

1 **Development of a Vitamin B12 deficiency Patient-Reported Outcome**

2 **Measure for clinical practice and research**

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16 **Abstract**

17 **Background:** It is difficult to recognise vitamin B12 deficiency and to evaluate the effect of

18 B12 treatment due to a broad range of variable clinical symptoms overlapping with other

19 diseases and diagnostic biomarkers that quickly normalise during treatment. This poses a risk

20 of delay in diagnosis and a challenge to uniformly monitor the effect of B12 treatment. There

21 is a need for a new clinical outcome measure suitable for clinical practice and clinical

22 evaluation studies.

23 **Objective:** To develop a Patient-Reported Outcome Measure (PROM) which measures the

24 severity of vitamin B12 deficiency symptoms.

25 **Methods:** The B12 PROM was developed by (1) gathering input from experts and literature

26 review to define a construct and develop a conceptual model, (2) reviewing the literature and
27 processing input from health care providers, scientists, and patients to develop items and
28 response options, and (3) improving items based on the feedback from laypersons, test
29 interviews, semi-structured cognitive interviews with patients, and forward and backward
30 translation.

31 **Results:** The B12 PROM includes 62 items grouped into eight categories of symptoms
32 related to vitamin B12 deficiency (General, Senses, Thinking, In limbs and/or face,
33 Movement, Emotions, Mouth & Abdomen, Urinary tract & Reproductive organs). Cognitive
34 interviews demonstrated good comprehensibility and comprehensiveness.

35 **Conclusions:** This study is the first step in the development of a disease-specific PROM for
36 vitamin B12 deficiency to measure the burden of symptoms. Further validation and reliability
37 testing are necessary before the PROM can be applied in clinical practice and research.

38

39 **Keywords**

40 Vitamin B12 deficiency, Patient-Reported Outcome Measure, PROM, questionnaire,
41 symptom score, clinical outcome measure, patient monitoring tool, severity of symptoms,
42 symptom burden, diagnosis, evaluation of treatment, cognitive interviews, content validity,
43 qualitative study

44

45 **Introduction**

46 Vitamin B12 deficiency requires early diagnosis and adequate treatment to prevent
47 permanent neurological damage.¹ As B12 deficiency leads to a broad range of variable
48 clinical symptoms^{2,3} and symptoms overlap with other diseases⁴, it is challenging to
49 recognise and monitor this disease. To our knowledge, there is no unequivocal measure to
50 recognise and monitor the symptoms of vitamin B12 deficiency. This poses a risk of delay in
51 diagnosis and a challenge to uniformly evaluate the effect of B12 treatment.

52 In the absence of an appropriate clinical outcome measure of vitamin B12 deficiency, there
53 are few published clinical trials that measure the clinical effects of vitamin B12 deficiency
54 treatment in patients. Most clinical trials focus on biochemical outcome measures as primary
55 outcomes, such as the normalisation of diagnostic biomarkers. However, diagnostic
56 biomarkers in the blood may quickly normalise during treatment^{5,6} while patients still
57 experience B12-related symptoms. The few trials that evaluated the effect of B12 therapy on
58 symptoms only evaluated a narrow range of symptoms without using a validated outcome
59 measure.⁷⁻¹⁰

60 To improve the identification and monitoring of patients with symptoms of B12 deficiency,
61 we aim to develop and validate a novel Patient-Reported Outcome Measure (PROM) specific
62 to vitamin B12 deficiency which is suitable for clinical practice and clinