)).ti,ab.
3.	exp macrocytic anemia/
4.	((b12 or b 12 or macrocytic or megaloblastic or pernicious or addison*) adj3 (anemia* or anaemia*)).ti,ab.
5.	intrinsic factor/

6.	intrinsic factor.ti,ab.
7.	or/1-6
8.	letter.pt. or letter/
9.	note.pt.
10.	editorial.pt.
11.	case report/ or case study/
12.	(letter or comment*).ti.
13.	(conference abstract or conference paper).pt.
14.	or/8-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animal/ not human/
18.	nonhuman/
19.	exp Animal Experiment/
20.	exp Experimental Animal/
21.	animal model/
22.	exp Rodent/
23.	(rat or rats or mouse or mice or rodent*).ti.
24.	or/16-23
25.	7 not 24
26.	limit 25 to English language
27.	quality adjusted life year/
28.	"quality of life index"/
29.	short form 12/ or short form 20/ or short form 36/ or short form 8/
30.	sickness impact profile/
31.	(quality adj2 (wellbeing or well being)).ti,ab.
32.	sickness impact profile.ti,ab.
33.	disability adjusted life.ti,ab.
34.	(qal* or qtime* or qwb* or daly*).ti,ab.
35.	(euroqol* or eq5d* or eq 5*).ti,ab.
36.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
37.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
38.	(hui or hui1 or hui2 or hui3).ti,ab.
39.	(health* year* equivalent* or hye or hyes).ti,ab.
40.	discrete choice*.ti,ab.
41.	rosser.ti,ab.
42.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
43.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
44.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
45.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
46.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
47.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
48.	or/27-47

49.	health economics/
50.	exp economic evaluation/
51.	exp health care cost/
52.	exp fee/
53.	budget/
54.	funding/
55.	budget*.ti,ab.
56.	cost*.ti.
57.	(economic* or pharmaco?economic*).ti.
58.	(price* or pricing*).ti,ab.
59.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
60.	(financ* or fee or fees).ti,ab.
61.	(value adj2 (money or monetary)).ti,ab.
62.	or/49-61
63.	26 and 48
64.	26 and 62
65.	limit 64 to yr="2014 -Current"
66.	63 or 65

NHS EED and HTA (CRD) search terms

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

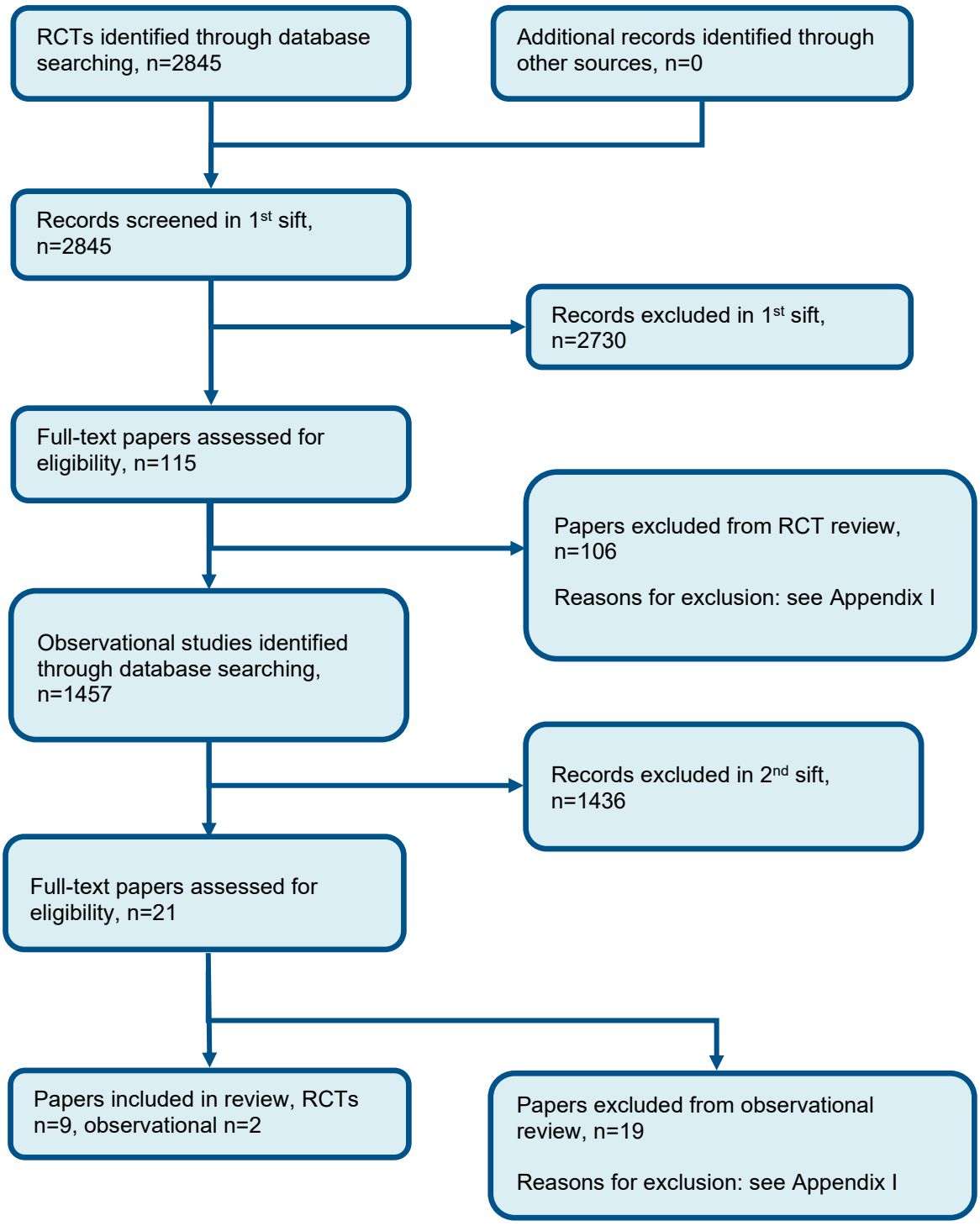
INAHTA search terms

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

Appendix C – Effectiveness evidence study selection

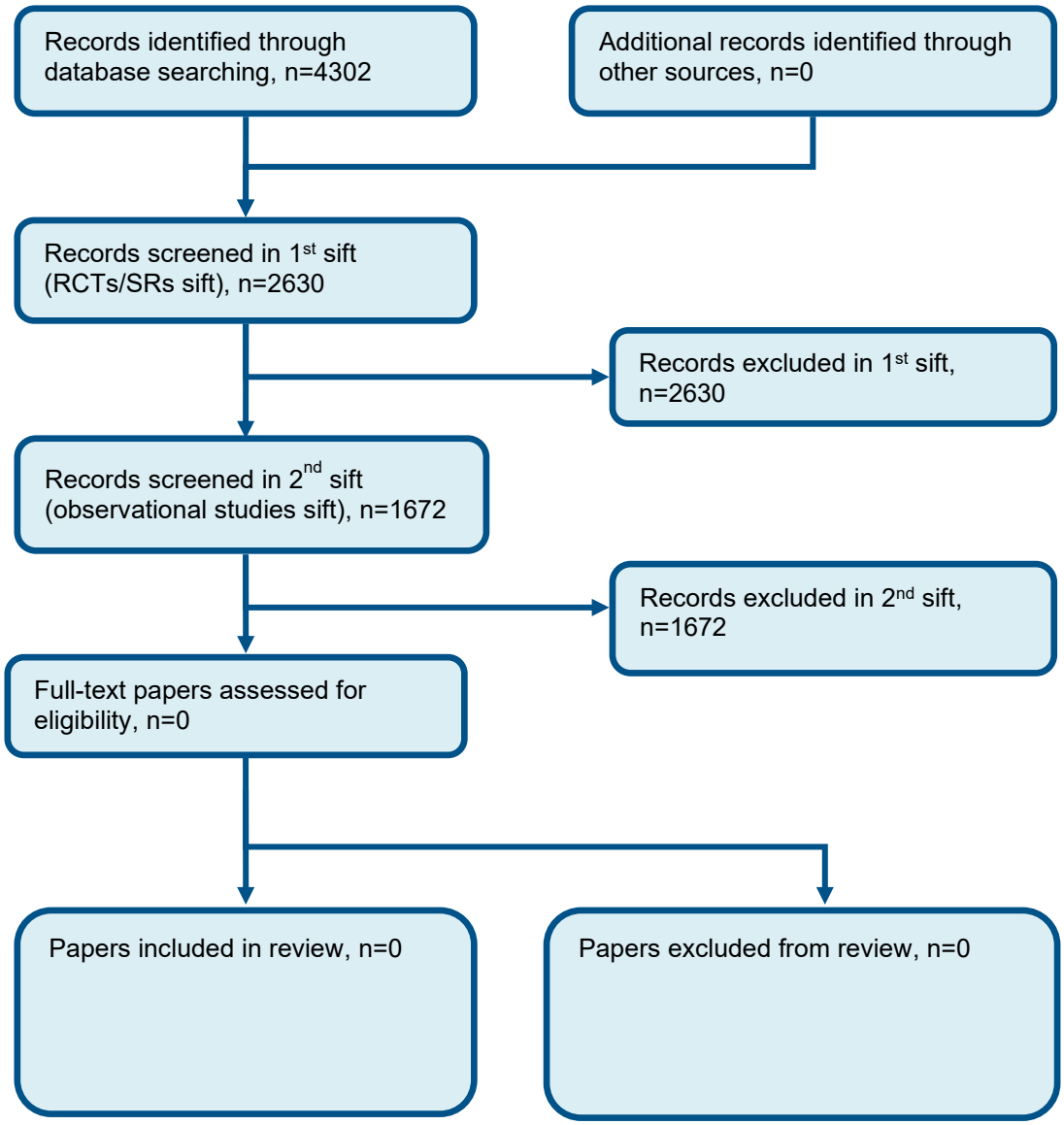
C.1 Vitamin B12 replacement

Figure 1: Flow chart of clinical study selection for the review of vitamin B12 replacement



C.2 Self-administration

Figure 2: Flow chart of clinical study selection for the review of self-administration versus healthcare professional administration


Records identified through database searching, n=4302
Additional records identified through other sources, n=0
Records screened in 1st sift (RCTs/SRs sift), n=2630
Records excluded in 1st sift, n=2630
Records screened in 2nd sift (observational studies sift), n=1672
Records excluded in 2nd sift, n=1672
Full-text papers assessed for eligibility, n=0
Papers included in review, n=0
Papers excluded from review, n=0

Appendix D – Effectiveness evidence

D.1 Vitamin B12 replacement

Castelli, 2011

Bibliographic Reference	Castelli, M. C.; Friedman, K.; Sherry, J.; Brazzillo, K.; Genoble, L.; Bhargava, P.; Riley, M. G.; Comparing the efficacy and tolerability of a new daily oral vitamin B12 formulation and intermittent intramuscular vitamin B12 in normalizing low cobalamin levels: a randomized, open-label, parallel-group study; Clinical Therapeutics; 2011; vol. 33 (no. 3); 358-371.e2

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	ClinicalTrials.gov: NCT01312831
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	5 medical centres
Study dates	February 2009 - May 2010

Sources of funding	Financed by Emisphere Technologies, Inc, which also manufactured and supplied the SNAC test formulation. Study authors are currently employed by Emisphere Technologies and may benefit from the success of products arising from this work
Inclusion criteria	Men or women whose clinical laboratory tests showed vitamin B12 deficiency, defined as serum cobalamin ≤350 pg/mL Aged ≥60 years or ≥18 years with gastrointestinal abnormalities (gastrointestinal surgery, ileal resection, gastric atrophy, celiac disease, Crohn's disease), history of prolonged use (>3 months) of proton pump inhibitor drugs, or a restricted diet (such as vegetarian or vegan) General good health and normal kidney function (determined by estimate creatinine clearance computed by the Cockcroft-Gault formula)
Exclusion criteria	Current treatment from a health care provider to treat vitamin B12 deficiency or symptoms Daily use of neutralizing antacids Inability to ingest oral medication Any clinically significant laboratory value at screening Hypersensitivity or allergic reaction to vitamin B12 Participation in a clinical research study involving a new chemical entity within 30 days of the first study dose Folate levels below the reference range provided by the clinical laboratory Folate, renal or B6 deficiency
Recruitment / selection of participants	Recruited from 5 medical centres
Intervention(s)	Participants received 1000mcg cyanocobalamin daily for 90 days, taken after an overnight fast with 50mL of water and 1-hour before the morning meal
Population subgroups	No additional information

Comparator	Participants received 1000mcg intramuscular cyanocobalamin on days 1, 3, 7, 10, 14, 21, 30, 60 and 90. B12 was administered by study personnel and was injected after an overnight fast, 1-hour before the morning meal
Number of participants	50 randomised, 48 completed (total) 24 randomised, 22 completed (oral cyanocobalamin) 26 randomised, 26 completed (IM cyanocobalamin)
Duration of follow-up	3 months
Indirectness	Downgraded due to population indirectness (mixed B12 deficiency causes)
Additional comments	Intention to treat

Study arms

Oral cyanocobalamin (N = 24)
1000mcg tablet taken after overnight fast once-daily for 90 days

Intramuscular cyanocobalamin (N = 26)
1000mcg injected in 1mL solution after overnight fast on study days 1, 3, 7, 10, 14, 21, 30, 60 and 90

Characteristics

Arm-level characteristics

Characteristic	Oral cyanocobalamin (N = 24)	Intramuscular cyanocobalamin (N = 26)
% Female Sample size	n = 19 ; % = 79.2	n = 20 ; % = 76.9
Mean age (SD) Mean (SD)	52.6 (15.3)	53.8 (15.7)

Characteristic	Oral cyanocobalamin (N = 24)	Intramuscular cyanocobalamin (N = 26)
Ethnicity Sample size	n = NA ; % = NA	n = NA
Caucasian Sample size	n = 18 ; % = 75	n = 22 ; % = 84.6
Black Sample size	n = 6 ; % = 25	n = 4 ; % = 15.4
Comorbidities Mean (SD)	NA (NA)	NA (NA)
Cobalamin level (pg/mL) Mean (SD)	285.5 (54.3)	262 (54.6)

Outcomes

Study timepoints

- Baseline
- 3 month

Continuous Outcomes

Outcome	Oral cyanocobalamin , Baseline, N = 24	Oral cyanocobalamin , 3 month, N = 22	Intramuscular cyanocobalamin , Baseline, N = 26	Intramuscular cyanocobalamin , 3 month, N = 26
Haematological values (total B12) (pg/mL) final values	390 (186)	1957 (946)	369 (180)	2057 (935)

Outcome	Oral cyanocobalamin , Baseline, N = 24	Oral cyanocobalamin , 3 month, N = 22	Intramuscular cyanocobalamin , Baseline, N = 26	Intramuscular cyanocobalamin , 3 month, N = 26
Mean (SD)				
Haematological values (holotranscobalamin) (pmol/L) final values Mean (SD)	40 (16)	646 (431)	34 (8)	877 (405)
Haematological values (methylmalonic acid) (nmol/L) final values Mean (SD)	220 (123)	124 (47)	232 (142)	149 (63)
Haematological values (homocysteine) (µmol/L) final values Mean (SD)	14 (5)	11 (3)	13 (3)	12 (4)

Haematological values (total B12) - Polarity - Higher values are better
Haematological values (holotranscobalamin) - Polarity - Higher values are better
Haematological values (methylmalonic acid) - Polarity - Lower values are better
Haematological values (homocysteine) - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	Oral cyanocobalamin , Baseline, N = 24	Oral cyanocobalamin , 3 month, N = 22	Intramuscular cyanocobalamin , Baseline, N = 26	Intramuscular cyanocobalamin , 3 month, N = 26
Adverse events general No of events	n = NA ; % = NA	n = 13 ; % = 54.2	n = NA ; % = NA	n = 15 ; % = 57.7

Adverse events general - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Haematological values (totalB12)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Haematological values (holotranscobalamin)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Haematological values (methylmalonic acid)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Haematological values (homocysteine)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Adverse events

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Couderc, 2015

Bibliographic Reference	Couderc, A. L.; Camalet, J.; Schneider, S.; Turpin, J. M.; Bereder, I.; Boulahssass, R.; Gonfrier, S.; Bayer, P.; Guerin, O.; Brocker, P.; Cobalamin deficiency in the elderly: aetiology and management: a study of 125 patients in a geriatric hospital; Journal of Nutrition, Health & Aging; 2015; vol. 19 (no. 2); 234-9

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Retrospective cohort study
Study location	France
Study setting	Geriatric university hospital
Study dates	September 2010 – November 2011
Sources of funding	No additional information
Inclusion criteria	All patients with serum cobalamin levels <200 pg/mL or <160 pg/mL for those who had previously received oral or IM cobalamin therapy
Exclusion criteria	No additional information

Recruitment / selection of participants	All patients who attended Nice geriatric university hospital and had confirmed cobalamin deficiency were enrolled
Intervention(s)	Oral cyanocobalamin regimens were: 1) 1000 ug/day for 1 month 2) 1000 ug/day for 15 days, then 1000 ug/10 days for 1 month, then 1000 ug/month for 2 months (used in 80% of participants) 3) 1000 ug three times per week for 1 month 4) 1000 ug/day for 1 week 5) 1000 ug/week for 1 month
Population subgroups	**Cause** Mixed: 12 with pernicious anaemia, 72 with food-cobalamin malabsorption, 15 with nutritional deficiency, 26 undetermined **Severity of deficiency** Inclusion cut-off: 200 pg/mL, mean population value: 144.7 pg/mL **Severity of symptoms** 38 patients had clinical signs of asthenia, oedema on the legs and dyspnea, 6 had signs of neuropathy, 15 had confusion and 53 had dementia **Age/comorbidities/polypharmacy** Median age: 85.5 +/- 7 years, 7 patients had undergone gastric surgery, 5 had alcoholism, 9 had a blood disease, 16 were on long-term metformin for diabetes mellitus, 6 were on ranitidine and 41 were on long-term omeprazole therapy for gastric disease

	Renal function Not reported **Ethnicity** Not reported
Comparator	Intramuscular cyanocobalamin regimens were: 1) 1000 ug/day for 1 week and then 1000 ug/month 2) 1000 ug three times a week for a month and then 1000 ug/month
Number of participants	
Duration of follow-up	Variable depending on treatment regimen
Indirectness	Downgrade for population indirectness due to mixed causes of B12 deficiency and for intervention indirectness due to mixed regimens
Additional comments	No additional information

Study arms

Oral cyanocobalamin (N = 111)

Intramuscular cyanocobalamin (N = 14)

Characteristics

Study-level characteristics

Characteristic	Study (N = 125)
% Female Sample size	n = 80
Mean age (SD) Mean (SD)	85.5 (7)
Ethnicity Nominal	NR
Comorbidities Nominal	NR

Outcomes

Study timepoints

- Baseline
- 3.5 month ((Outcomes were assessed 'after supplementation' (3.5 months was the most common follow-up time as 80.3% of orally supplemented participants were on regimen 4: 1000 ug/day for 15 days, 1000 ug/10days for a month, then 1000 ug/month for 2 months, totally 3.5 months). Due to the variety of treatment regimens used (detailed above), there is a range of follow-up times from 1 week to 3.5 months for the oral treatment. Both IM treatments were given for 5 weeks))

Continuous Outcomes

Outcome	Oral cyanocobalamin , Baseline, N = 111	Oral cyanocobalamin , 3.5 month, N = 111	Intramuscular cyanocobalamin, Baseline, N = 14	Intramuscular cyanocobalamin, 3.5 month, N = 14
Haematological outcomes - B12 (pg/mL) final values Mean (SD)	141.33 (35.1)	279.4 (128.5)	117.4 (49)	730.9 (711.5)

Haematological outcomes - B12 - Polarity - Higher values are better

Critical appraisal - ROBINS-I checklist
Continuous Outcomes-Haematological outcomes-B12-Mean SD-Oral cyanocobalamin -Intramuscular cyanocobalamin-t3.5

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Directly applicable

Dangour, 2015

Bibliographic Reference	Dangour, A. D.; Allen, E.; Clarke, R.; Elbourne, D.; Fletcher, A. E.; Letley, L.; Richards, M.; Whyte, K.; Uauy, R.; Mills, K.; Effects of vitamin B-12 supplementation on neurologic and cognitive function in older people: a randomized controlled trial; American Journal of Clinical Nutrition; 2015; vol. 102 (no. 3); 639-47

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	www.isrctn.com ISRCTN54195799
Study type	Randomised controlled trial (RCT)
Study location	England
Study setting	Seven general practises in South-East England
Study dates	Recruitment from January 2009 - May 2010
Sources of funding	Supported by the Food Standards Agency (N05072) and the Department of Health. National Health Service Research and Development and King's College Hospital Trust Research and Development provided service support costs. DSM donated the vitamin B-12 form used to manufacture study tablets.
Inclusion criteria	≥75 years old

	Moderate B12 deficiency (≥107 <210pmol/L) Haemoglobin concentration ≥110g/L (female) ≥120g/L (male)
Exclusion criteria	Diagnosis of pernicious anaemia or anaemia of any sort (haemoglobin concentration <110g/L for women, <120g/L for men) Very low B12 concentration (<107pmol/L) Alcohol addiction Pacemaker or other metallic implant Resident of a nursing home Self-reported B12 supplementation in previous 6 months Significant cognitive impairment (MMSE score <24)
Recruitment / selection of participants	Participants were identified through medical records from 7 general practices in the South East
Intervention(s)	Participants received 1mg cyanocobalamin daily for 12 months via oral tablet
Population subgroups	No additional information
Comparator	Identical tablets (size, shape, colour, smell and taste) were given to the placebo group in identical pots to the intervention group. Participants took tablets daily for 12 months.
Number of participants	201 randomised, 191 completed (total) 96 randomised, 94 completed (oral cyanocobalamin) 102 randomised, 97 completed (placebo)
Duration of follow-up	12 months

Indirectness	Downgraded for population indirectness (mixed causes of B12 deficiency)
Additional comments	No additional information

Study arms

Oral cyanocobalamin (N = 99)
Daily 1mg cyanocobalamin for 12 months

Placebo (N = 102)

Characteristics

Arm-level characteristics

Characteristic	Oral cyanocobalamin (N = 99)	Placebo (N = 102)
% Female Sample size	n = 53 ; % = 53.5	n = 54 ; % = 52.9
Mean age (SD) Mean (SD)	79.9 (3.5)	80.1 (3.7)
Ethnicity Nominal	NR	NR
Comorbidities Intervention n = 86, placebo n = 84	NA (NA to NA)	NA (NA to NA)

Characteristic	Oral cyanocobalamin (N = 99)	Placebo (N = 102)
Median (IQR)		
Total B12 Median (IQR)	222.9 (197.4 to 268.9)	228 (194.7 to 271)
HoloTC Median (IQR)	50.4 (38.2 to 68.3)	48.8 (39.8 to 62.9)
Hcy Median (IQR)	15.9 (14 to 18.9)	16.3 (13.3 to 19.9)

Outcomes

Study timepoints

- Baseline
- 12 month

Continuous Outcomes

Outcome	Oral cyanocobalamin , Baseline, N = 99	Oral cyanocobalamin , 12 month, N = 78	Placebo, Baseline, N = 102	Placebo, 12 month, N = 71
Haematological values (total B12) (pmol/L) final values, intervention n=74, placebo n=70 Mean (SD)	231.3 (52)	640.9 (199.3)	235.7 (60.7)	235.7 (77.5)

Outcome	Oral cyanocobalamin , Baseline, N = 99	Oral cyanocobalamin , 12 month, N = 78	Placebo, Baseline, N = 102	Placebo, 12 month, N = 71
Haematological values (holotranscobalamin) (pmol/L) final values, intervention n=71, placebo n=70 Mean (SD)	55.7 (21.5)	240 (162.9)	51.8 (17.5)	54.2 (29.5)
Haematological values (homocysteine) (µmol/L) final values, intervention n=73, placebo n=70 Mean (SD)	17.1 (4.6)	14.2 (4.2)	17.2 (5.6)	17.4 (6)
Haematological values (haemoglobin) (g/L) final values, B12 n=78, placebo n=71 Mean (SD)	140.5 (11)	140 (10.7)	137.9 (12.8)	137.2 (12.6)
Patient reported outcomes (cognition: California Verbal Learning Test) (Total words correct in first 3 trials) scale range 0-48, final values (follow-up B12 n=91, placebo n=93, SE converted to SD) Mean (SD)	22.8 (6)	23.9 (6.68)	22 (6.5)	24.6 (6.75)
Patient reported outcomes (general health: 30-item General Health Questionnaire) scale range unknown, final values (baseline B12 n=91, placebo n=93, follow-up B12 n=86, placebo n=82, SE converted to SD) Mean (SD)	2.5 (4.7)	2.4 (4.64)	2.9 (4.7)	2.7 (4.53)
Patient reported outcomes (cognition: California Verbal Learning Test - words recalled at delayed recall)	7.3 (2.6)	7.5 (0.3)	7 (3.1)	7.7 (0.4)

Outcome	Oral cyanocobalamin , Baseline, N = 99	Oral cyanocobalamin , 12 month, N = 78	Placebo, Baseline, N = 102	Placebo, 12 month, N = 71
scale range 0-16, final values (follow-up B12 n=91, placebo n=93, SE converted to SD) Mean (SD)				
Haematological values (folate) (nmol/L) final values (follow-up B12 n=72, placebo n=71) Mean (SD)	20.7 (12.3)	20.2 (11.6)	21 (13.8)	20.4 (14)

Haematological values (total B12) - Polarity - Higher values are better
Haematological values (holotranscobalamin) - Polarity - Higher values are better
Haematological values (homocysteine) - Polarity - Lower values are better
Haematological values (haemoglobin) - Polarity - Higher values are better
Patient reported outcomes (cognition: California Verbal Learning Test) - Polarity - Higher values are better
Patient reported outcomes (general health: 30-item General Health Questionnaire) - Polarity - Lower values are better
Patient reported outcomes (cognition: California Verbal Learning Test - words recalled at delayed recall) - Polarity - Higher values are better
Haematological values (folate) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

Haematological values (totalB12)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Haematological values (holotranscobalamin)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Haematological values (homocysteine)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Haematological values (haemoglobin)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Patient reported outcomes (cognition: California Verbal Learning Test)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Patient reported outcomes (general health: 30-item General Health Questionnaire)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes-Patient reported outcomes (cognition: California Verbal Learning Test-words recalled at delayed recall)-Mean SD-Oral cyanocobalamin -Placebo-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes-Haematological values (folate)-Mean SD-Oral cyanocobalamin -Placebo-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Dhonukshe-Rutten, 2005

Bibliographic Reference	Dhonukshe-Rutten, R. A.; van Zutphen, M.; de Groot, L. C.; Eussen, S. J.; Blom, H. J.; van Staveren, W. A.; Effect of supplementation with cobalamin carried either by a milk product or a capsule in mildly cobalamin-deficient elderly Dutch persons; American Journal of Clinical Nutrition; 2005; vol. 82 (no. 3); 568-74

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	The Netherlands
Study setting	Care homes
Study dates	No additional information
Sources of funding	No additional information
Inclusion criteria	Mild cobalamin deficiency (serum cobalamin concentrations between 100 and 300 pmol/L) Plasma MMA concentrations ≥0.30 pmol/L
Exclusion criteria	History of cobalamin deficiency, of high-cobalamin (≥50 g/d) or -folate (≥200 g/d) supplementation or injections, gastrointestinal surgery, renal dysfunction (serum creatinine ≥120 pmol/L), anaemia, or cancer were excluded on the basis of self-reports

Recruitment / selection of participants	Participants were recruited voluntarily via mail through staff at their sheltered residence
Intervention(s)	Participants received tablet boxes containing 1000 mcg cyanocobalamin tablets which were to be ingested daily for 12 weeks. Adherence was monitored through a self-report diary and through tablet counting. Both participants and study investigators were blinded.
Population subgroups	Deficiency cause - mixed Age - >65 Pregnancy/breastfeeding - not Religion/belief - not reported Dietary choices - not reported
Comparator	Participants received tablets that were identical to the cyanocobalamin group in appearance, smell and taste, but contained no B12. Adherence was monitored through a self-report diary and through tablet counting. Both participants and study investigators were blinded.
Number of participants	72 randomised (total) 23 allocated to oral cyanocobalamin, 19 completed 25 allocated to placebo, 24 completed *24 allocated to milk trial comparing B12 fortified milk to placebo (not relevant to this review)*
Duration of follow-up	12 weeks
Indirectness	Downgraded due to population indirectness (mixed B12 deficiency cause)
Additional comments	Complete case analysis

Study arms

Oral cyanocobalamin (N = 19)
Participants received daily 1000 mcg oral cyanocobalamin tablets for 12 weeks

Placebo (N = 24)
Participants received placebo tablets for 12 weeks

Characteristics

Arm-level characteristics

Characteristic	Oral cyanocobalamin (N = 19)	Placebo (N = 24)
% Female Sample size	n = 15 ; % = 79	n = 18 ; % = 75
Mean age (SD) Mean (SD)	82 (5.4)	82 (4.7)
Ethnicity Nominal	NR	NR
Comorbidities Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 12 week

Continuous Outcomes

Outcome	Oral cyanocobalamin, Baseline, N = 19	Oral cyanocobalamin, 12 week, N = 19	Placebo, Baseline, N = 24	Placebo, 12 week, N = 24
Haematological values (B12) (pmol/L) change scores Mean (SD)	NA (NA)	281 (136)	NA (NA)	1 (37)
Haematological values (MMA) (µmol/L) change scores (95%CI converted to SD) Mean (SD)	NA (NA)	-0.18 (3.44)	NA (NA)	0 (0.25)
Haematological values (Hcy) (µmol/L) change scores (95%CI converted to SD) Mean (SD)	NA (NA)	-1.8 (14.46)	NA (NA)	-0.1 (6.12)

Haematological values (B12) - Polarity - Higher values are better
Haematological values (MMA) - Polarity - Lower values are better
Haematological values (Hcy) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Continuous Outcomes-Haematological values(B12)-Mean SD-Oral cyanocobalamin-Placebo-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes-Haematological values (MMA)-Mean SD-Oral cyanocobalamin-Placebo-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes-Haematological values (Hcy)-Mean SD-Oral cyanocobalamin-Placebo-t12

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Eussen, 2005

Bibliographic Reference	Eussen, S. J.; de Groot, L. C.; Clarke, R.; Schneede, J.; Ueland, P. M.; Hoefnagels, W. H.; van Staveren, W. A.; Oral cyanocobalamin supplementation in older people with vitamin B12 deficiency: a dose-finding trial; Archives of Internal Medicine; 2005; vol. 165 (no. 10); 1167-72

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	The Netherlands
Study setting	Community based
Study dates	No additional information
Sources of funding	Supported by a grant 2100.0067 from ZonMw, the Hague, the Netherlands; grant 001-2002 from Kellogg's Benelux, Zaventem, Belgium; and grant QLK3-CT-2002-01775 from the Foundation to Promote Research Into Functional Vitamin B12 Deficiency and the European Union BIOMED Demonstration Project
Inclusion criteria	Free-living Aged >70 years

	Serum vitamin B12 concentration between 100 and 300 pmol/L Plasma MMA concentration ≥0.26 µmol/L Serum creatinine concentration ≤120 µmol/L Resident in the Wageningen area of the Netherlands Concomitant use of medications known to affect vitamin B12 absorption (eg, proton pump inhibitors, H2-antagonists, and metformin) was permitted if the medication had been provided at least 3 months before enrolment and was scheduled to be continued for the duration of the trial
Exclusion criteria	Self-reported anaemia, surgery or diseases of the stomach or small intestine Any life-threatening diseases Current use of multivitamin supplements containing folic acid, cobalamin, or pyridoxine hydrochloride Currently receiving cobalamin injections
Recruitment / selection of participants	Participants were identified through a database of individuals who had previously stated an interest in such research
Intervention(s)	Eligible people who agreed to be enrolled in a 3- to 4-week placebo run-in period before randomization and who had proved to be compliant (90% intake of capsules) during the run-in period were randomized to receive 16 weeks of treatment in a parallel-group design with daily oral doses of 2.5, 100, 250, 500, or 1000 µg of cyanocobalamin
Population subgroups	No additional information
Comparator	Doses compared to one another
Number of participants	120 randomised, 117 completed (total) 24 randomised, all completed (2.5mcg) * excluded as not a licensed dose 24 randomised, all completed (100mcg)

	25 randomised, 23 completed (250mcg) 22 randomised, 21 completed (500mcg) 25 randomised, all completed (1000mcg)
Duration of follow-up	16 weeks
Indirectness	Downgraded for population indirectness (mixed B12 deficiency cause)
Additional comments	Complete case analysis

Study arms

Oral cyanocobalamin (100mcg) (N = 24)
16 weeks daily supplementation

Oral cyanocobalamin (250mcg) (N = 25)
16 weeks daily supplementation

Oral cyanocobalamin (500mcg) (N = 22)
16 weeks daily supplementation

Oral cyanocobalamin (1000mcg) (N = 25)
16 weeks daily supplementation

Characteristics

Study-level characteristics

Characteristic	Study (N = 120)
% Female	n = 76 ; % = 63.3

Characteristic	Study (N = 120)
Sample size	
Mean age (SD) Mean (range) Median (IQR)	80 (64 to 94)
Ethnicity Nominal	NR
Comorbidities Mean (range) Median (IQR)	NA (NA to NA)
Total B12 (pmol/L) Median (IQR)	208 (113 to 362)
HoloTC (pmol/L) Median (IQR)	47 (8 to 121)
Hcy (µmol/L) Median (IQR)	14.5 (7.8 to 114)
MMA (µmol/L) Median (IQR)	0.33 (0.23 to 5.16)

Outcomes

Study timepoints

- Baseline
- 8 week
- 16 week

Continuous Outcomes

Outcome	Oral cyanocobalamin (100mcg), Baseline, N = 24	Oral cyanocobalamin (100mcg), 8 week, N = 24	Oral cyanocobalamin (100mcg), 16 week, N = 24	Oral cyanocobalamin (250mcg), Baseline, N = 25	Oral cyanocobalamin (250mcg), 8 week, N = 25	Oral cyanocobalamin (250mcg), 16 week, N = 23
Haematological values (B12) (pmol/L) change scores Mean (95% CI)	NA (NA to NA)	108 (72 to 145)	129 (74 to 183)	NA (NA to NA)	128 (100 to 157)	153 (111 to 195)
Haematological values (holotranscobalamin) (pmol/L) change scores Mean (95% CI)	NA (NA to NA)	26 (16 to 35)	28 (19 to 38)	NA (NA to NA)	40 (29 to 50)	48 (36 to 60)
Haematological values (homocysteine) (µmol/L) change scores Mean (95% CI)	NA (NA to NA)	-0.5 (-1.1 to -0.1)	-0.7 (-1.5 to 0.1)	NA (NA to NA)	-1 (-1.7 to -0.3)	-1.4 (-2.4 to -0.4)
Haematological values (methylmalonic acid) (µmol/L) change scores Mean (95% CI)	NA (NA to NA)	-0.09 (-0.14 to -0.04)	-0.08 (-0.13 to -0.03)	NA (NA to NA)	-0.13 (-0.21 to -0.05)	-0.14 (-0.22 to -0.05)

Haematological values (B12) - Polarity - Higher values are better
Haematological values (holotranscobalamin) - Polarity - Higher values are better

Haematological values (homocysteine) - Polarity - Lower values are better
Haematological values (methylmalonic acid) - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Haematological values (B12)t-8

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Haematological values (B12)t-16

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Haematological values (holotranscobalamin)t-8

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Haematological values (holotranscobalamin)t-16

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Haematological values (homocysteine)t-8

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Haematological values (homocysteine)t-16

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Haematological values (methylmalonic acid)t-8

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Haematological values (methylmalonic acid)t-16

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Kuzminski, 1998

Bibliographic Reference	Kuzminski, A. M.; Del Giacco, E. J.; Allen, R. H.; Stabler, S. P.; Lindenbaum, J.; Effective treatment of cobalamin deficiency with oral cobalamin; Blood; 1998; vol. 92 (no. 4); 1191-8

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	No additional information
Study dates	January 1993 - September 1996
Sources of funding	No additional information
Inclusion criteria	Serum cobalamin <160pg/mL Elevation of serum methylmalonic acid, total homocysteine, or of both metabolites greater than 3 standard deviations (SD) above the mean in normal controls
Exclusion criteria	*individual reasons for exclusion reported*

	Located outside the immediate geographic area of Bassett Hospital Incapacity to give informed consent Refusal to participate Associated life-threatening illness
Recruitment / selection of participants	Participants were recruited from 4 ambulatory care centres in New York State
Intervention(s)	Participants received 2,000 µg of oral cyanocobalamin (two 1,000 µg tablets; Nature's Bounty, Bohemia, NY) administered with breakfast daily for 4 months
Population subgroups	No additional information
Comparator	Participants received 1,000 µg of cyanocobalamin intramuscularly on days 1, 3, 7, 10, 14, 21, 30, 60, and 90, administered by a research nurse
Number of participants	33 randomised, all completed (total) 18 randomised (oral cyanocobalamin) 15 randomised (intramuscular cyanocobalamin)
Duration of follow-up	4 months
Indirectness	Downgraded for population indirectness (mixed B12 deficiency cause) Aetiology of deficiency: 7 patients had serum antibodies to intrinsic factor, establishing the diagnosis of pernicious anaemia. In 4, there was a history of gastric or ileal surgery. 7 patients in each group were felt to have severe chronic atrophic

	gastritis using a combination of serum pepsinogen and gastrin concentrations. 3 had poor dietary animal protein intake and 3 were taking agents reported to cause food cobalamin malabsorption. 38 participants were originally randomised but 5 were excluded from the final analysis because they were judged to have primary folate deficiency rather than cobalamin after completion of the trial
Additional comments	Complete case analysis

Study arms

Oral cyanocobalamin (N = 18)
Participants received 2000mcg cyanocobalamin via two 1000mcg tablets daily for 4 months

Intramuscular cyanocobalamin (N = 15)
Participants received 1000mcg cyanocobalamin on days 1, 3, 7, 10, 14, 21, 30, 60 and 90

Characteristics

Arm-level characteristics

Characteristic	Oral cyanocobalamin (N = 18)	Intramuscular cyanocobalamin (N = 15)
% Female Sample size	n = 12 ; % = 67	n = 13 ; % = 87
Mean age (SD) Mean (SD)	72 (11)	71 (15)
Ethnicity Nominal	NR	NR

Outcomes

Study timepoints

- Baseline
- 4 month

Continuous Outcomes

Outcome	Oral cyanocobalamin , Baseline, N = 18	Oral cyanocobalamin , 4 month, N = 18	Intramuscular cyanocobalamin , Baseline, N = 15	Intramuscular cyanocobalamin , 4 month, N = 15
Haematological values (total B12) (pg/mL) final values (IM B12 4 month n=14) Mean (SD)	93 (46)	1005 (595)	95 (92)	325 (165)
Haematological values (methylmalonic acid) (nmol/L) final values Mean (SD)	3850 (6930)	169 (90)	3630 (7040)	265 (190)
Haematological values (homocysteine) (µmol/L) final values Mean (SD)	37.2 (44.9)	10.6 (4.4)	40 (26.2)	12.2 (4.1)
Haematological values (mean corpuscular volume) (fL) final values Mean (SD)	100 (12)	90 (7)	102 (11)	91 (7)

Haematological values (total B12) - Polarity - Higher values are better

Haematological values (methylmalonic acid) - Polarity - Lower values are better
Haematological values (homocysteine) - Polarity - Lower values are better
Haemotological values (mean corpuscular volume) - Polarity - Lower values are better

Dichotomous Outcomes

Outcome	Oral cyanocobalamin , Baseline, N = 18	Oral cyanocobalamin , 4 month, N = 18	Intramuscular cyanocobalamin , Baseline, N = 15	Intramuscular cyanocobalamin , 4 month, N = 15
Patient reported outcomes (general health: marked improvement or clearing of paresthesias, ataxia or memory loss)) final values No of events	n = NA ; % = NA	n = 4 ; % = 22	n = NA ; % = NA	n = 4 ; % = 27

Patient reported outcomes (general health: marked improvement or clearing of paresthesias, ataxia or memory loss)) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Haematological values (totalB12)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Haematological values (methylmalonic acid)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Haematological values (homocysteine)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Haematological values (mean corpuscular volume)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Patient reported outcomes (general health: marked improvement or clearing of paresthesia, ataxia or memory loss)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Metaxas, 2017

Bibliographic Reference	Metaxas, C.; Mathis, D.; Jeger, C.; Hersberger, K. E.; Arnet, I.; Walter, P.; Early biomarker response and patient preferences to oral and intramuscular vitamin B12 substitution in primary care: a randomised parallel-group trial; Swiss Medical Weekly; 2017; vol. 147; w14421

Study details

Other publications associated with this study included in review	No additional information
Trial name / registration number	ClinicalTrials.gov: NCT01832129
Study type	Randomised controlled trial (RCT)
Study location	Switzerland
Study setting	Primary care
Study dates	November 2013 - December 2015
Sources of funding	No grants from any external funding body were received to conduct this study. Study medication for the O-oral group was sponsored by Wörwag Pharma GmbH & Co, Böblingen, Germany and immunological test kits were provided by Roche Diagnostics (Switzerland), Rotkreuz and Abbott Diagnostics (Switzerland), Baar.
Inclusion criteria	Venous B12 concentration <200pmol/L Indication for B12 supplementation according to their GP ≥18 years old
Exclusion criteria	Concurrent intake of supplements containing B12

	Previously diagnosed dementia Known hereditary transcobalamin transportation defects Unable to understand written/spoken German, French, Italian or English
Recruitment / selection of participants	Participants were recruited from 3 GP practices in Olten, Switzerland. A letter with the patient information leaflet and a written informed consent form was given to patients whose physician had ordered a laboratory test for the biochemical confirmation of VB12 deficiency. Patients were asked to bring the informed consent form to their next scheduled visit with their GP, during which the results of the laboratory test would be discussed. Eligible patients were asked by their GP to participate in the study.
Intervention(s)	Participants in the oral cyanocobalamin group were instructed to ingest one tablet of 1000 µg daily (B12 “Ankermann”; Wörwag Pharma GmbH & Co, Böblingen, Germany) for 28 consecutive days supplied in a 7x4 punch card with electronic adherence monitoring. Polymedication electronic monitoring system (POEMS) technology was used to assess adherence to the oral VB12 intake. POEMS consists of a film with imprinted electronic components that measure the electrical resistance and record the time of its changes when a loop is broken, i.e., when a cavity is emptied. A first punch card fitted with POEMS was handed out for 14 days. A second identical punch card was handed out for a further 2 weeks at the third visit 2 weeks later. Patients were instructed to return the punch cards for pill count and for the extraction of the electronic adherence data.
Population subgroups	No additional information
Comparator	Participants in the intramuscular hydroxocobalamin group received conventional supplementation with weekly injections of 1000 µg hydroxocobalamin (Vitarubin® Depot 1000 µg / 1ml; Streuli Pharma AG, Uznach, Switzerland, mixed with Lidocaine 1% 1 ml before injection).
Number of participants	37 randomised, all completed (total) 19 randomised, all completed (oral cyanocobalamin) 18 randomised, all completed (intramuscular hydroxocobalamin)
Duration of follow-up	28 days
Indirectness	Downgraded for population indirectness (mixed B12 deficiency cause)
Additional comments	Average treatment adherence by pill count was 99.6% ± 1.1%. No information on IM injection adherence.

Study arms

Oral cyanocobalamin (N = 19)
Received daily tablets containing 1000mcg cyanocobalamin for 28 days

Intramuscular hydroxocobalamin (N = 18)
Weekly injections of 1000mcg hydroxocobalamin for 28 days/4 weeks

Characteristics

Arm-level characteristics

Characteristic	Oral cyanocobalamin (N = 19)	Intramuscular hydroxocobalamin (N = 18)
% Female Sample size	n = 13 ; % = 68.4	n = 10 ; % = 55.6
Mean age (SD) Mean (SD)	47.3 (17.8)	51.5 (19.6)
Ethnicity Nominal	NR	NR
Comorbidities Mean (SD)	NA (NA)	NA (NA)
Total B12 (pmol/L) Mean (SD)	158 (27.4)	164 (20.1)
HoloTC (pmol/L) Mean (SD)	49 (17.7)	50.1 (23)

Characteristic	Oral cyanocobalamin (N = 19)	Intramuscular hydroxocobalamin (N = 18)
MMA (nmol/L) Mean (SD)	304 (172)	321 (183)
Hcy (µmol/L) Mean (SD)	14.8 (5.8)	13 (4.1)

Outcomes

Study timepoints

- Baseline
- 28 day

Continuous Outcomes

Outcome	Oral cyanocobalamin , Baseline, N = 19	Oral cyanocobalamin , 28 day, N = 19	Intramuscular hydroxocobalamin, Baseline, N = 18	Intramuscular hydroxocobalamin, 28 day, N = 18
Haematological values (total B12) (pmol/L) final values Mean (95% CI)	158 (145 to 172)	354 (298 to 410)	164 (154 to 174)	2796 (1277 to 4314)
Haematological values (holotranscobalamin) (pmol/L) final values Mean (95% CI)	49 (40.4 to 57.5)	156 (116 to 196)	50.1 (38.7 to 61.6)	1269 (103 to 2435)

Outcome	Oral cyanocobalamin , Baseline, N = 19	Oral cyanocobalamin , 28 day, N = 19	Intramuscular hydroxocobalamin, Baseline, N = 18	Intramuscular hydroxocobalamin, 28 day, N = 18
Haematological values (homocysteine) (µmol/L) final values Mean (95% CI)	14.8 (12 to 17.7)	13.8 (10.7 to 16.8)	13 (11 to 15.1)	8.5 (7.1 to 9.8)
Haematological values (methylmalonic acid) (nmol/L) final values Mean (95% CI)	304 (219 to 390)	168 (134 to 202)	321 (215 to 427)	156 (121 to 190)
Adverse events final values No of events	n = NA ; % = NA	n = 0 ; % = 0	n = NA ; % = NA	n = 0 ; % = 0

Haematological values (total B12) - Polarity - Higher values are better
Haematological values (holotranscobalamin) - Polarity - Higher values are better
Haematological values (homocysteine) - Polarity - Lower values are better
Haematological values (methylmalonic acid) - Polarity - Lower values are better
Adverse events - Polarity - Lower values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Haematological values (totalB12)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Haematological values (holotranscobalamin)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Haematological values (homocysteine)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Haematological values (methylmalonic acid)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes-Adverse events - No of Events-Oral cyanocobalamin -Intramuscular hydroxocobalamin-t28

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns
Overall bias and Directness	Overall Directness	Directly applicable

Smelt, 2016

Bibliographic Reference	Smelt, H. J.; Pouwels, S.; Said, M.; Berghuis, K. A.; Boer, A. K.; Smulders, J. F.; Comparison Between Different Intramuscular Vitamin B12 Supplementation Regimes: a Retrospective Matched Cohort Study; Obesity Surgery; 2016; vol. 26 (no. 12); 2873-2879

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Retrospective cohort study
Study location	The Netherlands
Study dates	2009-2015
Sources of funding	No additional information
Inclusion criteria	All patients who underwent a sleeve gastrectomy or Roux-en-Y gastric bypass
Exclusion criteria	Renal insufficiency and type 2 diabetes mellitus
Recruitment / selection of participants	All patients who underwent a sleeve gastrectomy or Roux-en-Y gastric bypass either as primary or a revisional procedure, from 2009 to 2015 in the Obesity Center Catharina Hospital

Intervention(s)	Vitamin B12 treatment consisted of IM hydroxocobalamin injections, each containing 1000 µg of hydroxocobalamin **Loading Group** Six injections with a loading dose of one injection every 2 weeks during the first 8 weeks. Afterwards, one injection after 3 months **No Loading Group** Three injections without loading dose. One injection in the first, second, and the third month
Population subgroups	**Cause** Surgical **Severity of deficiency** Baseline mean B12 ranged from 200-226.2 (range 140-300 pmol/L) **Severity of symptoms** Not reported **Age/comorbidities/polypharmacy** Mean age ranged from 39-44.7 years, the majority of participants were 2 years post operation, but ranged from 0 to >5 years, 25.4% were using high-dose weight loss supplements, 68.3% were using multivitamin supplements **Renal function** Not reported **Ethnicity** Not reported
Comparator	IM treatment regimes were compared to one another and to no treatment

Number of participants	63 participants in total, 21 per treatment arm
Duration of follow-up	3 months
Indirectness	None
Additional comments	No additional information

Study arms

Intramuscular hydroxocobalamin with loading dose (N = 21)

Intramuscular hydroxocobalamin with no loading dose (N = 21)

No treatment (N = 21)

Characteristics

Arm-level characteristics

Characteristic	Intramuscular hydroxocobalamin with loading dose (N = 21)	Intramuscular hydroxocobalamin with no loading dose (N = 21)	No treatment (N = 21)
% Female Sample size	n = 16 ; % = 76	n = 18 ; % = 86	n = 15 ; % = 71
Mean age (SD) Mean (SD)	43.5 (8.6)	39 (11.9)	44.7 (9)
Ethnicity Nominal	NR	NR	NR

Characteristic	Intramuscular hydroxocobalamin with loading dose (N = 21)	Intramuscular hydroxocobalamin with no loading dose (N = 21)	No treatment (N = 21)
Comorbidities Nominal	NR	NR	NR

Outcomes

Study timepoints

- Baseline
- 3 month

Continuous Outcomes

Outcome	Intramuscular hydroxocobalamin with loading dose, Baseline, N = 21	Intramuscular hydroxocobalamin with loading dose, 3 month, N = 21	Intramuscular hydroxocobalamin with no loading dose, Baseline, N = 21	Intramuscular hydroxocobalamin with no loading dose, 3 month, N = 21	No treatment, Baseline, N = 21	No treatment, 3 month, N = 21
Haematological values - B12 (pmol/L) final values Mean (SD)	200.5 (36)	550.3 (451.8)	200 (45.6)	332.9 (296.5)	226.2 (34.6)	211.4 (37.6)
Haematological values - MMA (nmol/L) final values Mean (SD)	504 (261.3)	181.1 (64.5)	455.8 (168.1)	281.7 (134.7)	407.1 (156)	514.3 (235.9)

Haematological values - B12 - Polarity - Higher values are better
Haematological values - MMA - Polarity - Lower values are better

Critical appraisal - ROBINS-I checklist
Continuous Outcomes-Haematological values-B12-Mean SD-Intramuscular hydroxocobalamin with loading dose-Intramuscular hydroxocobalamin with no loading dose-No treatment-t3

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Directly applicable

Continuous Outcomes-Haematological values-MMA-Mean SD-Intramuscular hydroxocobalamin with loading dose-Intramuscular hydroxocobalamin with no loading dose-No treatment-t3

Section	Question	Answer
Overall bias	Risk of bias judgement	Serious
Overall bias	Directness	Directly applicable

Ubbink, 1994

Bibliographic Reference	Ubbink, J. B.; Vermaak, W. J.; van der Merwe, A.; Becker, P. J.; Delport, R.; Potgieter, H. C.; Vitamin requirements for the treatment of hyperhomocysteinemia in humans; Journal of Nutrition; 1994; vol. 124 (no. 10); 1927-33

Study details

Secondary publication of another included study- see primary study for details	No additional information
Other publications associated with this study included in review	No additional information
Trial name / registration number	No additional information
Study type	Randomised controlled trial (RCT)
Study location	South Africa
Study setting	Two pathology practices
Study dates	No additional information
Sources of funding	Sponsored by the Atherosclerosis Risk Factor Research Program and Vesta Medicines Pty Ltd.
Inclusion criteria	White males aged 20-73 years Confirmed hyperhomocysteinemia (>16.3 µmol/L)
Exclusion criteria	No additional information

Recruitment / selection of participants	Participants were identified from people attending 2 major pathology practices for routine medical investigations for life insurance purposes. Blood samples were assessed for homocysteine, with second samples for those who were above the normal reference range (>16.3µmol/L)
Intervention(s)	Participants were required to take one oral cyanocobalamin (0.4mg) tablet after dinner each day for 6 weeks. All tablets received also contained 3mg of beta-carotene
Population subgroups	No additional information
Comparator	Participants were required to take one similar placebo tablet after dinner each day for 6 weeks. All tablets received also contained 3mg of beta-carotene
Number of participants	40 randomised, 34 completed (total) 20 randomised, 17 completed (oral cyanocobalamin) 20 randomised, 17 completed (placebo) *Study also contained 3 other treatment arms providing folic acid (n=20), pyridoxine hydrochloric acid (n=20), and a combination of the two plus B12 (n=20)*
Duration of follow-up	6 weeks
Indirectness	Downgraded for population indirectness (mixed B12 deficiency cause)
Additional comments	Complete case analysis

Study arms

Oral cyanocobalamin (N = 17)

Participants received 0.4mg oral cyanocobalamin in tablet form per day

Placebo (N = 17)

Characteristics

Arm-level characteristics

Characteristic	Oral cyanocobalamin (N = 17)	Placebo (N = 17)
% Female Sample size	n = 0 ; % = 0	n = 0 ; % = 0
Mean age (SD) Mean (SD)	35 (12.5)	40.6 (14.5)
Ethnicity White Sample size	n = 17 ; % = 100	n = 17 ; % = 100

Outcomes

Study timepoints

- Baseline
- 6 week

Continuous Outcomes

Outcome	Oral cyanocobalamin, Baseline, N = 17	Oral cyanocobalamin, 6 week, N = 17	Placebo, Baseline, N = 17	Placebo, 6 week, N = 17
Haematological values (homocysteine) (µmol/L) final values Mean (SD)	30.5 (16.9)	26 (11.8)	30.6 (24.2)	30.7 (24)

Outcome	Oral cyanocobalamin, Baseline, N = 17	Oral cyanocobalamin, 6 week, N = 17	Placebo, Baseline, N = 17	Placebo, 6 week, N = 17
Haematological values (total B12) (pmol/L) final values Mean (SD)	217.6 (122.6)	378.5 (188.8)	217.2 (75.7)	210.6 (76.5)
Haematological values (folate) (nmol/L) final values Mean (SD)	4.1 (1)	4.1 (1.3)	5.7 (3.6)	6.1 (5.6)

Haematological values (homocysteine) - Polarity - Lower values are better
Haematological values (total B12) - Polarity - Higher values are better
Haematological values (folate) - Polarity - Higher values are better

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT
Haematological values (homocysteine)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Haematological values (totalB12)

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Continuous Outcomes-Haematological values(folate)-Mean SD-Oral cyanocobalamin-Placebo-t6

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

D.2 Self-administration

No evidence identified.

Appendix E – Forest plots

E.1 Vitamin B12 replacement

E.1.1 Oral Cyanocobalamin vs Intramuscular Cyanocobalamin

Figure 3: Patient reported outcomes at >3 months (general health: marked improvement or clearing of paraesthesia's, ataxia or memory loss, final values, higher is better)

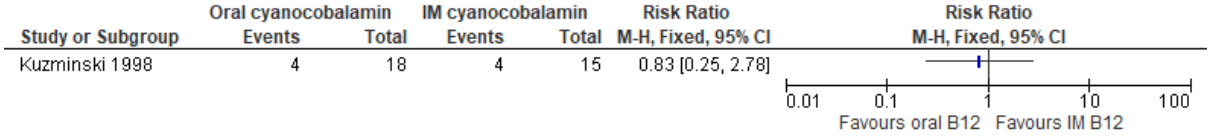


Figure 4: Haematological values at ≤3 months (B12, pg/mL, final values, higher is better)

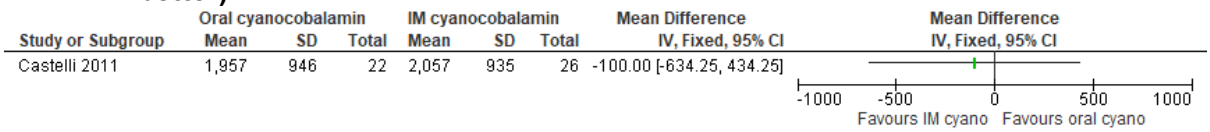


Figure 5: Haematological values at >3 months (B12, pg/mL, final values, higher is better)

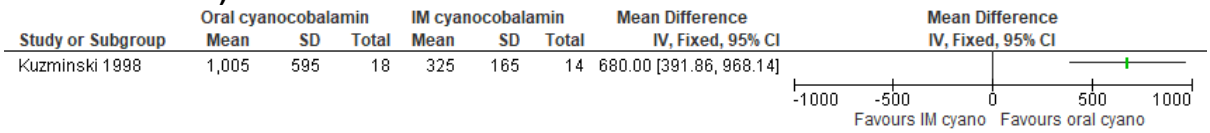


Figure 6: Haematological values at ≤3 months (holoTC, pmol/L, final values, higher is better)

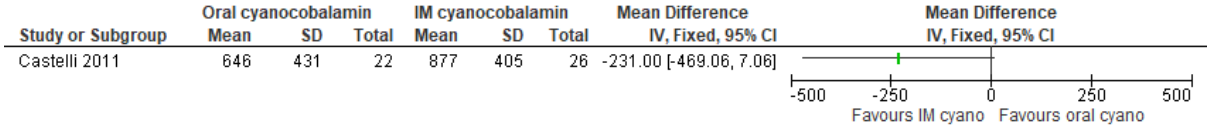


Figure 7: Haematological values at ≤3 months (MMA, nmol/L, final values, lower is better)

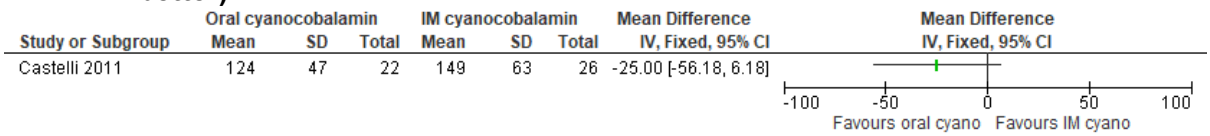


Figure 8: Haematological values at >3 months (MMA, nmol/L, final values, lower is better)

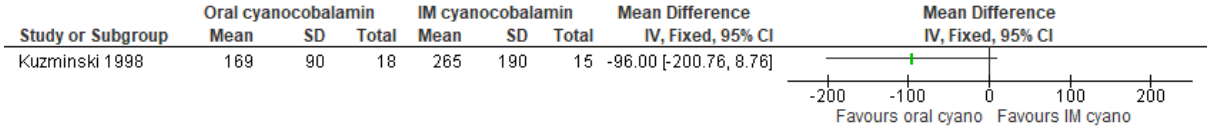


Figure 9: Haematological values at ≤3 months (Hcy, µmol/L, final values, lower is better)

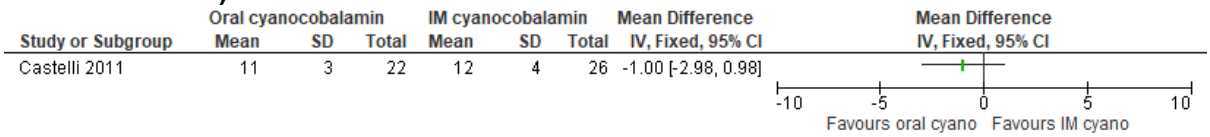


Figure 10: Haematological values at >3 months (Hcy, nmol/L, final values, lower is better)

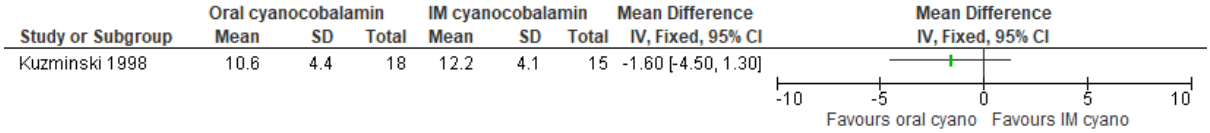


Figure 11: Haematological values at >3 months (MCV, fL, final values, lower is better)

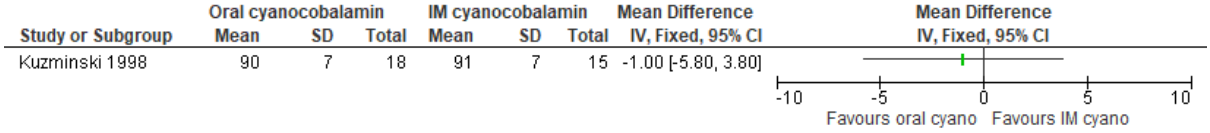
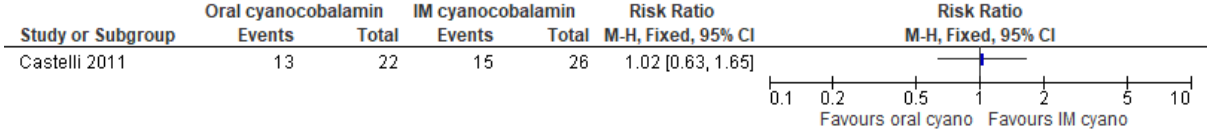


Figure 12: Adverse events at ≤3 months (general, final values, lower is better)



E.1.2 Oral Cyanocobalamin vs Placebo

Figure 13: Patient reported outcomes at >3 months (general health: 30-item General Health Questionnaire, scale range unknown, final values, polarity unknown)

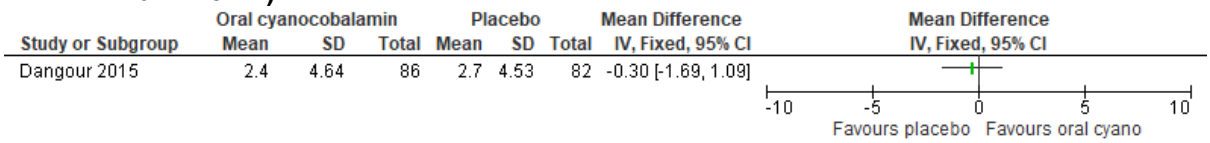


Figure 14: Patient reported outcomes at >3 months (cognition: California Verbal Learning Test (sum of correct words in first 3 trials), scale range 0-48, final values, higher is better)

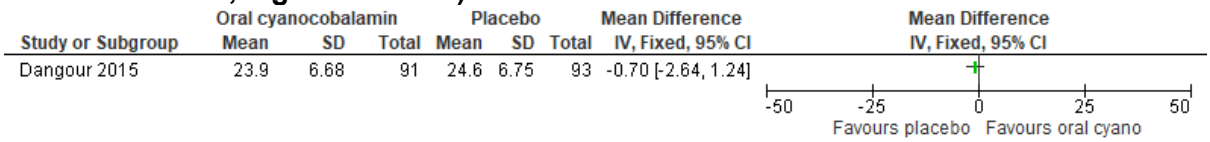


Figure 15: Patient reported outcomes at >3 months (cognition: California Verbal Learning Test - words recalled at delayed recall, scale range 0-16, final values, higher is better)

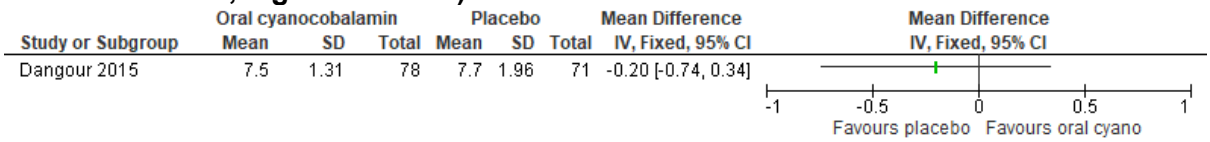


Figure 16: Haematological values at ≤3 months (B12, pmol/L, final values, higher is better, cyanocobalamin dose: 0.4 mg)

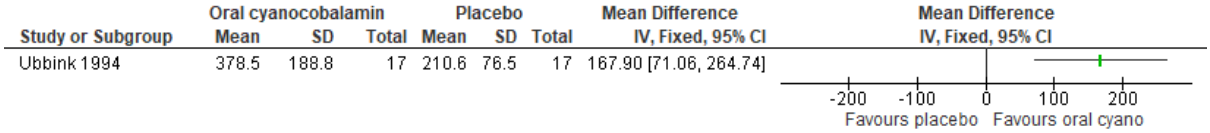


Figure 17: Haematological values at ≤3 months (B12, pmol/L, change scores, higher is better, cyanocobalamin dose: 1 mg)

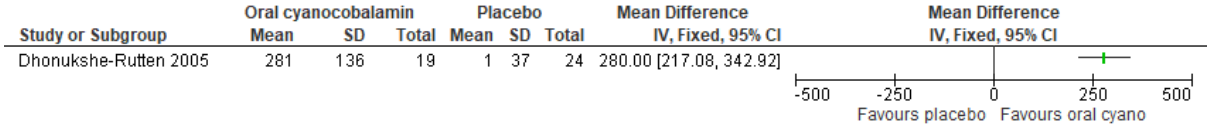


Figure 18: Haematological values at >3 months (B12, pmol/L, final values, higher is better)

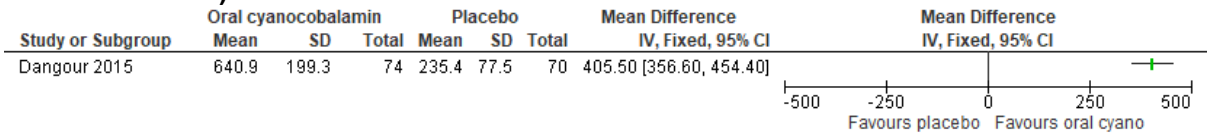


Figure 19: Haematological values at >3 months (holoTC, pmol/L, final values, higher is better)

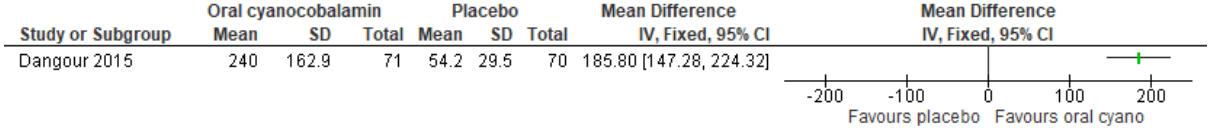


Figure 20: Haematological values at ≤3 months (Hcy, umol/L, final values, lower is better, cyanocobalamin dose: 0.4 mg)

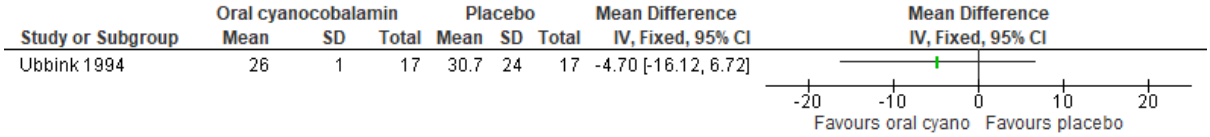


Figure 21: Haematological values at ≤3 months (Hcy, umol/L, change scores, lower is better, cyanocobalamin dose: 1 mg)

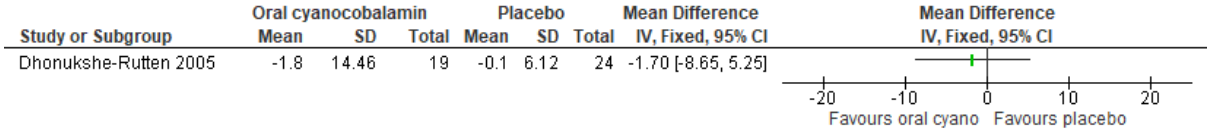


Figure 22: Haematological values at >3 months (Hcy, µmol/L, final values, lower is better)

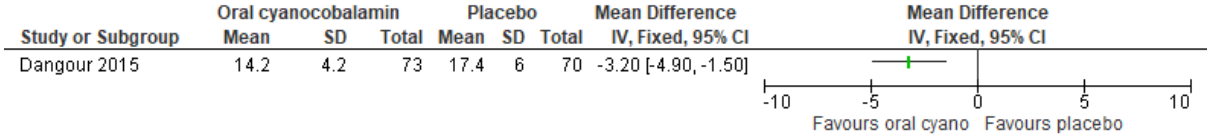


Figure 23: Haematological values at ≤3 months (MMA, µmol/L, change scores, lower is better)

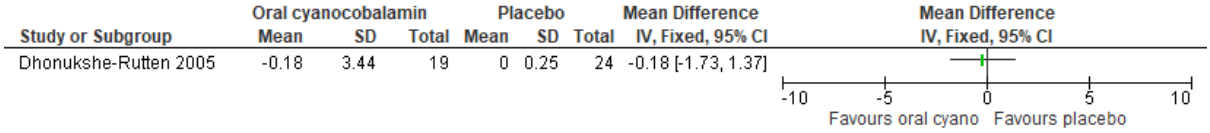


Figure 24: Haematological values at >3 months (haemoglobin, g/L, final values, higher is better)

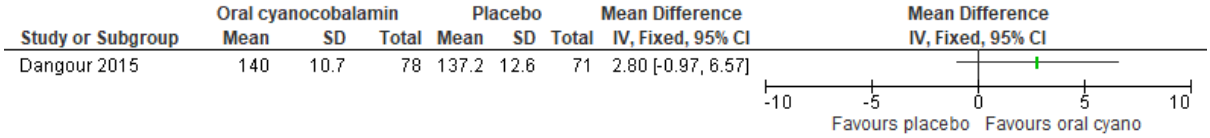


Figure 25: Haematological values at ≤3 months (folate, nmol/L, final values, higher is better)

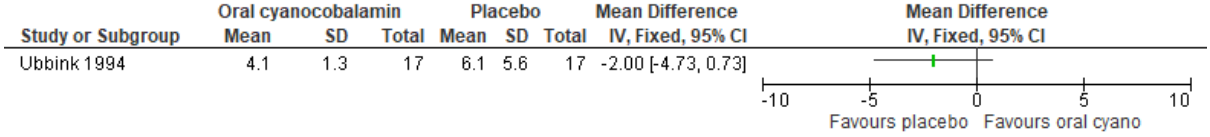
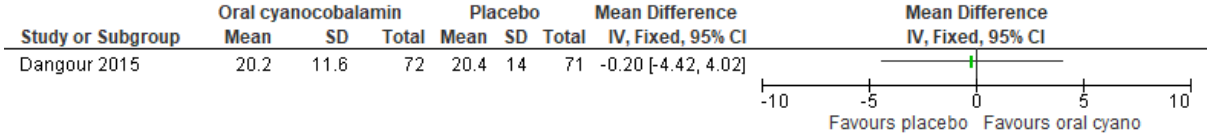
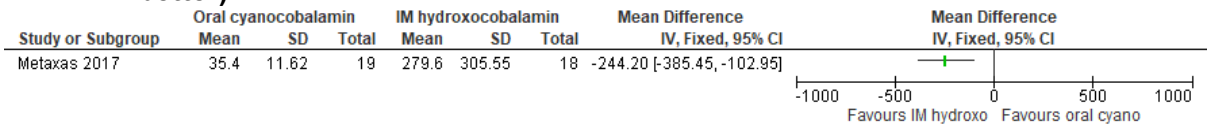


Figure 26: Haematological values at >3 months (folate, nmol/L, final values, higher is better)



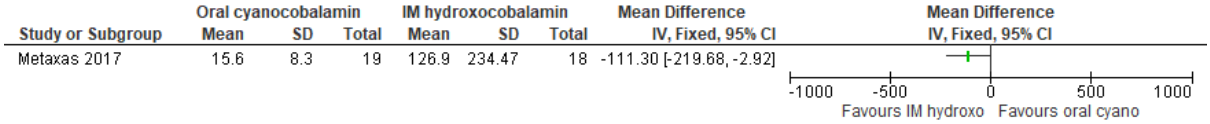
E.1.3 Oral Cyanocobalamin vs Intramuscular Hydroxocobalamin

Figure 27: Haematological values at ≤3 months (B12, pmol/L, final values, higher is better)



Values divided by 10 to fit forest plot. Actual values: mean (SD) IM hydroxocobalamin = 2796 (3054.57), oral cyanocobalamin = 354 (116.19)

Figure 28: Haematological values at ≤3 months (holoTC, pmol/L, final values, higher is better)



Values divided by 10 to fit forest plot. Actual values: mean (SD) IM hydroxocobalamin = 1269 (2344.72), oral cyanocobalamin = 156 (82.99)

Figure 29: Haematological values at ≤3 months (Hcy, µmol/L, final values, lower is better)

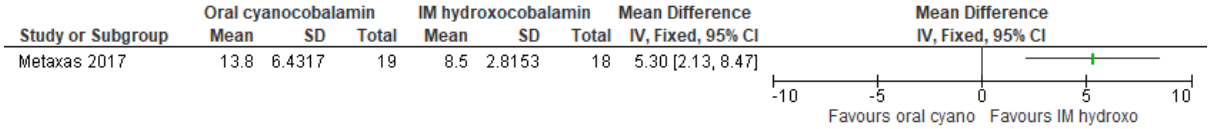


Figure 30: Haematological values at ≤3 months (MMA, nmol/L, final values, lower is better)

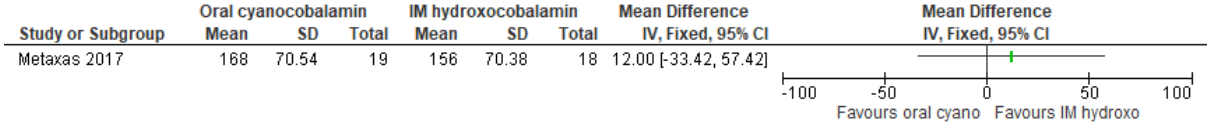
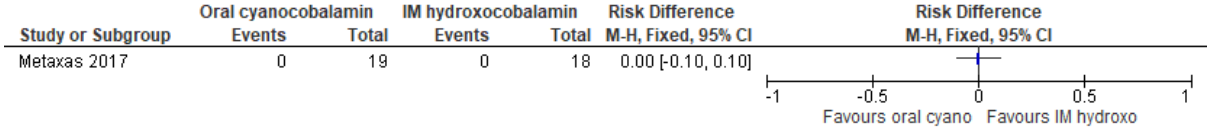


Figure 31: Adverse events at ≤3 months (final values, lower is better)



E.1.4 Oral Cyanocobalamin 100mcg vs 250mcg

Figure 32: Haematological values at ≤3 months (B12, pmol/L, change scores, higher is better)

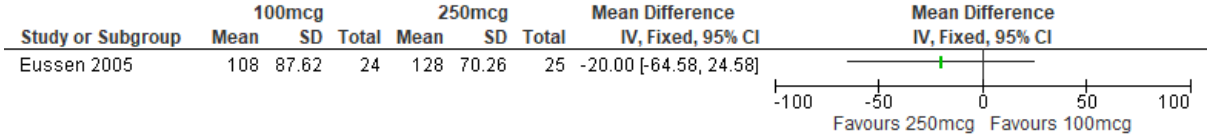


Figure 33: Haematological values at >3 months (B12, pmol/L, change scores, higher is better)

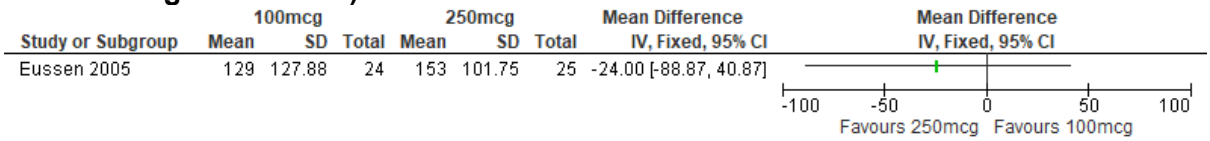


Figure 34: Haematological values at ≤3 months (holoTC, pmol/L, change scores, higher is better)

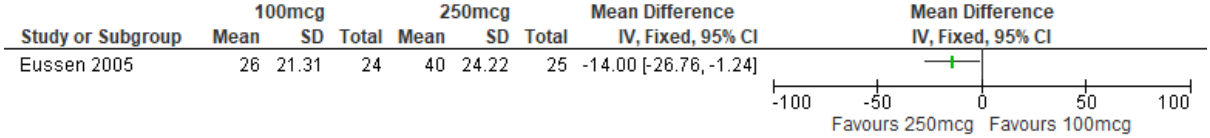


Figure 35: Haematological values at >3 months (holoTC, pmol/L, change scores, higher is better)

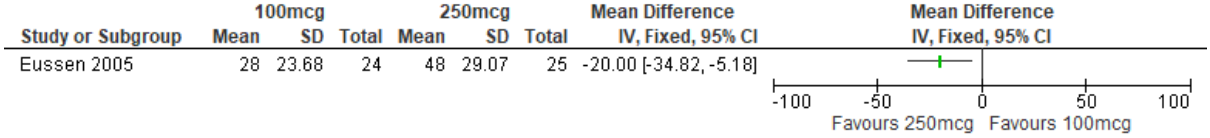


Figure 36: Haematological values at ≤3 months (Hcy, µmol/L, change scores, lower is better)

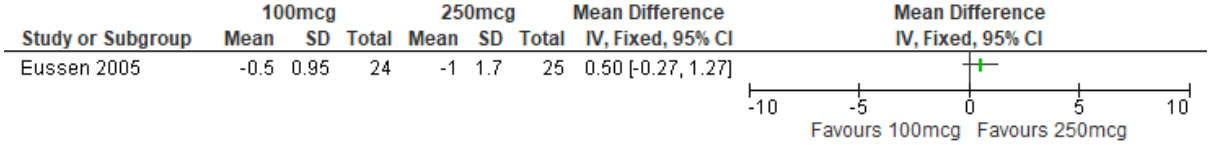


Figure 37: Haematological values at >3 months (Hcy, µmol/L, change scores, lower is better)

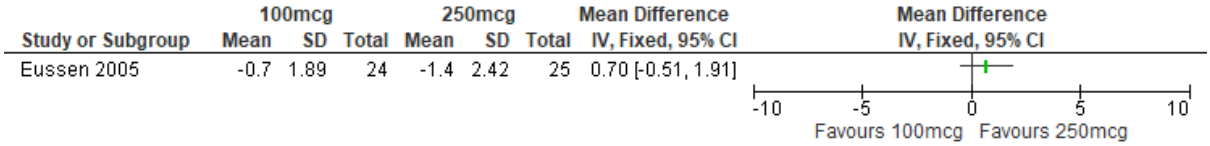


Figure 38: Haematological values at ≤3 months (MMA, µmol/L, change scores, lower is better)

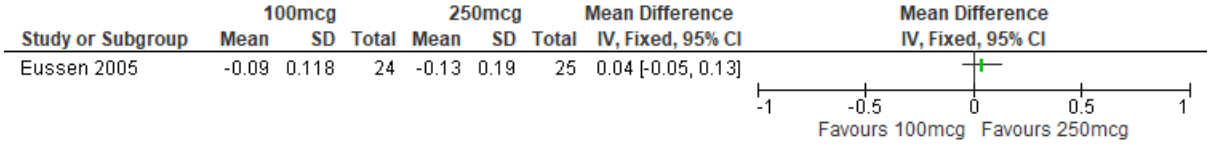
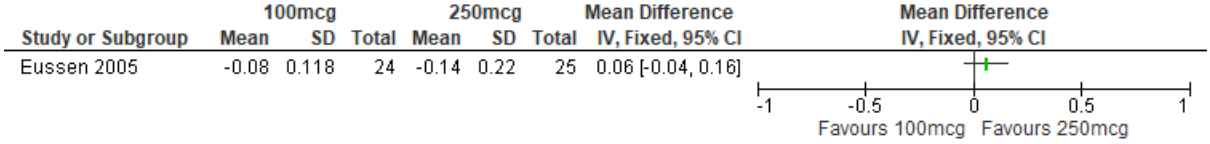


Figure 39: Haematological values at >3 months (MMA, µmol/L, change scores, lower is better)



E.1.5 Oral Cyanocobalamin 100mcg vs 500mcg

Figure 40: Haematological values at ≤3 months (B12, pmol/L, change scores, higher is better)

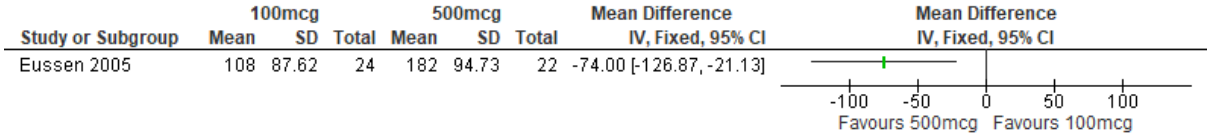


Figure 41: Haematological values at >3 months (B12, pmol/L, change scores, higher is better)

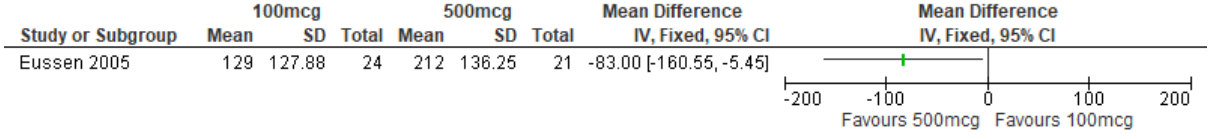


Figure 42: Haematological values at ≤3 months (holoTC, pmol/L, change scores, higher is better)

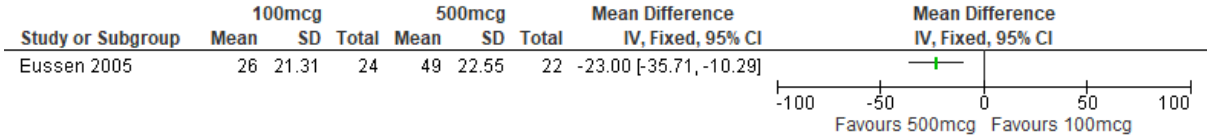


Figure 43: Haematological values at >3 months (holoTC, pmol/L, change scores, higher is better)

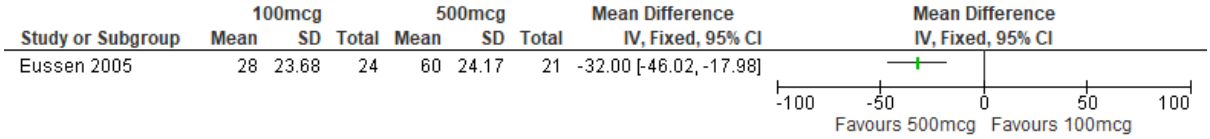


Figure 44: Haematological values at ≤3 months (Hcy, µmol/L, change scores, lower is better)

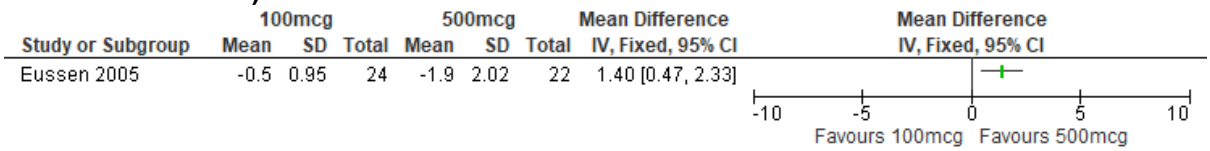


Figure 45: Haematological values at >3 months (Hcy, µmol/L, change scores, lower is better)

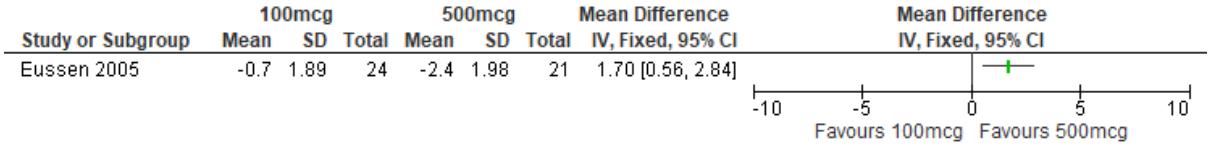


Figure 46: Haematological values at ≤3 months (MMA, µmol/L, change scores, lower is better)

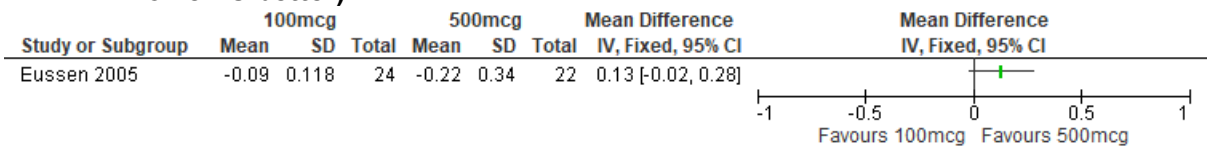
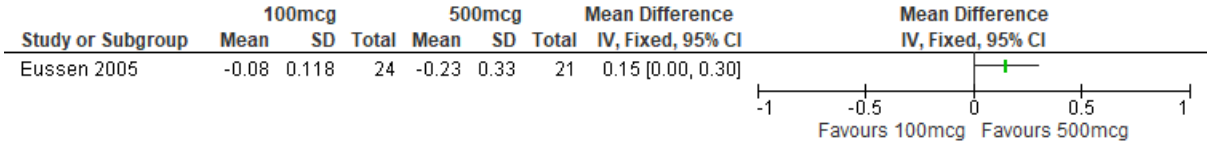


Figure 47: Haematological values at >3 months (MMA, µmol/L, change scores, lower is better)



E.1.6 Oral Cyanocobalamin 100mcg vs 1000mcg

Figure 48: Haematological values at ≤3 months (B12, pmol/L, change scores, higher is better)

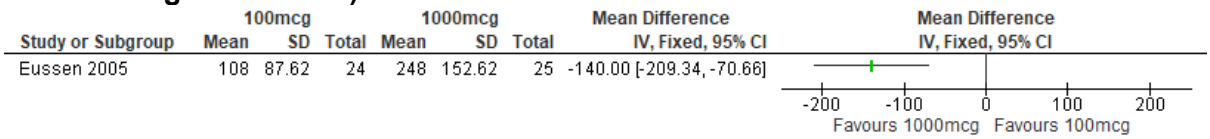


Figure 49: Haematological values at ≤3 months (holoTC, pmol/L, change scores, higher is better)

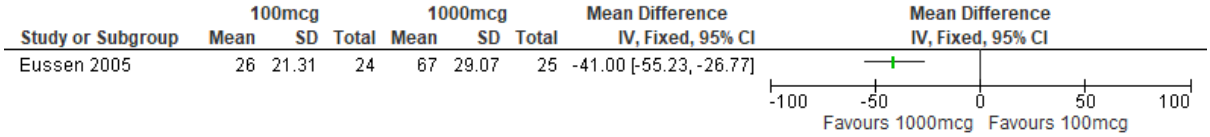


Figure 50: Haematological values at >3 months (holoTC, pmol/L, change scores, higher is better)

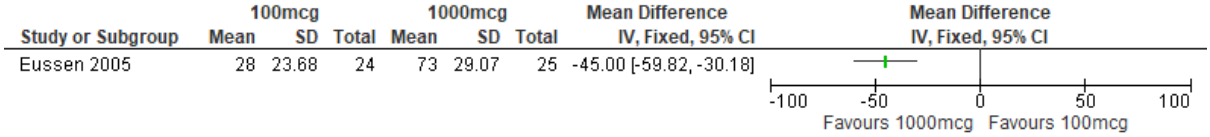


Figure 51: Haematological values at ≤3 months (Hcy, µmol/L, change scores, lower is better)

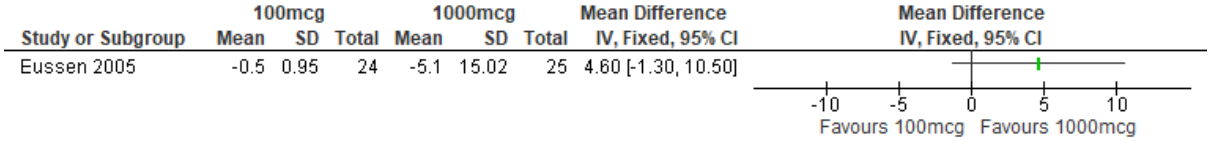


Figure 52: Haematological values at >3 months (Hcy, µmol/L, change scores, lower is better)

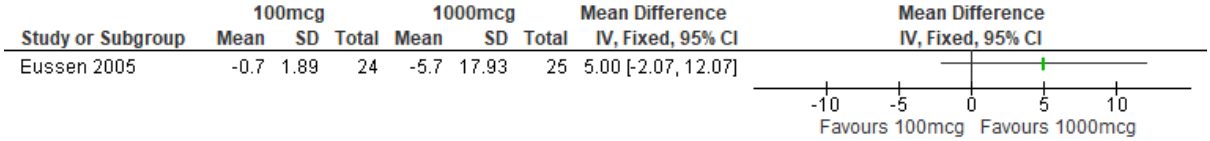


Figure 53: Haematological values at ≤3 months (MMA, µmol/L, change scores, lower is better)

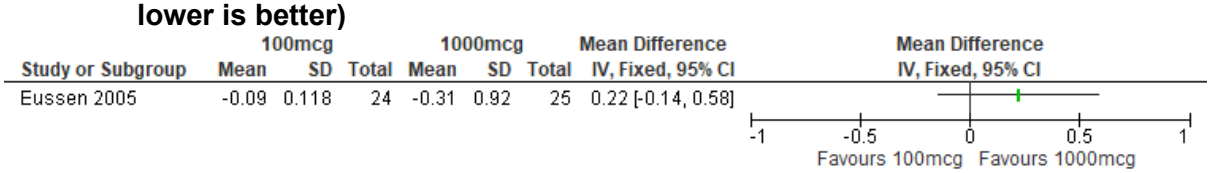
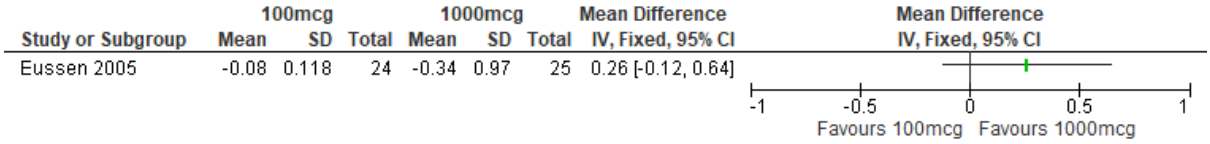


Figure 54: Haematological values at >3 months (MMA, µmol/L, change scores, lower is better)



E.1.7 Oral Cyanocobalamin 250mcg vs 500mcg

Figure 55: Haematological values at ≤3 months (B12, pmol/L, change scores, higher is better)

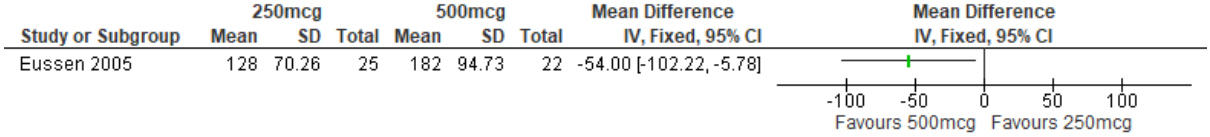


Figure 56: Haematological values at >3 months (B12, pmol/L, change scores, higher is better)

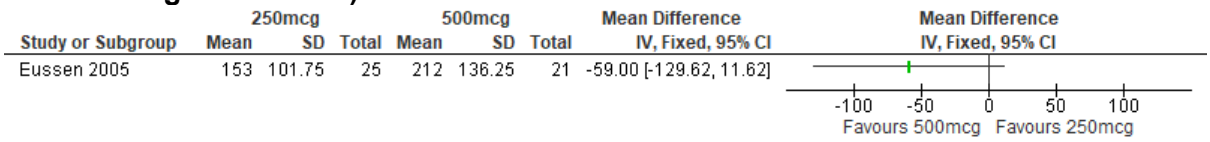


Figure 57: Haematological values at ≤3 months (holoTC, pmol/L, change scores, higher is better)

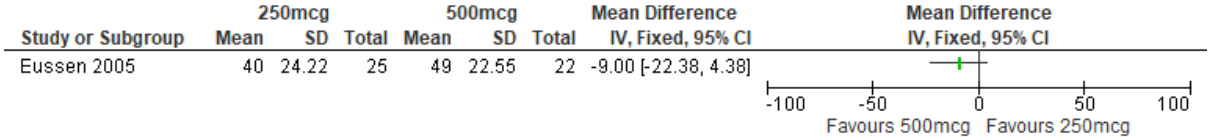


Figure 58: Haematological values at >3 months (holoTC, pmol/L, change scores, higher is better)

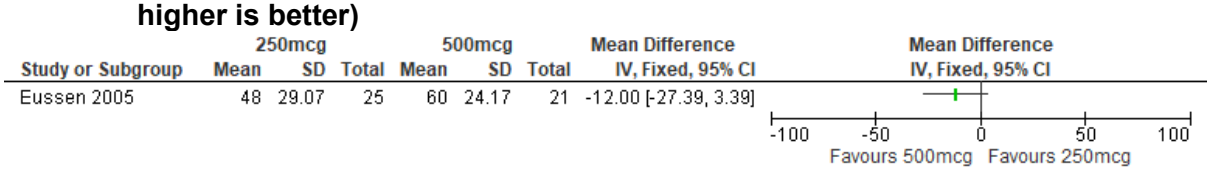


Figure 59: Haematological values at ≤3 months (Hcy, µmol/L, change scores, lower is better)

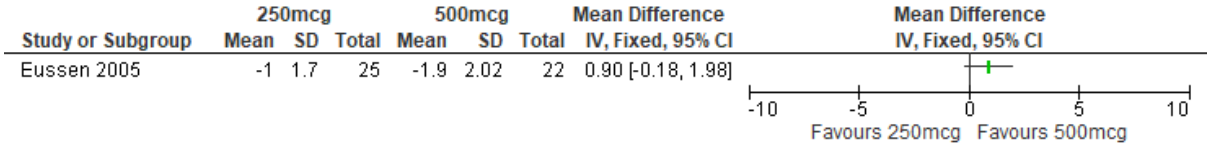


Figure 60: Haematological values at >3 months (Hcy, µmol/L, change scores, lower is better)

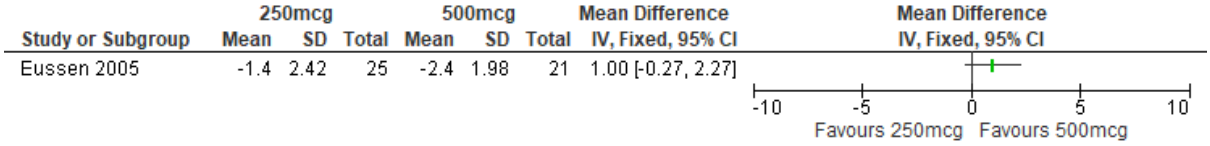


Figure 61: Haematological values at ≤3 months (MMA, µmol/L, change scores, lower is better)

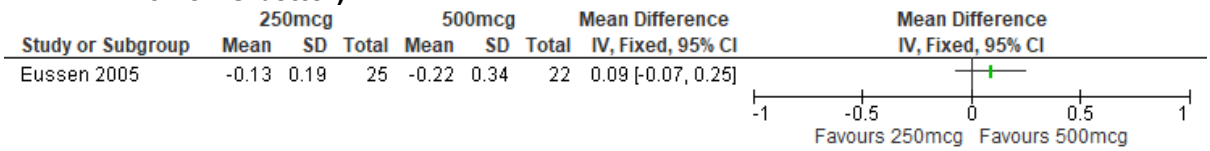
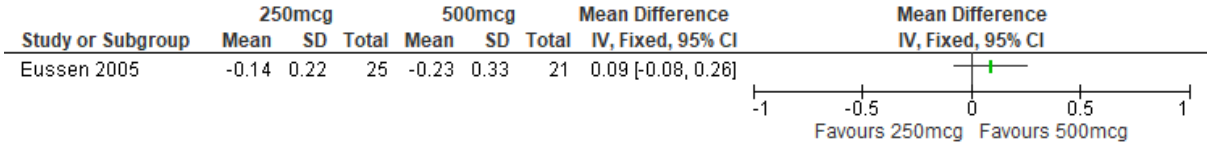


Figure 62: Haematological values at >3 months (MMA, µmol/L, change scores, lower is better)



E.1.8 Oral Cyanocobalamin 250mcg vs 1000mcg

Figure 63: Haematological values at ≤3 months (B12, pmol/L, change scores, higher is better)

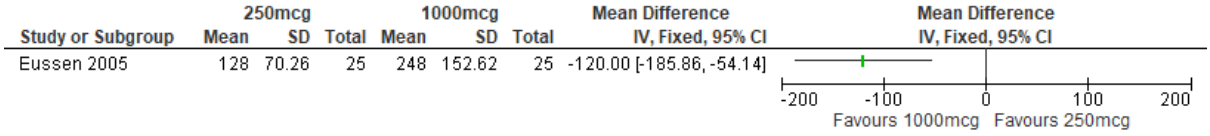


Figure 64: Haematological values at ≤3 months (holoTC, pmol/L, change scores, higher is better)

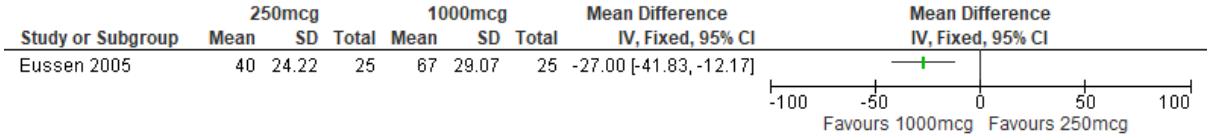


Figure 65: Haematological values at >3 months (holoTC, pmol/L, change scores, higher is better)

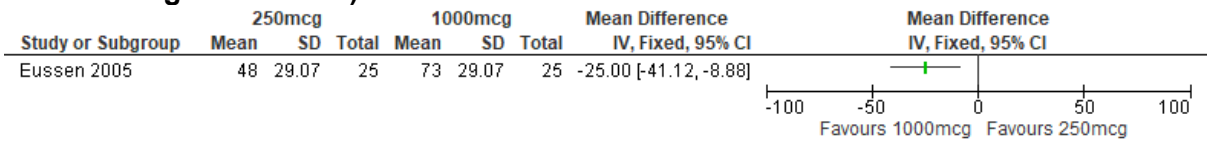


Figure 66: Haematological values at ≤3 months (Hcy, µmol/L, change scores, lower is better)

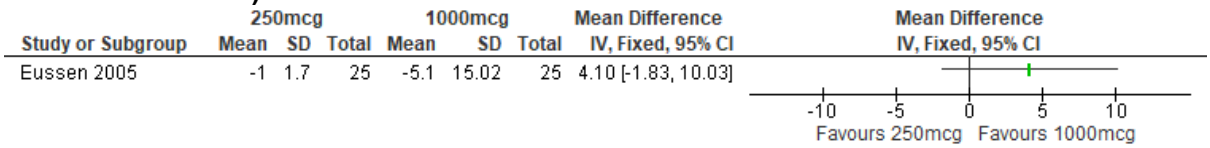


Figure 67: Haematological values at >3 months (Hcy, µmol/L, change scores, lower is better)

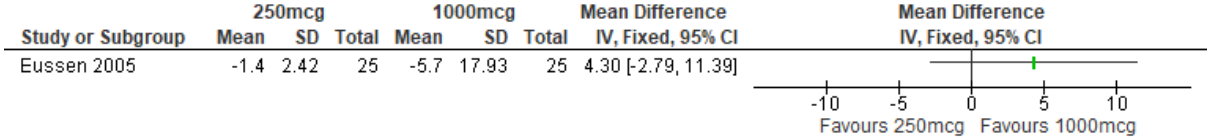


Figure 68: Haematological values at ≤3 months (MMA, µmol/L, change scores, lower is better)

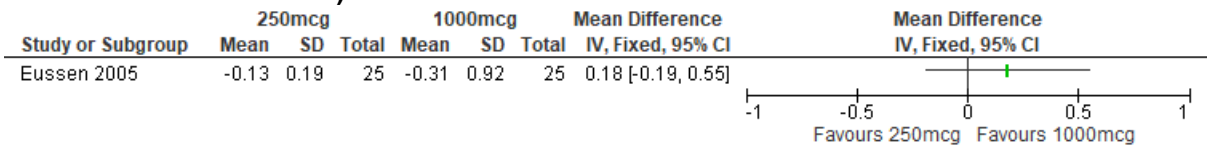
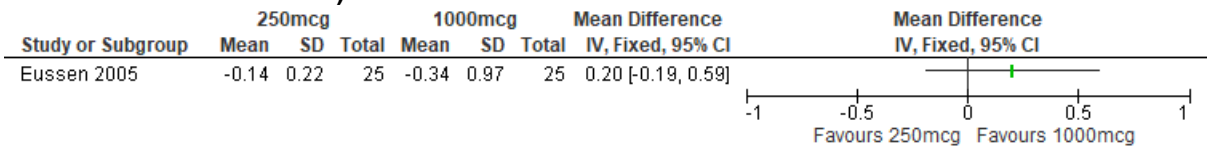


Figure 69: Haematological values at >3 months (MMA, µmol/L, change scores, lower is better)



E.1.9 Oral Cyanocobalamin 500mcg vs 1000mcg

Figure 70: Haematological values at ≤3 months (B12, pmol/L, change scores, higher is better)

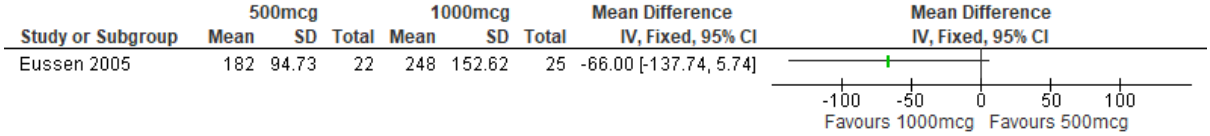


Figure 71: Haematological values at ≤3 months (holoTC, pmol/L, change scores, higher is better)

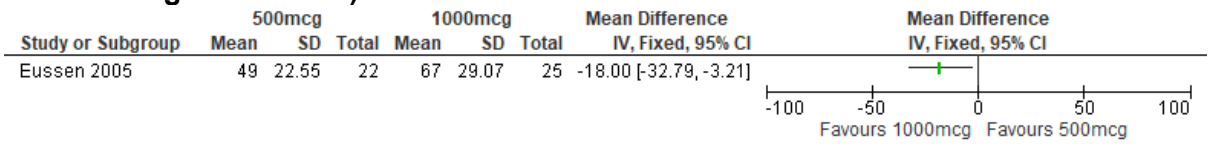


Figure 72: Haematological values at >3 months (holoTC, pmol/L, change scores, higher is better)

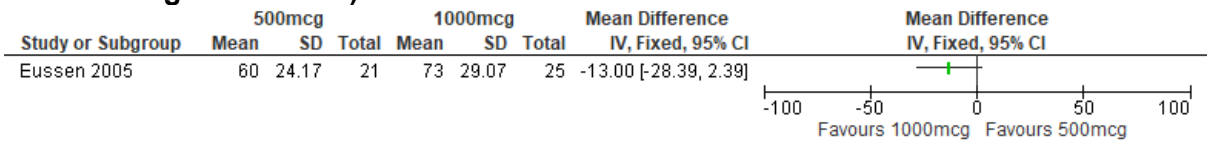


Figure 73: Haematological values at ≤3 months (Hcy, µmol/L, change scores, lower is better)

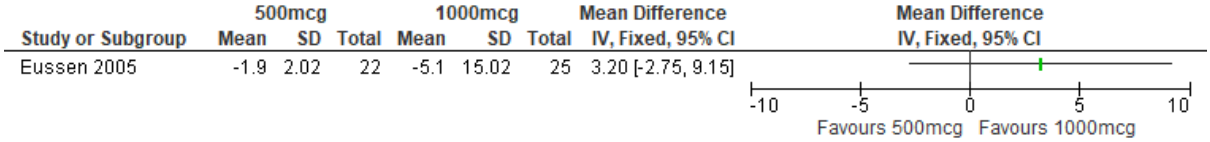


Figure 74: Haematological values at >3 months (Hcy, µmol/L, change scores, lower is better)

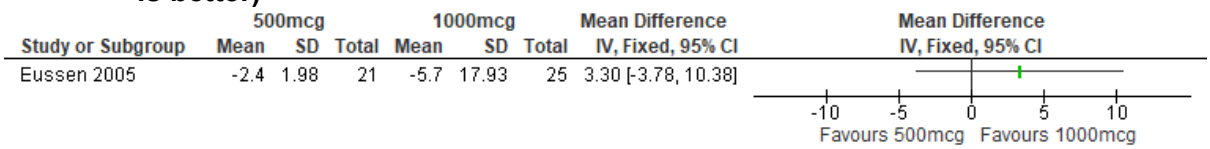


Figure 75: Haematological values at ≤3 months (MMA, µmol/L, change scores, lower is better)

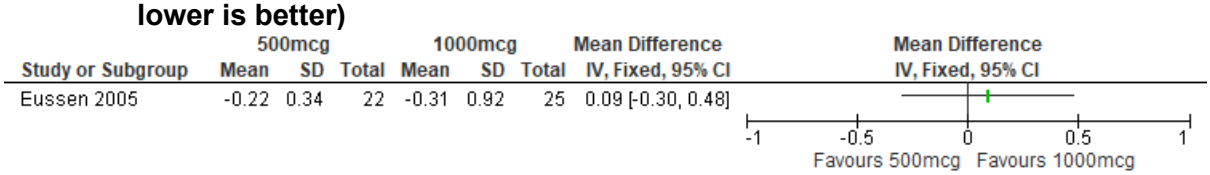
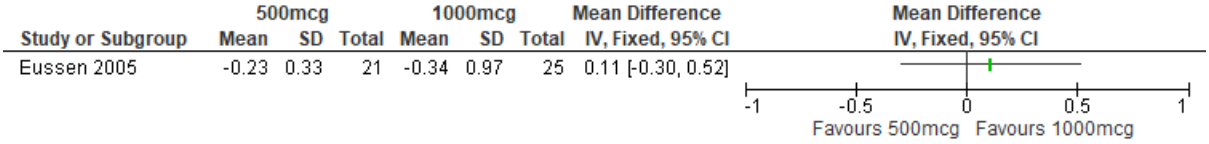


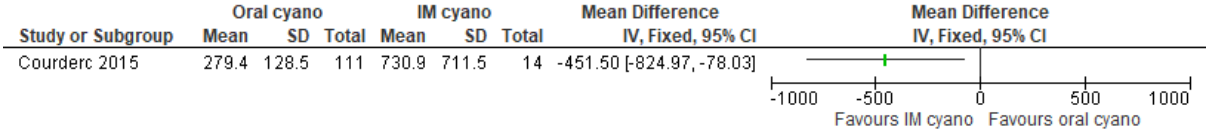
Figure 76: Haematological values at >3 months (MMA, µmol/L, change scores, lower is better)



Observational evidence

E.1.10 Oral cyanocobalamin vs intramuscular cyanocobalamin

Figure 77: Haematological values at >3 months (B12, pg/mL, final values, higher is better)



E.1.11 Intramuscular hydroxocobalamin (with loading dose) vs intramuscular hydroxocobalamin (no loading dose)

Figure 78: Haematological values at ≤3 months (B12, pmol/L, final values, higher is better)

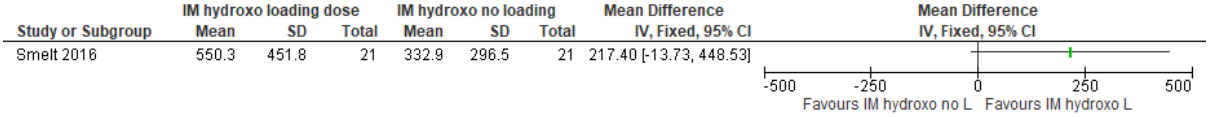
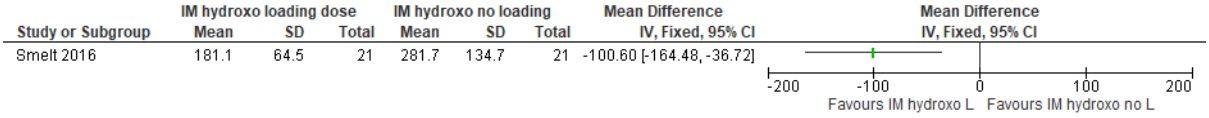


Figure 79: Haematological values at ≤3 months (MMA, nmol/L final values, lower is better)



E.1.12 Intramuscular hydroxocobalamin (with loading dose) vs no treatment

Figure 80: Haematological values at ≤3 months (B12, pmol/L, final values, higher is better)

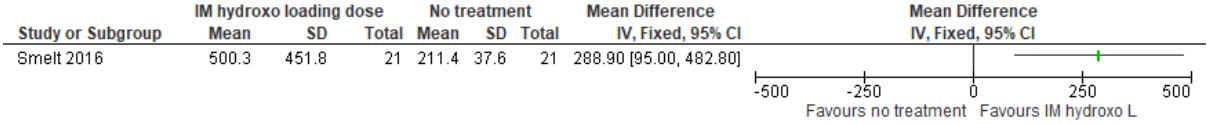
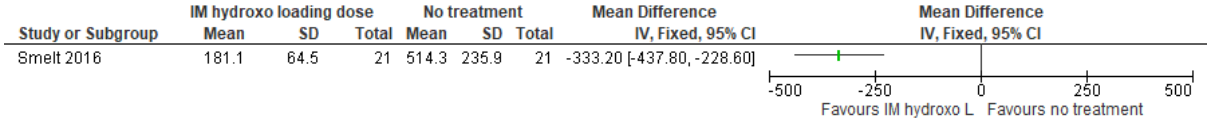


Figure 81: Haematological values at ≤3 months (MMA, nmol/L final values, lower is better)



E.1.13 Intramuscular hydroxocobalamin (no loading dose) vs no treatment

Figure 82: Haematological values at ≤3 months (B12, pmol/L, final values, higher is better)

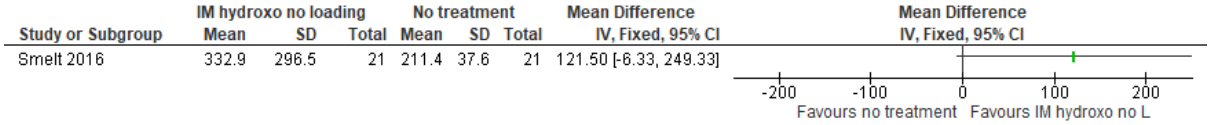
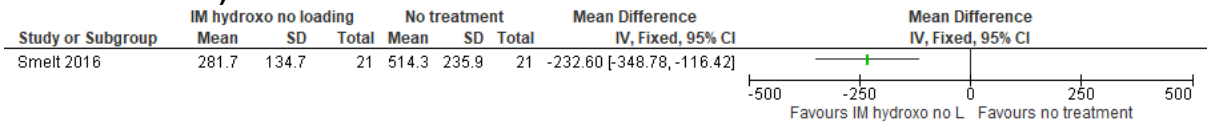


Figure 83: Haematological values at ≤3 months (MMA, nmol/L final values, lower is better)



E.2 Self-administration

No forest plots.

Appendix F – GRADE tables

F.1 Vitamin B12 replacement

F.1.1 Oral Cyanocobalamin vs Intramuscular Cyanocobalamin

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cyanocobalamin	intramuscular cyanocobalamin	Relative (95% CI)	Absolute (95% CI)		
Patient reported outcomes at >3 months (general health: marked improvement or clearing of paraesthesias, ataxia or memory loss, final values, higher is better)												
1	randomised trials	very serious[a]	not serious	serious[b]	very serious[c]	none	4/18 (22.2%)	4/15 (26.7%)	**RR 0.83** (0.25 to 2.78)	**45 fewer per 1,000** (from 200 fewer to 475 more)	⨁◯◯◯ Very low	CRITICAL
Haematological values at ≤3 months (B12, pg/mL, final values, higher is better)												
1	randomised trials	not serious	not serious	serious[b]	very serious[c]	none	22	26	-	MD **100 pg/mL lower** (634.25 lower to 434.25 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at >3 months (B12, pg/mL, final values, higher is better)												
1	randomised trials	serious[d]	not serious	serious[b]	not serious	none	18	14	-	MD **680 pg/mL higher** (391.86 higher to 968.14 higher)	⨁⨁◯◯ Low	CRITICAL
Haematological values at ≤3 months (holoTC, pmol/L, final values, higher is better)												
1	randomised trials	not serious	not serious	serious[b]	very serious[c]	none	22	26	-	MD **231 pmol/L lower** (469.06 lower to 7.06 higher)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cyanocobalamin	intramuscular cyanocobalamin	Relative (95% CI)	Absolute (95% CI)		
Haematological values at ≤3 months (MMA, nmol/L, final values, lower is better)												
1	randomised trials	not serious	not serious	serious[b]	not serious	none	22	26	-	MD **25 nmol/L lower** (56.18 lower to 6.18 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Haematological values at >3 months (MMA, nmol/L, final values, lower is better)												
1	randomised trials	serious[d]	not serious	serious[b]	not serious	none	18	15	-	MD **96 nmol/L lower** (200.76 lower to 8.76 higher)	⨁⨁◯◯ Low	CRITICAL
Haematological values at ≤3 months (Hcy, µmol/L, final values, lower is better)												
1	randomised trials	not serious	not serious	serious[b]	serious[c]	none	22	26	-	MD **1 µmol/L lower** (2.98 lower to 0.98 higher)	⨁⨁◯◯ Low	CRITICAL
Haematological values at >3 months (Hcy, nmol/L, final values, lower is better)												
1	randomised trials	serious[d]	not serious	serious[b]	not serious	none	18	15	-	MD **1.6 µmol/L lower** (4.5 lower to 1.3 higher)	⨁⨁◯◯ Low	CRITICAL
Haematological values at >3 months (MCV, fL, final values, lower is better)												
1	randomised trials	serious[d]	not serious	serious[b]	serious[c]	none	18	15	-	MD **1 fL lower** (5.8 lower to 3.8 higher)	⨁◯◯◯ Very low	CRITICAL
Adverse events at ≤3 months (general, final values, lower is better)												
1	randomised trials	serious[e]	not serious	serious[b]	very serious[c]	none	13/22 (59.1%)	15/26 (57.7%)	**RR 1.02** (0.63 to 1.65)	**12 more per 1,000** (from 213 fewer to 375 more)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by 2 increments due to bias arising from deviations from the intended intervention and measurement of the outcome

b. Downgraded due to population indirectness (mixed B12 deficiency cause)

c. Downgraded by 1 increment if confidence intervals overlapped one MID and 2 increments if confidence intervals overlapped both MIDs

d. Downgraded by 1 increment due to deviations from the intended intervention

e. Downgraded by 1 increment due to bias due to measurement of the outcome

F.1.2 Oral Cyanocobalamin vs Placebo

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cyanocobalamin	placebo	Relative (95% CI)	Absolute (95% CI)		
Patient reported outcomes at >3 months (general health: 30-item General Health Questionnaire, scale range unknown, final values, polarity unknown)												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	86	82	-	MD **0.3 lower** (1.69 lower to 1.09 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Patient reported outcomes at >3 months (cognition: California Verbal Learning Test (sum of correct words in first 3 trials), scale range 0-48, final values, higher is better)												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	91	93	-	MD **0.7 lower** (2.64 lower to 1.24 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Patient reported outcomes at >3 months (cognition: California Verbal Learning Test - words recalled at delayed recall, scale range 0-16, final values, higher is better)												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	78	71	-	MD **0.2 lower** (0.74 lower to 0.34 higher)	⨁⨁⨁◯ Moderate	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cyanocobalamin	placebo	Relative (95% CI)	Absolute (95% CI)		
Haematological values at <3 months (B12, pmol/L, final values, higher is better, cyanocobalamin dose: 0.4 mg)												
1	randomised trials	very serious[b]	not serious	serious[a]	not serious	none	17	17	-	MD **167.9 higher** (71.06 higher to 264.74 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at <3 months (B12, pmol/L, change scores, higher is better, cyanocobalamin dose: 1 mg)												
1	randomised trials	very serious[c]	not serious	serious[a]	not serious	none	19	24	-	MD **280 higher** (217.08 higher to 342.92 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at >3 months (B12, pmol/L, final values, higher is better)												
1	randomised trials	very serious[c]	not serious	serious[a]	not serious	none	74	70	-	MD **405.5 higher** (356.6 higher to 454.4 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at >3 months (holoTC, pmol/L, final values, higher is better)												
1	randomised trials	very serious[c]	not serious	serious[a]	not serious	none	71	70	-	MD **185.8 higher** (147.28 higher to 224.32 higher)	⨁◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cyanocobalamin	placebo	Relative (95% CI)	Absolute (95% CI)		
Haematological values at <3 months (Hcy, umol/L, final values, lower is better, cyanocobalamin dose: 0.4 mg)												
1	randomised trials	very serious[b]	not serious	serious[a]	serious[e]	none	17	17	-	MD **4.7 lower** (16.12 lower to 6.72 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at <3 months (Hcy, umol/L, change scores, lower is better, cyanocobalamin dose: 1 mg)												
1	randomised trials	very serious[c]	not serious	serious[a]	very serious[e]	none	19	24	-	MD **1.7 lower** (8.65 lower to 5.25 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at >3 months (Hcy, µmol/L, final values, lower is better)												
1	randomised trials	very serious[c]	not serious	serious[a]	serious[d]	none	73	70	-	MD **3.2 µmol/L lower** (4.9 lower to 1.5 lower)	⨁◯◯◯ Very low	CRITICAL
Haematological values at ≤3 months (MMA, µmol/L, change scores, lower is better)												
1	randomised trials	very serious[b]	not serious	serious[a]	very serious[d]	none	19	24	-	MD **0.18 lower** (1.73 lower to 1.37 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at >3 months (haemoglobin, g/L, final values, higher is better)												
1	randomised trials	very serious[c]	not serious	serious[a]	serious[d]	none	78	71	-	MD **2.8 g/L higher** (0.97 lower to 6.57 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at ≤3 months (folate, nmol/L, final values, higher is better)												
1	randomised trials	very serious[b]	not serious	not serious	serious[d]	none	17	17	-	MD **2 lower** (4.73 lower to 0.73 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at >3 months (folate, nmol/L, final values, higher is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cyanocobalamin	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious[c]	not serious	serious[a]	not serious	none	72	71	-	MD **0.2 lower** (4.42 lower to 4.02 higher)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded due to population indirectness (mixed cause of B12 deficiency)

b. Downgraded by 2 increments due to bias arising from the randomisation process and missing outcome data

c. Downgraded by 2 increments due to missing outcome data

d. Downgraded by 1 increment if the confidence interval overlapped one MID or 2 increments if the confidence interval overlapped both MIDs

F.1.3 Oral Cyanocobalamin vs Intramuscular Hydroxocobalamin

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cyanocobalamin	intramuscular hydroxocobalamin	Relative (95% CI)	Absolute (95% CI)		
Haematological values at ≤3 months (B12, pmol/L, final values, higher is better)												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	19	18	-	MD **2442 pmol/L lower** (3854.08 lower to 1029.92 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Haematological values at ≤3 months (holoTC, pmol/L, final values, higher is better)												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	19	18	-	MD **1113 pmol/L lower** (2196.83 lower to 29.17 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Haematological values at ≤3 months (Hcy, µmol/L, final values, lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cyanocobalamin	intramuscular hydroxocobalamin	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	19	18	-	MD **5.3 µmol/L higher** (2.13 higher to 8.47 higher)	⨁⨁◯◯ Low	CRITICAL
Haematological values at ≤3 months (MMA, nmol/L, final values, lower is better)												
1	randomised trials	not serious	not serious	serious[a]	not serious	none	19	18	-	MD **12 nmol/L higher** (33.42 lower to 57.42 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Adverse events at ≤3 months (final values, lower is better)												
1	randomised trials	serious[c]	not serious	serious[a]	very serious[d]	none	0/19 (0.0%)	0/18 (0.0%)	not estimable	**0 fewer per 1,000** (from 100 fewer to 100 more)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded due to population indirectness (mixed B12 deficiency cause)

b. Downgraded by 1 increment if the confidence interval overlapped one MID and 2 increments if the confidence interval overlapped both MIDs

c. Downgraded by 1 increment due to bias arising from measurement of the outcome

d. Downgraded due to zero events and small sample size (no imprecision: sample size >350, serious imprecision: sample size >70 ≤350, very serious imprecision: sample size <70)

F.1.4 Oral Cyanocobalamin 100mcg vs 250mcg

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cyanocobalamin 100mcg	250mcg	Relative (95% CI)	Absolute (95% CI)		
Haematological values at ≤3 months (B12, pmol/L, change scores, higher is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cyanocobalamin 100mcg	250mcg	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	24	25	-	MD **20 pmol/L lower** (64.58 lower to 24.58 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at >3 months (B12, pmol/L, change scores, higher is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	24	25	-	MD **24 pmol/L lower** (88.87 lower to 40.87 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at ≤3 months (holoTC, pmol/L, change scores, higher is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	24	25	-	MD **14 pmol/L lower** (26.76 lower to 1.24 lower)	⨁◯◯◯ Very low	CRITICAL
Haematological values at >3 months (holoTC, pmol/L, change scores, higher is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	24	25	-	MD **20 pmol/L lower** (34.82 lower to 5.18 lower)	⨁◯◯◯ Very low	CRITICAL
Haematological values at ≤3 months (Hcy, µmol/L, change scores, lower is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	24	25	-	MD **0.5 µmol/L higher** (0.27 lower to 1.27 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at >3 months (Hcy, µmol/L, change scores, lower is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	24	25	-	MD **0.7 µmol/L higher** (0.51 lower to 1.91 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at ≤3 months (MMA, µmol/L, change scores, lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cyanocobalamin 100mcg	250mcg	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	24	25	-	MD **0.04 µmol/L higher** (0.05 lower to 0.13 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at >3 months (MMA, µmol/L, change scores, lower is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	24	25	-	MD **0.06 µmol/L higher** (0.04 lower to 0.16 higher)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by 1 increment due to bias arising from the randomisation process

b. Downgraded due to population indirectness (mixed B12 deficiency cause)

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes)

F.1.5 Oral Cyanocobalamin 100mcg vs 500mcg

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cyanocobalamin 100mcg	500mcg	Relative (95% CI)	Absolute (95% CI)		
Haematological values at ≤3 months (B12, pmol/L, change scores, higher is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	24	22	-	MD **74 pmol/L lower** (126.87 lower to 21.13 lower)	⨁◯◯◯ Very low	CRITICAL
Haematological values at >3 months (B12, pmol/L, change scores, higher is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cyanocobalamin 100mcg	500mcg	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	24	21	-	MD **83 pmol/L lower** (160.55 lower to 5.45 lower)	⨁◯◯◯ Very low	CRITICAL
Haematological values at ≤3 months (holoTC, pmol/L, change scores, higher is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	24	22	-	MD **23 pmol/L lower** (35.71 lower to 10.29 lower)	⨁◯◯◯ Very low	CRITICAL
Haematological values at >3 months (holoTC, pmol/L, change scores, higher is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	not serious	none	24	21	-	MD **32 pmol/L lower** (46.02 lower to 17.98 lower)	⨁⨁◯◯ Low	CRITICAL
Haematological values at ≤3 months (Hcy, µmol/L, change scores, lower is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	24	22	-	MD **1.4 µmol/L higher** (0.47 higher to 2.33 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at >3 months (Hcy, µmol/L, change scores, lower is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	24	21	-	MD **1.7 µmol/L higher** (0.56 higher to 2.84 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at ≤3 months (MMA, µmol/L, change scores, lower is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	24	22	-	MD **0.13 µmol/L higher** (0.02 lower to 0.28 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at >3 months (MMA, µmol/L, change scores, lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cyanocobalamin 100mcg	500mcg	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	24	21	-	MD **0.15 µmol/L higher** (0 to 0.3 higher)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by 1 increment due to bias arising from the randomisation process

b. Downgraded due to population indirectness (mixed B12 deficiency cause)

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes)

F.1.6 Oral Cyanocobalamin 100mcg vs 1000mcg

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cyanocobalamin 100mcg	1000mcg	Relative (95% CI)	Absolute (95% CI)		
Haematological values at ≤3 months (B12, pmol/L, change scores, higher is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	not serious	none	24	25	-	MD **140 pmol/L lower** (209.34 lower to 70.66 lower)	⨁⨁◯◯ Low	CRITICAL
Haematological values at ≤3 months (holoTC, pmol/L, change scores, higher is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	not serious	none	24	25	-	MD **41 pmol/L lower** (55.23 lower to 26.77 lower)	⨁⨁◯◯ Low	CRITICAL
Haematological values at >3 months (holoTC, pmol/L, change scores, higher is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	not serious	none	24	25	-	MD **45 pmol/L lower** (59.82 lower to 30.18 lower)	⨁⨁◯◯ Low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cyanocobalamin 100mcg	1000mcg	Relative (95% CI)	Absolute (95% CI)		
Haematological values at ≤3 months (Hcy, µmol/L, change scores, lower is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	not serious	none	24	25	-	MD **4.6 µmol/L higher** (1.3 lower to 10.5 higher)	⨁⨁◯◯ Low	CRITICAL
Haematological values at >3 months (Hcy, µmol/L, change scores, lower is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	24	25	-	MD **5 µmol/L higher** (2.07 lower to 12.07 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at ≤3 months (MMA, µmol/L, change scores, lower is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	24	25	-	MD **0.22 µmol/L higher** (0.14 lower to 0.58 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at >3 months (MMA, µmol/L, change scores, lower is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	24	25	-	MD **0.26 µmol/L higher** (0.12 lower to 0.64 higher)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by 1 increment due to bias arising from the randomisation process

b. Downgraded due to population indirectness (mixed B12 deficiency cause)

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes)

F.1.7 Oral Cyanocobalamin 250mcg vs 500mcg

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cyanocobalamin 250mcg	500mcg	Relative (95% CI)	Absolute (95% CI)		
Haematological values at ≤3 months (B12, pmol/L, change scores, higher is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	25	22	-	MD **54 pmol/L lower** (102.22 lower to 5.78 lower)	⨁◯◯◯ Very low	CRITICAL
Haematological values at >3 months (B12, pmol/L, change scores, higher is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	25	21	-	MD **59 pmol/L lower** (129.62 lower to 11.62 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at ≤3 months (holoTC, pmol/L, change scores, higher is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	25	22	-	MD **9 pmol/L lower** (22.38 lower to 4.38 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at >3 months (holoTC, pmol/L, change scores, higher is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	25	21	-	MD **12 pmol/L lower** (27.39 lower to 3.39 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at ≤3 months (Hcy, µmol/L, change scores, lower is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	25	22	-	MD **0.9 µmol/L higher** (0.18 lower to 1.98 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at >3 months (Hcy, µmol/L, change scores, lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cyanocobalamin 250mcg	500mcg	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	25	21	-	MD **1 µmol/L higher** (0.27 lower to 2.27 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at ≤3 months (MMA, µmol/L, change scores, lower is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	25	22	-	MD **0.09 µmol/L higher** (0.07 lower to 0.25 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at >3 months (MMA, µmol/L, change scores, lower is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	25	21	-	MD **0.09 µmol/L higher** (0.08 lower to 0.26 higher)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by 1 increment due to bias arising from the randomisation process

b. Downgraded due to population indirectness (mixed B12 deficiency cause)

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes)

F.1.8 Oral Cyanocobalamin 250mcg vs 1000mcg

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cyanocobalamin 250mcg	1000mcg	Relative (95% CI)	Absolute (95% CI)		
Haematological values at ≤3 months (B12, pmol/L, change scores, higher is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cyanocobalamin 250mcg	1000mcg	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	25	25	-	MD **120 pmol/L lower** (185.86 lower to 54.14 lower)	⨁◯◯◯ Very low	CRITICAL
Haematological values at ≤3 months (holoTC, pmol/L, change scores, higher is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	25	25	-	MD **27 pmol/L lower** (41.83 lower to 12.17 lower)	⨁◯◯◯ Very low	CRITICAL
Haematological values at >3 months (holoTC, pmol/L, change scores, higher is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	25	25	-	MD **25 pmol/L lower** (41.12 lower to 8.88 lower)	⨁◯◯◯ Very low	CRITICAL
Haematological values at ≤3 months (Hcy, µmol/L, change scores, lower is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	25	25	-	MD **4.1 µmol/L higher** (1.83 lower to 10.03 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at >3 months (Hcy, µmol/L, change scores, lower is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	25	25	-	MD **4.3 µmol/L higher** (2.79 lower to 11.39 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at ≤3 months (MMA, µmol/L, change scores, lower is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	25	25	-	MD **0.18 µmol/L higher** (0.19 lower to 0.55 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at >3 months (MMA, µmol/L, change scores, lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cyanocobalamin 250mcg	1000mcg	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	25	25	-	MD **0.2 µmol/L higher** (0.19 lower to 0.59 higher)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by 1 increment due to bias arising from the randomisation process

b. Downgraded due to population indirectness (mixed B12 deficiency cause)

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes)

F.1.9 Oral Cyanocobalamin 500mcg vs 1000mcg

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cyanocobalamin 500mcg	1000mcg	Relative (95% CI)	Absolute (95% CI)		
Haematological values at ≤3 months (B12, pmol/L, change scores, higher is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	22	25	-	MD **66 pmol/L lower** (137.74 lower to 5.74 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at ≤3 months (holoTC, pmol/L, change scores, higher is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	22	25	-	MD **18 pmol/L lower** (32.79 lower to 3.21 lower)	⨁◯◯◯ Very low	CRITICAL
Haematological values at >3 months (holoTC, pmol/L, change scores, higher is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cyanocobalamin 500mcg	1000mcg	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	21	25	-	MD **13 pmol/L lower** (28.39 lower to 2.39 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at ≤3 months (Hcy, µmol/L, change scores, lower is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	22	25	-	MD **3.2 µmol/L higher** (2.75 lower to 9.15 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at >3 months (Hcy, µmol/L, change scores, lower is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	21	25	-	MD **3.3 µmol/L higher** (3.78 lower to 10.38 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at ≤3 months (MMA, µmol/L, change scores, lower is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	22	25	-	MD **0.09 µmol/L higher** (0.3 lower to 0.48 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values at >3 months (MMA, µmol/L, change scores, lower is better)												
1	randomised trials	serious[a]	not serious	Serious[b]	Serious[c]	none	21	25	-	MD **0.11 µmol/L higher** (0.3 lower to 0.52 higher)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by 1 increment due to bias arising from the randomisation process

b. Downgraded due to population indirectness (mixed B12 deficiency cause)

c. Downgraded by 1 increment if the confidence interval crossed one MID and by 2 increments if the confidence interval crossed two MIDs (0.8 and 1.25 for dichotomous outcomes; 0.5 * median of baseline SD of the intervention and control group for continuous outcomes)

F.1.10 Oral Cyanocobalamin vs intramuscular cyanocobalamin

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral cyanocobalamin	intramuscular cyanocobalamin	Relative (95% CI)	Absolute (95% CI)		
Haematological values - B12 at >3 months (pg/mL, final values, higher is better)												
1	observational studies	very serious[a]	not serious	Very serious[b]	not serious	none	111	14	-	MD **451.5 pg/mL lower** (824.97 lower to 78.03 lower)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by 2 increments due to risk of bias arising from confounding, selection of participants into the study, classification of the interventions, deviations from the intended interventions, missing data and measurement of the outcome

b. Downgraded by 2 increments due to mixed causes of B12 deficiency and mixed treatment regimens

F.1.11 Intramuscular hydroxocobalamin (with loading dose) vs intramuscular hydroxocobalamin (no loading dose)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intramuscular hydroxocobalamin (loading dose)	intramuscular hydroxocobalamin (no loading dose)	Relative (95% CI)	Absolute (95% CI)		
Haematological values - B12 at <3 months (pmol/L, final values, higher is better)												
1	observational studies	very serious[a]	not serious	not serious	serious[b]	none	21	21	-	MD **217.4 pmol/L higher** (13.73 lower to 448.53 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values - MMA at <3 months (nmol/L, final values, lower is better)												
1	observational studies	very serious[a]	not serious	not serious	serious[b]	none	21	21	-	MD **100.6 nmol/L lower** (164.48 lower to 36.72 lower)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by 2 increments due to risk of bias arising from confounding and selection of participants into the study

b. Downgraded by 1 increment if the confidence interval crossed one MID and 2 increments if the confidence interval cross both MIDs

F.1.12 Intramuscular hydroxocobalamin (with loading dose) vs no treatment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intramuscular hydroxocobalamin (loading dose)	no treatment	Relative (95% CI)	Absolute (95% CI)		
Haematological values - B12 at <3 months (pmol/L, final values, higher is better)												
1	observational studies	very serious[a]	not serious	not serious	not serious	none	21	21	-	MD **288.9 pmol/L higher** (95 higher to 482.8 higher)	⨁⨁◯◯ Low	CRITICAL
Haematological values - MMA at <3 months (nmol/L, final values, lower is better)												
1	observational studies	very serious[a]	not serious	not serious	not serious	none	21	21	-	MD **333.2 nmol/L lower** (437.8 lower to 228.6 lower)	⨁⨁◯◯ Low	CRITICAL

a. Downgraded by 2 increments due to risk of bias arising from confounding and selection of participants into the study

F.1.13 Intramuscular hydroxocobalamin (no loading dose) vs no treatment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intramuscular hydroxocobalamin (no loading dose)	no treatment	Relative (95% CI)	Absolute (95% CI)		
Haematological values - B12 at <3 months (pmol/L, final values, higher is better)												
1	observational studies	very serious[a]	not serious	not serious	serious[b]	none	21	21	-	MD **121.5 pmol/L higher** (6.33 lower to 249.33 higher)	⨁◯◯◯ Very low	CRITICAL
Haematological values - MMA at <3 months (nmol/L, final values, lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intramuscular hydroxocobalamin (no loading dose)	no treatment	Relative (95% CI)	Absolute (95% CI)		
1	observational studies	very serious[a]	not serious	not serious	not serious	none	21	21	-	MD **232.6 nmol/L lower** (348.78 lower to 116.42 lower)	⨁⨁◯◯ Low	CRITICAL

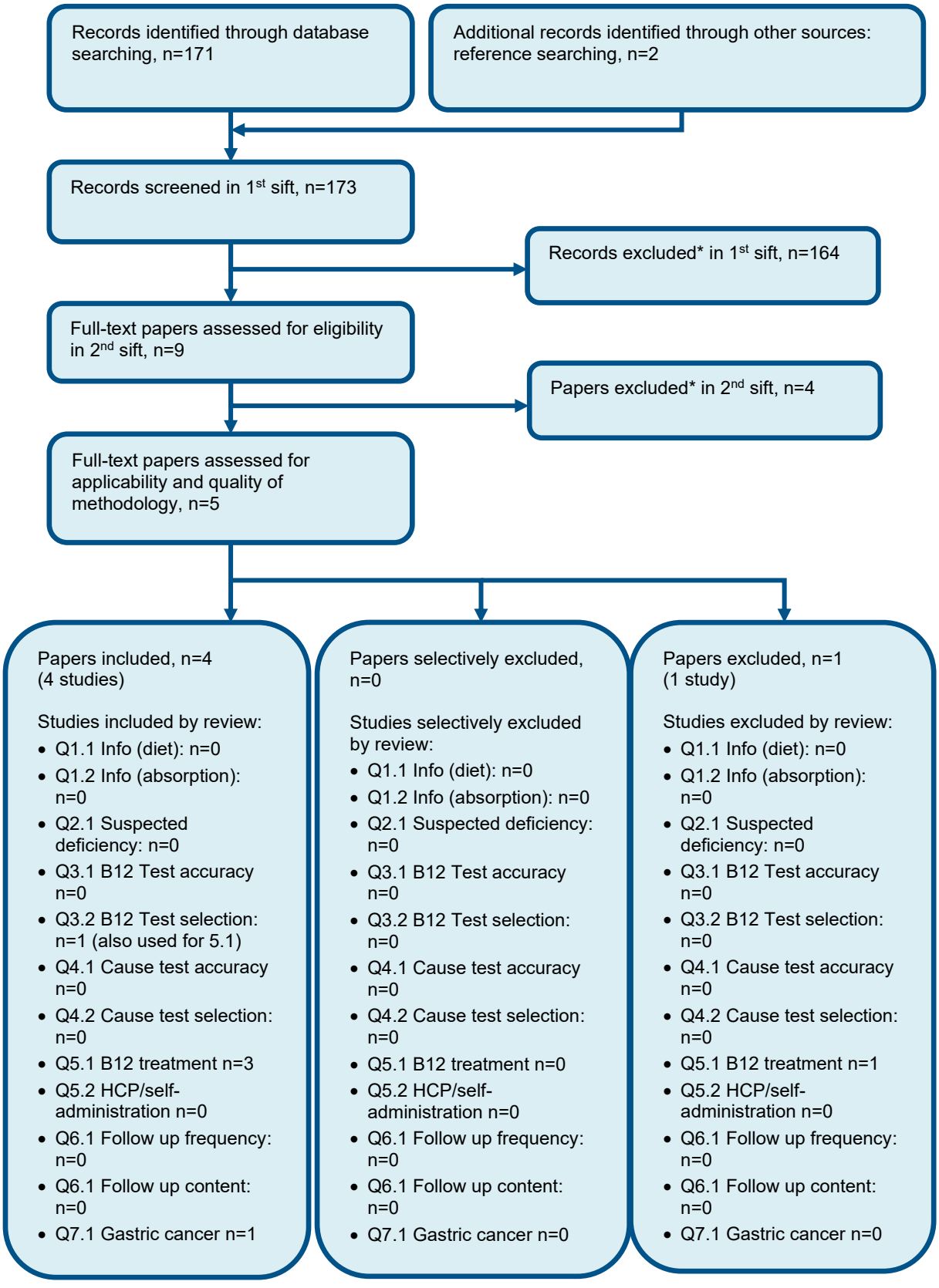
a. Downgraded by 2 increments due to risk of bias arising from confounding and selection of participants into the study

b. Downgraded by 1 increment if the confidence interval crossed one MID and 2 increments if the confidence interval crossed both MIDs

F.2 Self-administration

No GRADE tables.

Appendix G – Economic evidence study selection



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

Appendix H – Economic evidence tables

H.1 Vitamin B12 replacement

Study	Houle 2014[6]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-comparison analysis **Study design**: simple decision model **Approach to analysis:** RCT evidence was used to assume that IM and oral treatment were identical in effectiveness. Cost savings were estimated from switching people on IM treatment to oral **Perspective:** Canada, Ministry of Health **Time horizon/Follow-up** 5 years **Discounting:** Costs: 5%; Outcomes: N/A	**Population:** People that are 65 years and older currently receiving intramuscular vitamin B12 therapy **Cohort settings:** Start age: >65 Male: Not reported **Intervention 1:** B12 10ml vial for injection, 1ml/1000mcg administered once per month **Intervention 2:** B12 tablet (oral) 1000mcg, one tablet once daily	**Total costs (mean per patient):** Intervention 1: NR Intervention 2:NR Incremental (2−1): -£279 **Currency & cost year:** 2012 Canadian Dollars (presented here as 2012 UK pounds[(a)]) **Cost components incorporated:** Medication cost, dispensing fee of oral, fee for intramuscular administration (in pharmacy and in physician office), blood sampling cost (staff time), cost for laboratory test and laboratory processing cost, physician consultation cost,	N/A	N/A as no difference in outcomes Results indicate that by switching to oral there is a cost saving of £279 per patient over 5 years. **Analysis of uncertainty:** Sensitivity analysis results were presented for two parameters that were altered – discount rate and the additional physician visits in the i.m. group. Sensitivity analysis showed that the latter variable had a significant impact on the cost saving potential of the switch from intramuscular treatment to oral treatment. When there was an additional physician visit for 25% of people in the i.m. group, rather than the 10% (base case), there is £443 saving per patient. Although not reported in the tables, the author wrote that the cost saving was lower in year 1 when switching from intramuscular to oral treatment due to the additional laboratory monitoring. For the base case scenario, in the first year the saving reported by the authors were £27 per patient. From year 2 there is a £71 saving per patient per year.
Data sources				
Health outcomes: N/A. **Quality-of-life weights:** N/A. **Cost sources:** Drug manufacturers (oral cost), Alberta Ministry of Health (pharmacy fee, dispensing fee, co-pay fee), Alberta Health Drug Benefit list (medication cost), Alberta Health Services (laboratory costs)				
Comments				

Source of funding: NR **Limitations:** The study was conducted from a Canadian perspective. The B12 ingredient is not explicitly stated, if the intramuscular version is cyanocobalamin, this is not used in NHS primary care. There is no account of whether there may be any outcome differences or the direct impact on patients i.e., side effects/acceptability. Limited short term clinical evidence is used to estimate that the interventions are identical in terms of clinical effectiveness. The study incorporates costs of converting therapy which may not be directly applicable for example the increased blood test monitoring which doesn't routinely take place since the onset of COVID-19 whereby patients on parenteral have been converted to oral treatment with no increased initial monitoring. The price of oral B12 treatment is much lower than the current NHS drug tariff. For the cost of the oral treatment, this is assumed to be funded 70% by the patient therefore savings and model results may not be reflective of NHS savings and may change the outcome. **Other:**	
Overall applicability:(c) Partially applicable	**Overall quality:**(d) Potentially serious limitations

Abbreviations: NR= not reported; RCT= randomised controlled trial
(a) Converted using 2012 purchasing power parities[14]
(b) Directly applicable / Partially applicable / Not applicable
(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	**Mnatzaganian 2015[11]**			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Decision Tree **Approach to analysis:** Informed by the guidelines-supported management algorithm, a decision tree comparing five study strategies was developed. **Perspective:** Australia – Medicare **Time horizon:** 3 months **Discounting:**	**Population:** 18 years of age or older-newly presenting in general practice with fatigue whose symptoms could not be explained by medical assessment and who had a low pretest probability of serious illness. **Intervention 1:** Do not test and do no treat; if symptoms continue, reassess after a period of 3 months. **Intervention 2:** Order serum test and treat with i.m.	**Total costs (mean per patient):** Intervention 1: £65 Intervention 2: £136 Intervention 3: £113 Intervention 4: £221 Intervention 5: £127 **Incremental costs** Intervention 2 – 1 = £71 Intervention 3 – 2 = -£23 Intervention 4 – 3 = £108 Intervention 5 – 4 = -£94 **Currency & cost year:**	**QALYs (mean per patient):** Intervention 1: 0.69 Intervention 2: 0.70 Intervention 3: 0.70 Intervention 4: 0.71 Intervention 5: 0.71 **Incremental QALYs** Intervention 2 – 1 = 0.01 Intervention 3 – 2 = 0 Intervention 4 – 3 = 0.01 Intervention 5 – 4 = 0	Oral treatment was less costly in both cases compared to i.m. when patients undergo a test or if no test is conducted. There were no differences in QALYs thus oral treatment is the lower cost option compared to i.m. treatment. Probability Intervention 5 cost effective (£20K/£30K threshold): 100% **Analysis of uncertainty:** A pa was performed which included sensitivity and specificity of the diagnostic test, cost, and utility input parameter values. Further deterministic sensitivity analysis was done with varying the prevalence levels of cobalamin deficiency at 1%, 5% 10% and 20%. The sensitivity analyses PSA and

Costs: NA Outcomes: NA	Hydroxocobalamin (1,000 µg) nine injections. **Intervention 3:** Order serum test and treat with oral supplement (1,000 mcg) – one a day **Intervention 4:** No test, but treat all with i.m. **Intervention 5:** No test, but treat all with oral supplement	2013 USA dollars (presented here as 2013 UK pounds[(g)])] **Cost components incorporated:** GP-patient consultation fee, serum cobalamin test, Patient Episode Initiation (specimen) fees, medication costs, service costs for IM injections.		one – way, showed that at 1% prevalence the "do not test, do not treat" strategy was the most cost-effective. If prevalence was more than 1% not testing but treating all those presenting with unexplained fatigue with oral supplements was the most cost effective strategy.
Data sources				
Health outcomes: The sensitivity and specificity of the serum cobalamin test derived from SR and meta-analysis of studies (Willis et al., 2011). Effectiveness of medication – RCT/SR. **Quality-of-life weights:** EQ-5D utility score derived without using UK-tariff but using hypothetical state scenarios from an Australian perspective. **Cost sources:** Pharmaceutical Benefits Scheme fees, Medicare Australia				
Comments				
Source of funding: National Health and Medical Research Council of Australia **Limitations:** This study doesn't compare the different available diagnostic tests for B12 deficiency. However it focuses on diagnosis and intervention together using serum cobalamin testing with oral and i.m. treatment. The population of the study focused on patients presenting with fatigue; however fatigue is only one symptom indicative of B12 deficiency or pernicious anaemia so this study does not capture all potential B12 deficient patients. Only the first consultation was considered; all screening tests that could have been ordered—other than serum cobalamin—were not included in this economic evaluation. The cost of misdiagnosis/referral to specialists was not included which could have a significant impact of the cost-effectiveness. The UK tariff was not used for EQ-5D; The utility scores were derived using hypothetical state scenarios which may not be comparable to one obtained by using patient data. There is uncertainty regarding the baseline prevalence of B12 deficiency. In addition to that the time horizon of three months may not be adequate and the risk of recurrence of deficiency or symptoms after three months were not explored. **Other:**			
Overall applicability:[(a)] Partially applicable **Overall quality:**[(b)] Potentially serious limitations				

Abbreviations: CUA= cost–utility analysis; da= deterministic analysis; EQ-5D= Euroqol 5 dimensions (scale: 0.0 [death] to 1.0 [full health], negative values mean worse than death); NR= not reported; i.m.= intramuscular; mcg = microgram; pa= probabilistic analysis; QALYs= quality-adjusted life years

(a) Converted using [2013] purchasing power parities[14]
(b) Directly applicable / Partially applicable / Not applicable
(c) Minor limitations / Potentially serious limitations / Very serious limitations

Study	Vidal-Alaball 2006[18]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost-comparison analysis **Study design:** Deterministic decision analytic model **Approach to analysis:** •A cost-comparison analysis model based on RCT data assuming no difference in outcomes of treatment strategies. **Perspective:** UK NHS **Time horizon/Follow-up:** 2 years **Discounting:** Costs: 3.5%; Outcomes: n/a	**Population:** Patients currently on i.m. vitamin B12 treatment **Cohort settings:** Start age: NR Male: NR **Intervention 1:** Continue i.m. Hydroxocobalamin Dose - One every 3 months Strength – 1mg **Intervention 2:** Converting to Oral Cyanocobalamin tablets, Dose – One a day Strength – N/R	**Total costs (mean per patient):** Intervention 1: £111.98 Intervention 2: £161.1 Incremental (2−1): From Year 2: £49.12 **Currency & cost year:** 2006 UK sterling pounds **Cost components incorporated:** Medication cost, laboratory cost, GP/nursing time (for i.m.), conversion costs from i.m. to oral (assuming three additional physician visits and additional blood testing), syringe and needle (for i.m.).	N/A	Over the two-year time horizon of the study, continuing i.m. treatment was the the lowest cost and most cost effective strategy. **Analysis of uncertainty:** After the first year which incorporated conversion costs, oral treatment was less costly than i.m. so with a longer time horizon oral treatment would be the lower cost strategy. Sensitivity analysis showed that the variable ‘‘home visit’’ had the most significant impact on the results. After the conversion period, home visits only had an impact on the intramuscular regime. The authors found that even if there were no home visits required, oral treatment from year two was always less costly than intramuscular (£35.55 oral versus £55.99 i.m.) as there is less need for nursing time. If home visits are required the cost of i.m. rises too £99.99. For newly diagnosed patients that start on oral compared to i.m. the costs of conversion are not required and hence this strategy would cost less. No other sensitivity analysis reported.

Health outcomes: N/A **Quality-of-life weights:** n/a **Cost sources:** Medication: British National Formulary/internet/health shops. Clinician costs - estimated from practice income.

Comments

Source of funding: NR **Limitations**

The population in the evaluation were patients already prescribed i.m. B12 treatment. However, it is not clear whether the patients had B12 deficiency or pernicious anaemia. The time horizon within the study was two years which may be appropriate for patients with simple deficiency however it may not identify all the differences for patients with pernicious anaemia. One assumption within the study was that there is no outcome difference between the treatment types however the study notes that there is only limited evidence from two randomised trials to support this.

As the population within the study are currently receiving i.m. treatment, the comparison with oral treatment leads to additional conversion costs that would not be incurred if patients were initially started on oral. Furthermore, the conversion costs which may not be directly applicable as the regimen within the study has incorporated three additional blood tests which may not happen in usual practice and thus overestimate the conversion costs and therefore the strategy cost of the oral treatment. During COVID-19, patients that were switched from i.m. to oral were not generally recommended additional blood testing. Also, the costs of parenteral treatment may be overestimated as the model assumes only nurses undertake the injections however in some primary care settings Health Care Assistants may have a more prominent role in administering this medication rather than GPs/nurses and therefore this may reduce the estimated cost. Another pertinent point is that there is no mention of the strength or dosage of the oral treatment and therefore this may impact the suitability of the regimen as it may not be clinically suitable.

The sensitivity analysis is not exhaustive and not well reported, it is not clear which parameters have been explored during the sensitivity analysis.

There is no account of whether there may be any outcome differences or the direct impact on patients i.e., side effects/acceptability. Furthermore, there's an assumption that adherence is equal with both treatments. However, there would be suspicion that adherence of taking daily treatment may be lower than a treatment which is potentially booked via an appointment and received once every three months.

The authors state that they have used costs from online health shops which may not be suitable and also may not reflect the cost to the NHS. There are also other costs not stated but assumed to be expert opinion. The source of funding for the study is not reported.

Other:

Overall applicability:[a] Directly applicable **Overall quality:**[b] Potentially serious limitations

Abbreviations: NR= not reported; i.m.= intramuscular

(a) Directly applicable / Partially applicable / Not applicable

(b)*Minor limitations / Potentially serious limitations / Very serious limitations*

H.2 Self-administration

No economic evidence tables.

Appendix I – Excluded studies

I.1 Vitamin B12 replacement

Clinical studies

Table 27: Studies excluded from the clinical review

Study	Code [Reason]
Anand, S., Thomas, S., Jayachandra, M. et al. (2019) Effects of maternal B12 supplementation on neurophysiological outcomes in children: a study protocol for an extended follow-up from a placebo randomised control trial in Bangalore, India. BMJ Open 9(2): e024426	- study protocol
Andres, E., Affenberger, S., Vinzio, S. et al. (2005) Food-cobalamin malabsorption in elderly patients: clinical manifestations and treatment. American Journal of Medicine 118(10): 1154-9	- Data not reported in an extractable format
Andres, E., Affenberger, S., Zimmer, J. et al. (2006) Current hematological findings in cobalamin deficiency. A study of 201 consecutive patients with documented cobalamin deficiency. Clinical and Laboratory Haematology 28(1): 50-56	- Data not reported in an extractable format
Andres, E., Dali-Youcef, N., Vogel, T. et al. (2009) Oral cobalamin (vitamin B(12)) treatment. An update. International Journal of Laboratory Hematology 31(1): 1-8	- Systematic review used as source of primary studies
Andres, E.; Fothergill, H.; Mecili, M. (2010) Efficacy of oral cobalamin (vitamin B12) therapy. Expert Opinion on Pharmacotherapy 11(2): 249-56	- Systematic review used as source of primary studies
Andres, E., Kaltenbach, G., Noblet-Dick, M. et al. (2006) Hematological response to short-term oral cyanocobalamin therapy for the treatment of cobalamin deficiencies in elderly patients. Journal of Nutrition, Health & Aging 10(1): 3-6	- Full text paper not available
Andres, E., Kurtz, J. E., Perrin, A. E. et al. (2001) Oral cobalamin therapy for the treatment of patients with food-cobalamin malabsorption. American Journal of Medicine 111(2): 126-9	- Study design not relevant to this review protocol
Andres, E.; Noel, E.; Kaltenbach, G. (2004) P.o. versus i.m. cobalamin treatment in megaloblastic anemia. Clinical therapeutics 26(6): 936authorreply937	- Not a peer-reviewed publication
Andres, E., Perrin, A. E., Demangeat, C. et al. (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(4): 221-226	- Comparator in study does not match that specified in this review protocol
Andres, E., Vidal-Alaball, J., Federici, L. et al. (2007) Clinical aspects of cobalamin deficiency in elderly patients. Epidemiology, causes,	- Systematic review used as source of primary studies

Study	Code [Reason]
clinical manifestations, and treatment with special focus on oral cobalamin therapy. European Journal of Internal Medicine 18(6): 456-62	
Andres, E., Vogel, T., Federici, L. et al. (2008) Update on oral cyanocobalamin (vitamin B12) treatment in elderly patients. Drugs & Aging 25(11): 927-32	- Systematic review used as source of primary studies
Andres, E., Zulfiqar, A. A., Serraj, K. et al. (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. Journal of Clinical Medicine 7(10): 26	- Systematic review used as source of primary studies
Andres, E.; Zulfiqar, A. A.; Vogel, T. (2020) State of the art review: oral and nasal vitamin B12 therapy in the elderly. Qjm 113(1): 5-15	- No additional studies not identified in search included
Andrès, E., Loukili, N. H., Noel, E. et al. (2005) Effects of oral crystalline cyanocobalamin 1000 ug/d in the treatment of pernicious anemia: an open-label, prospective study in ten patients. Current Therapeutic Research 66(1): 13-22	- Comparator in study does not match that specified in this review protocol
Anonymous (2006) Oral as good as intramuscular vitamin B12 replacement. Journal of Family Practice 55(11): 940	- Duplicate reference
Anonymous (2006) Oral as good as IM vitamin B12 replacement. South African Family Practice 48(9): 12	- Systematic review used as source of primary studies
Arendt, J. F. H., Horvath-Puho, E., Sorensen, H. T. et al. (2021) Plasma Vitamin B12 Levels, High-Dose Vitamin B12 Treatment, and Risk of Dementia. Journal of Alzheimer's Disease 79(4): 1601-1612	- No outcomes relevant to this protocol
Arican, Pinar, Bozkurt, Oznur, Cavusoglu, Dilek et al. (2020) Various neurological symptoms with vitamin B12 deficiency and posttreatment evaluation. Journal of Pediatric Neurosciences 15(4): 365-369	- Study design not relevant to this review protocol
Baer, Janine and Peter, Mary St (2011) Vitamin b12 assessment and intervention in younger adult women. Journal for Nurse Practitioners 7(2): 117-122	- Full text paper not available
Bahadir, A.; Reis, P. G.; Erduran, E. (2014) Oral vitamin B12 treatment is effective for children with nutritional vitamin B12 deficiency. Journal of Paediatrics and Child Health 50(9): 721-725	- Study design not relevant to this review protocol
Bastrup-Madsen, P. and Paulsen, L. (1955) Oral treatment of megaloblastic anaemia with small amounts of vitamin B12 and intrinsic factor. Acta haematologica 13(4): 193-206	- Study design not relevant to this review protocol
Berlin, R., Berlin, H., Brante, G. et al. (1978) Vitamin B12 body stores during oral and parenteral treatment of pernicious anaemia. Acta Medica Scandinavica 204(1-2): 81-84	- Population not relevant to this review protocol
Bhowmik, B., Siddiquee, T., Mdala, I. et al. (2021) Vitamin D3 and B12 supplementation in	- Population not relevant to this review protocol

Study	Code [Reason]
pregnancy. Diabetes Research & Clinical Practice 174: 108728	
Bial, A. K. (2006) Review: Limited evidence from 2 randomised controlled trials suggests that oral and intramuscular vitamin B12 have similar effectiveness for vitamin B12 deficiency. Evidence Based Medicine 11(1): 9	- Systematic review used as source of primary studies
Bjorke-Monsen, A. L., Torsvik, I., Saetran, H. et al. (2008) Common metabolic profile in infants indicating impaired cobalamin status responds to cobalamin supplementation. Pediatrics 122(1): 83-91	- Population not relevant to this review protocol
Bjorkegren, K. and Svardsudd, K. (2004) A population-based intervention study on elevated serum levels of methylmalonic acid and total homocysteine in elderly people: Results after 36 months of follow-up. Journal of Internal Medicine 256(5): 446-452	- Population not relevant to this review protocol
Bjorkegren, K. and Svardsudd, K. (1999) Elevated serum levels of methylmalonic acid and homocysteine in elderly people. A population-based intervention study. Journal of Internal Medicine 246(3): 317-324	- Not a peer-reviewed publication
Blacher, J., Czernichow, S., Raphael, M. et al. (2007) Very low oral doses of vitamin B-12 increase serum concentrations in elderly subjects with food-bound vitamin B-12 malabsorption. Journal of Nutrition 137(2): 373-8	- Study does not contain an intervention relevant to this review protocol
Boddy, K., King, P., Mervyn, L. et al. (1968) Retention of cyanocobalamin, hydroxocobalamin, and coenzyme B12 after parenteral administration. Lancet 2(7570): 710-2	- Population not relevant to this review protocol
Bolaman, Z., Kadikoylu, G., Yukselen, V. et al. (2003) Oral versus intramuscular cobalamin treatment in megaloblastic anemia: a single-center, prospective, randomized, open-label study. Clinical Therapeutics 25(12): 3124-34	- Study does not contain an intervention relevant to this review protocol
Bronstrup, A., Hages, M., Prinz-Langenohl, R. et al. (1998) Effects of folic acid and combinations of folic acid and vitamin B-12 on plasma homocysteine concentrations in healthy, young women. American Journal of Clinical Nutrition 68(5): 1104-10	- Population not relevant to this review protocol
Buccianti, G., Bamonti Catena, F., Patrosso, C. et al. (2001) Reduction of the homocysteine plasma concentration by intravenously administered folinic acid and vitamin B12 in uraemic patients on maintenance haemodialysis. American Journal of Nephrology 21(4): 294-299	- Study does not contain an intervention relevant to this review protocol
Butler, C. C., Vidal-Alaball, J., Cannings-John, R. et al. (2006) Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency: a systematic review of randomized controlled trials. Family Practice 23(3): 279-85	- Systematic review used as source of primary studies
Cameron, D. G.; Townsend, S. R.; English, A. (1954) Pernicious anaemia II: maintenance	- Population not relevant to this review protocol

Study	Code [Reason]
treatment with crystalline vitamin B12. Canadian medical association journal 70(4): 398-400	
Castelli, M. C., Wong, D. F., Friedman, K. et al. (2011) Pharmacokinetics of oral cyanocobalamin formulated with sodium N-[8-(2-hydroxybenzoyl)amino]caprylate (SNAC): an open-label, randomized, single-dose, parallel-group study in healthy male subjects. Clinical Therapeutics 33(7): 934-45	- Population not relevant to this review protocol
Chalmers, J. N. and Hall, Z. M. (1954) Treatment of pernicious anaemia with oral vitamin B12 without known source of intrinsic factor. British medical journal 1(4872): 1179-1181	- Study design not relevant to this review protocol
Chalmers, J. N. and Shinton, N. K. (1965) Comparison of hydroxocobalamin and cyanocobalamin in the treatment of pernicious anaemia. Lancet 2(7426): 1305-8	- Study design not relevant to this review protocol
Chan, C. Q.; Low, L. L.; Lee, K. H. (2016) Oral Vitamin B12 Replacement for the Treatment of Pernicious Anemia. Frontiers in Medicine 3: 38	- No additional studies not identified in search included
Chan, J. C., Liu, H. S., Kho, B. C. et al. (2008) Longitudinal study of Chinese patients with pernicious anaemia. Postgraduate Medical Journal 84(998): 644-50	- Comparator in study does not match that specified in this review protocol
Chandelia, S., Chandra, J., Narayan, S. et al. (2012) Addition of cobalamin to iron and folic acid improves hemoglobin rise in nutritional anemia. Indian Journal of Pediatrics 79(12): 1592-6	- Study does not contain an intervention relevant to this review protocol
Dahele, A. and Ghosh, S. (2001) Vitamin B12 deficiency in untreated celiac disease. American Journal of Gastroenterology 96(3): 745-50	- Population not relevant to this review protocol
Dangour, A. D., Allen, E., Clarke, R. et al. (2011) A randomised controlled trial investigating the effect of vitamin B12 supplementation on neurological function in healthy older people: the Older People and Enhanced Neurological function (OPEN) study protocol [ISRCTN54195799]. Nutrition Journal 10: 22	- study protocol
Dawson, D. W.; Lewis, M. J.; Wadsworth, L. D. (1975) Changes in erythroblast morphology as an index of response to cyanocobalamin in patients with megaloblastic anaemia. British Journal of Haematology 31(1): 77-85	- Study design not relevant to this review protocol
De La Fourniere, F., Ferry, M., Cnockaert, X. et al. (1997) Vitamin B12 deficiency and dementia: a multicenter epidemiologic and therapeutic study. Preliminary therapeutic trial. Semaine des hopitaux 73(56): 133-140	- Study not reported in English
De, L. F. F., Ferry, M., Cnockaert, X. et al. (1997) Vitamin B12 deficiency and dementia: a multicenter epidemiologic and therapeutic study. Preliminary therapeutic trial. DEFICIENCE EN VITAMINE B12 ET ETAT DEMENTIEL: ETUDE EPIDEMIOLOGIQUE MULTICENTRIQUE ET	- Duplicate reference

Study	Code [Reason]
THERAPEUTIQUE. ESSAI PRELIMINAIRE. Semaine des hopitaux 73(56): 133-140	
Devi, S., Mukhopadhyay, A., Dwarkanath, P. et al. (2017) Combined Vitamin B-12 and Balanced Protein-Energy Supplementation Affect Homocysteine Remethylation in the Methionine Cycle in Pregnant South Indian Women of Low Vitamin B-12 Status. Journal of Nutrition 147(6): 1094-1103	- Data not reported in an extractable format
Didangelos, T., Karlafti, E., Kotzakioulafi, E. et al. (2021) Vitamin B12 Supplementation in Diabetic Neuropathy: A 1-Year, Randomized, Double-Blind, Placebo-Controlled Trial. Nutrients 13(2): 27	- Study does not contain an intervention relevant to this review protocol
Duggan, C., Srinivasan, K., Thomas, T. et al. (2014) Vitamin B-12 supplementation during pregnancy and early lactation increases maternal, breast milk, and infant measures of vitamin B-12 status. Journal of Nutrition 144(5): 758-64	- Population not relevant to this review protocol
Favrat, B., Vaucher, P., Herzig, L. et al. (2011) Oral vitamin B12 for patients suspected of subtle cobalamin deficiency: a multicentre pragmatic randomised controlled trial. BMC Family Practice 12: 2	- Population not relevant to this review protocol
Finkelstein, J. L., Kurpad, A. V., Thomas, T. et al. (2017) Vitamin B12 status in pregnant women and their infants in South India. European Journal of Clinical Nutrition 71(9): 1046-1053	- Population not relevant to this review protocol
Glass, G. B.; Skeggs, H. R.; Lee, D. H. (1966) Hydroxocobalamin. V. Prolonged maintenance of high vitamin B12 blood levels following a short course of hydroxocobalamin injections. Blood 27(2): 234-41	- Study design not relevant to this review protocol
Gomollon, F., Gargallo, C. J., Munoz, J. F. et al. (2017) Oral cyanocobalamin is effective in the treatment of vitamin B12 deficiency in crohn's disease. Nutrients 9(3nopagination)	- Study design not relevant to this review protocol
Greibe, E., Mahalle, N., Bhide, V. et al. (2019) Effect of 8-week oral supplementation with 3-microg cyano-B12 or hydroxo-B12 in a vitamin B12-deficient population. European Journal of Nutrition 58(1): 261-270	- Study design not relevant to this review protocol
Greibe, E., Mahalle, N., Bhide, V. et al. (2018) Increase in circulating holotranscobalamin after oral administration of cyanocobalamin or hydroxocobalamin in healthy adults with low and normal cobalamin status. European Journal of Nutrition 57(8): 2847-2855	- Data not reported in an extractable format
Health Quality, Ontario (2013) Vitamin B12 and cognitive function: an evidence-based analysis. Ontario Health Technology Assessment Series 13(23): 1-45	- Systematic review used as source of primary studies

Study	Code [Reason]
Hemsted, E. H. and Mills, J. (1958) Vitamin B12 in pernicious anaemia: intramuscular or oral. Lancet 2(7060): 1302-1303	- Study design not relevant to this review protocol
Hill, M. H., Flatley, J. E., Barker, M. E. et al. (2013) A vitamin B-12 supplement of 500 mug/d for eight weeks does not normalize urinary methylmalonic acid or other biomarkers of vitamin B-12 status in elderly people with moderately poor vitamin B-12 status. Journal of Nutrition 143(2): 142-7	- No outcomes relevant to this protocol
Hoffer, L. J., Djahangirian, O., Bourgouin, P. E. et al. (2005) Comparative effects of hydroxocobalamin and cyanocobalamin on plasma homocysteine concentrations in end-stage renal disease. Metabolism: Clinical & Experimental 54(10): 1362-7	- Population not relevant to this review protocol
Hoffer, L. J., Saboohi, F., Golden, M. et al. (2005) Cobalamin dose regimen for maximum homocysteine reduction in end-stage renal disease. Metabolism: Clinical & Experimental 54(6): 835-40	- Population not relevant to this review protocol
Hughes, D., Elwood, P. C., Shinton, N. K. et al. (1970) Clinical trial of the effect of vitamin B12 in elderly subjects with low serum B12 levels. British Medical Journal 1(5707): 458-60	- No outcomes relevant to this protocol
Hvas, A. M.; Ellegaard, J.; Nexo, E. (2001) Vitamin B12 treatment normalizes metabolic markers but has limited clinical effect: a randomized placebo-controlled study. Clinical Chemistry 47(8): 1396-404	- Data not reported in an extractable format
Hvas, A. M., Juul, S., Lauritzen, L. et al. (2004) No effect of vitamin B-12 treatment on cognitive function and depression: a randomized placebo controlled study. Journal of Affective Disorders 81(3): 269-73	- Data not reported in an extractable format
Hvas, A. M., Juul, S., Nexo, E. et al. (2003) Vitamin B-12 treatment has limited effect on health-related quality of life among individuals with elevated plasma methylmalonic acid: a randomized placebo-controlled study. Journal of Internal Medicine 253(2): 146-52	- Data not reported in an extractable format
Hvas, A. M., Morkbak, A. L., Hardlei, T. F. et al. (2011) The vitamin B12 absorption test, CobaSorb, identifies patients not requiring vitamin B12 injection therapy. Scandinavian Journal of Clinical & Laboratory Investigation 71(5): 432-8	- Population not relevant to this review protocol
Kaltenbach, G., Andres, E., Barnier-Figue, G. et al. (2005) Dose of oral cobalamin therapy curing within one week low vitamin B12 levels in elderly patients. Presse medicale 34(5): 358-362	- Full text paper not available
Keche, Y. N.; Yegnanarayan, R.; Bhat, S. (2016) Effect of vitamin B12 supplementation on glycemic control in poorly controlled hyperhomocysteinemic type 2 diabetic patients. Bangladesh Journal of Pharmacology 11(1): 50-53	- No outcomes relevant to this protocol

Study	Code [Reason]
Killander, A. and Werner, I. (1968) Maintenance therapy of pernicious anaemia. Comparison of cyanocobalamin, hydroxocobalamin and a cyanocobalamin-zinc-tannate complex. Acta haematologica 40(6): 305-314	- Study design not relevant to this review protocol
Kim, H. I., Hyung, W. J., Song, K. J. et al. (2011) Oral vitamin B12 replacement: an effective treatment for vitamin B12 deficiency after total gastrectomy in gastric cancer patients. Annals of Surgical Oncology 18(13): 3711-7	- Study does not contain an intervention relevant to this review protocol
Kumaran, K., Yajnik, P., Lubree, H. et al. (2017) The Pune Rural Intervention in Young Adolescents (PRIYA) study: design and methods of a randomised controlled trial. BMC Nutrition 3: 41	- study protocol
Kvestad, I., Taneja, S., Kumar, T. et al. (2015) Vitamin B12 and Folic Acid Improve Gross Motor and Problem-Solving Skills in Young North Indian Children: a Randomized Placebo-Controlled Trial. PloS one 10(6): e0129915	- Population not relevant to this review protocol
Kwok, T., Chook, P., Qiao, M. et al. (2012) Vitamin B-12 supplementation improves arterial function in vegetarians with subnormal vitamin B-12 status. Journal of nutrition, health & aging 16(6): 569-573	- Study design not relevant to this review protocol
Kwok, T., Lee, J., Ma, R. C. et al. (2017) A randomized placebo controlled trial of vitamin B12 supplementation to prevent cognitive decline in older diabetic people with borderline low serum vitamin B12. Clinical Nutrition 36(6): 1509-1515	- Study does not contain an intervention relevant to this review protocol
Kwok, T., Tang, C., Woo, J. et al. (1998) Randomized trial of the effect of supplementation on the cognitive function of older people with subnormal cobalamin levels. International Journal of Geriatric Psychiatry 13(9): 611-6	- No outcomes relevant to this protocol
Lane, L. A. and Rojas-Fernandez, C. (2002) Treatment of vitamin b(12)-deficiency anemia: oral versus parenteral therapy. Annals of Pharmacotherapy 36(78): 1268-72	- Systematic review used as source of primary studies
Lee, M. K., Wong, P. K., Kung, K. et al. (2011) Review of vitamin B12 deficiency management in a family medicine clinic. Hong Kong Practitioner 33(2): 64-71	- Comparator in study does not match that specified in this review protocol
Limvorapitak, W. and Auewarakul, C. U. (2016) Clinical Features and Outcomes of Patients with Non-Iron Nutritional Deficiency Anemia in an In-Patient Setting at Siriraj Hospital: A 10-Year Retrospective Study. Journal of the Medical Association of Thailand 99(6): 637-44	- No outcomes relevant to this protocol
Lowenstein, L., Brunton, L., Shapiro, L. et al. (1957) Maintenance therapy of pernicious anaemia with oral administration of intrinsic factor and vitamin B12. Canadian medical association journal 77(10): 923-930	- Study does not contain an intervention relevant to this review protocol

Study	Code [Reason]
Lubis, Z., Hardinsyah, Hidayat, S. et al. (2018) Effect of vitamin B12 supplement on serum levels of vitamin B12 and memorizing ability on preschool children. International Journal of Pharmaceutical Sciences and Research 9(10): 4436-4440	- Population not relevant to this review protocol
Mahawar, K. K., Reid, A., Graham, Y. et al. (2018) Oral Vitamin B12 Supplementation After Roux-en-Y Gastric Bypass: a Systematic Review. Obesity Surgery 28(7): 1916-1923	- Population not relevant to this review protocol
Malouf, R and Areosa, Sastre A (2003) Vitamin B12 for cognition. Cochrane Database of Systematic Reviews	- Population not relevant to this review protocol
Markun, S., Gravestock, I., Jager, L. et al. (2021) Effects of Vitamin B12 Supplementation on Cognitive Function, Depressive Symptoms, and Fatigue: A Systematic Review, Meta-Analysis, and Meta-Regression. Nutrients 13(3): 12	- Population not relevant to this review protocol
Mearns, G. J., Koziol-McLain, J., Obolonkin, V. et al. (2014) Preventing vitamin B12 deficiency in South Asian women of childbearing age: a randomised controlled trial comparing an oral vitamin B12 supplement with B12 dietary advice. European Journal of Clinical Nutrition 68(8): 870-5	- Population not relevant to this review protocol
Miles, L. M., Allen, E., Clarke, R. et al. (2017) Impact of baseline vitamin B12 status on the effect of vitamin B12 supplementation on neurologic function in older people: secondary analysis of data from the OPEN randomised controlled trial. European journal of clinical nutrition 71(10): 1166-1172	- Secondary publication of an included study that does not provide any additional relevant information
Mulder, H. and Snelder, H. A. A. (1997) Vitamin B12 replacement and its effects on bone mass and bone markers in patients with osteoporosis associated with pernicious anaemia. Clinical Drug Investigation 14(5): 434-437	- Comparator in study does not match that specified in this review protocol
Nagpal, J., Mathur, M. R., Rawat, S. et al. (2020) Efficacy of maternal B12 supplementation in vegetarian women for improving infant neurodevelopment: protocol for the MATCOBIND multicentre, double-blind, randomised controlled trial. BMJ Open 10(5): e034987	- study protocol
Namikawa, Tsutomu, Maeda, Masahiro, Yokota, Keiichiro et al. (2021) Enteral Vitamin B12 Supplementation Is Effective for Improving Anemia in Patients Who Underwent Total Gastrectomy. Oncology 99(4): 225-233	- Study design not relevant to this review protocol
Orhan Kilic, B., Kilic, S., Sahin Eroglu, E. et al. (2021) Sublingual methylcobalamin treatment is as effective as intramuscular and peroral cyanocobalamin in children age 0-3 years. Hematology (United Kingdom) 26(1): 1013-1017	- Study does not contain an intervention relevant to this review protocol
Ozen, S.; Ozer, M. A.; Akdemir, M. O. (2017) Vitamin B12 deficiency evaluation and treatment	- Population not relevant to this review protocol

Study	Code [Reason]
in severe dry eye disease with neuropathic ocular pain. Graefes Archive for Clinical & Experimental Ophthalmology 255(6): 1173-1177	
Parry-Strong, A., Langdana, F., Haeusler, S. et al. (2016) Sublingual vitamin B12 compared to intramuscular injection in patients with type 2 diabetes treated with metformin: a randomised trial. New Zealand Medical Journal 129(1436): 67-75	- Study does not contain an intervention relevant to this review protocol
Rakshitha; Rao, G. M.; Saritha Kamath, U. (2020) Effect of vitamin b12 supplementation on neurologic and cognitive functions in older peoplea review. Biomedicine (India) 40(3): 264-266	- Systematic review used as source of primary studies
Ramos, Rafael Jacques, Mottin, Cláudio Corá, Alves, Leticia Biscaino et al. (2021) Vitamin B12 supplementation orally and intramuscularly in people with obesity undergoing gastric bypass. Obesity Research & Clinical Practice 15(2): 177-179	- Study design not relevant to this review protocol
Rhode, B. M., Tamim, H., Gilfix, B. M. et al. (1995) Treatment of vitamin B12 deficiency after gastric surgery for severe obesity. Obesity Surgery 5(2): 154-158	- Study design not relevant to this review protocol
Sanz-Cuesta, T., Escortell-Mayor, E., Cura-Gonzalez, I. et al. (2020) Oral versus intramuscular administration of vitamin B12 for vitamin B12 deficiency in primary care: a pragmatic, randomised, non-inferiority clinical trial (OB12). BMJ Open 10(8): e033687	- Study does not contain an intervention relevant to this review protocol
Sanz-Cuesta, T., Gonzalez-Escobar, P., Riesgo-Fuertes, R. et al. (2012) Oral versus intramuscular administration of vitamin B12 for the treatment of patients with vitamin B12 deficiency: a pragmatic, randomised, multicentre, non-inferiority clinical trial undertaken in the primary healthcare setting (Project OB12). BMC Public Health 12: 394	- study protocol
Saraswathy, A. R., Dutta, A., Simon, E. G. et al. (2012) Randomized open label trial comparing efficacy of oral versus intramuscular vitamin b12 supplementation for treatment of vitamin b12 deficiency. Gastroenterology 1(5supplement1): 216	- Conference abstract
Schijns, W., Homan, J., van der Meer, L. et al. (2018) Efficacy of oral compared with intramuscular vitamin B-12 supplementation after Roux-en-Y gastric bypass: a randomized controlled trial. American Journal of Clinical Nutrition 108(1): 6-12	- Study does not contain an intervention relevant to this review protocol
Schwartz, M.; Lous, P.; Meulengracht, E. (1958) Absorption of vitamin B12 in pernicious anaemia; defective absorption induced by prolonged oral treatment. Lancet 2(7058): 1200-1204	- Study design not relevant to this review protocol
Seal, E. C., Metz, J., Flicker, L. et al. (2002) A randomized, double-blind, placebo-controlled	- Study does not contain an intervention relevant to this review protocol

Study	Code [Reason]
study of oral vitamin B12 supplementation in older patients with subnormal or borderline serum vitamin B12 concentrations. Journal of the American Geriatrics Society 50(1): 146-51	
Seynabou, F., Fatou Samba Diago, N., Oulimata Diop, D. et al. (2016) Biermer anemia: Hematologic characteristics of 66 patients in a Clinical Hematology Unit at Senegal. Medecine et Sante Tropicales 26(4): 402-407	- Population not relevant to this review protocol Not all participants were B12 deficient
Sezer, R. G., Akoglu, H. A., Bozaykut, A. et al. (2018) Comparison of the efficacy of parenteral and oral treatment for nutritional vitamin B12 deficiency in children. Hematology (Amsterdam, Netherlands): 1-5	- Study design not relevant to this review protocol
Shahab-Ferdows, S., Anaya-Loyola, M. A., Vergara-Castaneda, H. et al. (2012) Vitamin B-12 supplementation of rural Mexican women changes biochemical vitamin B-12 status indicators but does not affect hematology or a bone turnover marker. Journal of Nutrition 142(10): 1881-7	- Population not relevant to this review protocol
Sil, A., Kumar, H., Mondal, R. D. et al. (2018) A randomized, open labeled study comparing the serum levels of cobalamin after three doses of 500 mcg vs. a single dose methylcobalamin of 1500 mcg in patients with peripheral neuropathy. The Korean journal of pain 31(3): 183-190	- Population not relevant to this review protocol
Singh, C., Kawatra, R., Gupta, J. et al. (2016) Therapeutic role of Vitamin B12 in patients of chronic tinnitus: A pilot study. Noise & Health 18(81): 93-7	- Population not relevant to this review protocol
Smelt, H. J.; Pouwels, S.; Smulders, J. F. (2017) Different Supplementation Regimes to Treat Perioperative Vitamin B12 Deficiencies in Bariatric Surgery: a Systematic Review. Obesity Surgery 27(1): 254-262	- Systematic review used as source of primary studies
Smelt, H. J., Smulders, J. F., Said, M. et al. (2016) Improving Bariatric Patient Aftercare Outcome by Improved Detection of a Functional Vitamin B12 Deficiency. Obesity Surgery 26(7): 1500-4	- Population not relevant to this review protocol
Solomon, L. R. (2016) Vitamin B12-responsive neuropathies: A case series. Nutritional Neuroscience 19(4): 162-8	- Study design not relevant to this review protocol No comparison between B12 administration routes
Srinivasan, K., Thomas, S., Anand, S. et al. (2020) Vitamin B-12 Supplementation during Pregnancy and Early Lactation Does Not Affect Neurophysiologic Outcomes in Children Aged 6 Years. Journal of Nutrition 150(7): 1951-1957	- Population not relevant to this review protocol
Srinivasan, K., Thomas, T., Kapanee, A. R. et al. (2017) Effects of maternal vitamin B12 supplementation on early infant neurocognitive outcomes: a randomized controlled clinical trial. Maternal & Child Nutrition 13(2): 04	- Population not relevant to this review protocol

Study	Code [Reason]
Stabler, S. P., Allen, R. H., Dolce, E. T. et al. (2006) Elevated serum S-adenosylhomocysteine in cobalamin-deficient elderly and response to treatment. American Journal of Clinical Nutrition 84(6): 1422-9	- Study design not relevant to this review protocol
Strand, T. A., Ulak, M., Chandyo, R. K. et al. (2017) The effect of vitamin B12 supplementation in Nepalese infants on growth and development: study protocol for a randomized controlled trial. Trials 18(1nopagination)	- study protocol
Syed, E. U.; Wasay, M.; Awan, S. (2013) Vitamin B12 supplementation in treating major depressive disorder: a randomized controlled trial. The Open Neurology Journal 7: 44-8	- Population not relevant to this review protocol
Sánchez, H., Albala, C., Lera, L. et al. (2011) Comparison of two modes of vitamin B12 supplementation on neuroconduction and cognitive function among older people living in Santiago, Chile: a cluster randomized controlled trial. a study protocol. Nutrition journal 10: 100	- study protocol
Tayebi, A., Biniaz, V., Savari, S. et al. (2016) Effect of Vitamin B12 supplementation on serum homocysteine in patients undergoing hemodialysis: A randomized controlled trial. Saudi Journal of Kidney Diseases & Transplantation 27(2): 256-62	- Study does not contain an intervention relevant to this review protocol
Thompson, R. B.; Ashby, D. W.; Armstrong, E. (1962) Long-term trial of oral vitamin B12 in pernicious anaemia. Lancet 2(7256): 577-9	- Study design not relevant to this review protocol
Torsvik, I. K., Ueland, P. M., Markestad, T. et al. (2015) Motor development related to duration of exclusive breastfeeding, B vitamin status and B12 supplementation in infants with a birth weight between 2000-3000 g, results from a randomized intervention trial. BMC Pediatrics 15: 218	- Population not relevant to this review protocol
Torsvik, I. K., Ueland, P. M., Markestad, T. et al. (2015) Motor development related to duration of exclusive breastfeeding, B vitamin status and B12 supplementation in infants with a birth weight between 2000-3000 g, results from a randomized intervention trials. BMC Pediatrics 15(1)	- Duplicate reference
Torsvik, I., Ueland, P. M., Markestad, T. et al. (2013) Cobalamin supplementation improves motor development and regurgitations in infants: results from a randomized intervention study. American Journal of Clinical Nutrition 98(5): 1233-40	- Population not relevant to this review protocol
van Asselt, D. Z., Pasman, J. W., van Lier, H. J. et al. (2001) Cobalamin supplementation improves cognitive and cerebral function in older, cobalamin-deficient persons. Journals of Gerontology Series A-Biological Sciences & Medical Sciences 56(12): M775-9	- Study design not relevant to this review protocol

Study	Code [Reason]
van Dyck, C. H., Lyness, J. M., Rohrbaugh, R. M. et al. (2009) Cognitive and psychiatric effects of vitamin B12 replacement in dementia with low serum B12 levels: a nursing home study. International Psychogeriatrics 21(1): 138-47	- Study design not relevant to this review protocol
Vidal-Alaball, J., Butler, C. C., Cannings-John, R. et al. (2005) Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. Cochrane Database of Systematic Reviews: cd004655	- Systematic review used as source of primary studies
Wang, H, Li, L, Qin, Ll et al. (2018) Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. Cochrane Database of Systematic Reviews	- Population not relevant to this review protocol
Williams, J. A.; Baume, P. E.; Meynell, M. J. (1966) Partial gastrectomy: the value of permanent vitamin-B-12 therapy. Lancet 1(7433): 342-4	- Study design not relevant to this review protocol
Withey, J. L.; Jones, J. H.; Kilpatrick, G. S. (1963) Long-term trial of oral treatment of pernicious anaemia with vitamin-B12-peptide. British Medical Journal 1(5345): 1583-5	- Study design not relevant to this review protocol
Yajnik, C. S., Behere, R. V., Bhat, D. S. et al. (2019) A physiological dose of oral Vitamin B-12 improves hematological, biochemical-metabolic indices and peripheral nerve function in B-12 deficient Indian adolescent women. PLoS ONE 14(10)	- Comparator in study does not match that specified in this review protocol
Yajnik, C. S., Lubree, H. G., Thuse, N. V. et al. (2007) Oral vitamin B12 supplementation reduces plasma total homocysteine concentration in women in India. Asia Pacific Journal of Clinical Nutrition 16(1): 103-9	- Population not relevant to this review protocol
Zaqqa, M. Q., Ismail, Y. A., Khatib, A. M. et al. (2005) Effect of oral mecobalamin treatment on chest pain in patients with cobalamin deficiency and no evidence of coronary artery disease. A randomized, placebo-controlled trial. Saudi Medical Journal 26(7): 1144-5	- Study does not contain an intervention relevant to this review protocol
Zec, M., Roje, D., Matovinovic, M. et al. (2020) Vitamin B12 Supplementation in Addition to Folic Acid and Iron Improves Hematological and Biochemical Markers in Pregnancy: A Randomized Controlled Trial. Journal of Medicinal Food 23(10): 1054-1059	- Population not relevant to this review protocol

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2006 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 28: Studies excluded from the health economic review

Reference	Reason for exclusion
Masucci L, Goeree R. (2013) Vitamin B12 intramuscular injections versus oral supplements: a budget impact analysis. Ontario Health Technology Assessment Series. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3874775/pdf	Excluded as rated very serious limitations due to omitting the cost of oral B12 treatment whilst only reporting the cost of parenteral treatment only. Also partially applicable, reasons include: Canadian setting may not reflect current NHS context.

I.2 Self-administration

Clinical studies

No excluded studies.

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2006 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

None

Appendix J – Research recommendations – full details

J.1 Research recommendation

What is the clinical and cost effectiveness of vitamin B12 replacement for vitamin B12 deficiency, including the dose, frequency and route of administration?

J.1.1 Why this is important

Evidence for treatment efficacy was limited to mostly haematological outcomes, with little evidence on the effects of different treatment strategies on quality of life, or other patient-reported outcomes. Given the limited utility of haematological values, there is a need for further research on the optimal treatment strategy for different causes of deficiency, particularly focussing on patient reported outcomes.

J.1.2 Rationale for research recommendation

Importance to 'patients' or the population	If the most effective treatment strategies for different causes of vitamin B12 deficiency were determined, they could be offered to patients. This would lead to improved outcomes for people with diagnosed vitamin B12 deficiency.
Relevance to NICE guidance	Optimal treatment strategy for vitamin B12 deficiency was reviewed in this guideline and there is a lack of data on patient reported outcomes and for different causes of vitamin B12 deficiency. Further research would inform future guideline updates.
Relevance to the NHS	The outcome would affect the types of treatment for vitamin B12 deficiency provided by the NHS.
National priorities	Not applicable
Current evidence base	Minimal data on patient reported outcomes and by cause of vitamin B12 deficiency.
Equality considerations	None known

J.1.3 Modified PICO table

Population	People with diagnosed vitamin B12 deficiency. Stratify by: • Cause (dietary/non-dietary/nitrous oxide induced/other drug-induced)

Intervention	Vitamin B12 replacement:
	• Hydroxocobalamin
	  ○ Intramuscular injection
	  ○ Subcutaneous injection
	• Cyanocobalamin
	  ○ Oral tablets
	  ○ Intramuscular injection
	  ○ Subcutaneous injection
	• Combinations and sequences of the interventions above
	
	Stratify by:

	• Dosage • Frequency • Duration
Comparator	• Each other (any differences in drug, route of administration, dosage, frequency, or duration) • Dietary advice (for dietary causes) • Changing drug treatment (for drug-induced causes)

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

Study design	Randomised controlled trial
Timeframe	Time point: short term (up to 3 months), long term (over 3 months)
Additional information	Whilst haematological values are relatively easy outcomes to measure and are useful in providing objective measures of efficacy, they have limitations and should therefore be measured and interpreted alongside patient reported outcomes such as quality of life and symptom measures.

J.2 Research recommendation

What is the clinical and cost effectiveness of self-administration of vitamin B12 replacement injections for deficiency compared with administration by a healthcare professional?

J.2.1 Why this is important

No evidence was identified on the effectiveness of self-administration of intramuscular or subcutaneous vitamin B12 replacement. Many people with vitamin B12 deficiency self-administered their B12 injections during the COVID pandemic. Self-administered injections

may be more cost effective than injections given by a healthcare professional, but it is unclear if this is suitable for all people with vitamin B12 deficiency. It is also unclear whether subcutaneous injections are as effective and safe as intramuscular injections.

J.2.2 Rationale for research recommendation

Importance to 'patients' or the population	If self-administration of intramuscular or subcutaneous vitamin B12 injections is found to be as clinically effective and safe as healthcare professional administration, people may be given the option to self-administer their treatment. For some people, this would be the preferable option.
Relevance to NICE guidance	Research would inform future updates of this guideline.
Relevance to the NHS	The outcome would affect the availability of self-administered injections as treatment for vitamin B12 deficiency provided by the NHS. This could potentially be cost saving as it would reduce the number of appointments with a healthcare professional needed to administer the injections.
National priorities	Not applicable
Current evidence base	No evidence was identified on the effectiveness of self-administration of vitamin B12 replacement.
Equality considerations	The research recommendation addresses inequalities related to age and disability. It is recommended that those with physical or mental barriers to self-administration such as older age or learning disabilities are studied separately because they are more likely to require help with administration from a carer or family member. There may be differences in patient experience of the intervention and adherence.

J.2.3 Modified PICO table

Population	People with diagnosed vitamin B12 deficiency. Stratify by: • physical/mental barriers to self-administration (people with barriers and people without barriers) • newly diagnosed or established treatment
Intervention	Self-administration (including family/carer administration) of vitamin B12 replacement injections: • Hydroxocobalamin intramuscular injection • Hydroxocobalamin subcutaneous injection • Cyanocobalamin intramuscular injection • Cyanocobalamin subcutaneous injection

Comparator	Healthcare professional administration of vitamin B12 replacement injections: • Hydroxocobalamin intramuscular injection • Hydroxocobalamin subcutaneous injection • Cyanocobalamin intramuscular injection • Cyanocobalamin subcutaneous injection
Outcome	• quality of life (such as EQ5D, SF36) • patient-reported outcomes (PROM scores including some/all symptoms): o fatigue o sleep o peripheral neuropathy o cognition o psychiatric symptoms o pain • haematological values • complications and adverse events o mortality o bleeds o self-harm o nerve damage o frailty/falls o severe cognitive effects o postural hypotension • adherence to treatment • school/education/work absence
Study design	Randomised controlled trial
Timeframe	Time point: short term (up to 3 months), long term (over 3 months)
Additional information	Whilst haematological values are relatively easy outcomes to measure and are useful in providing objective measures of efficacy, they have limitations and should therefore be measured and interpreted alongside patient reported outcomes such as quality of life and symptom measures.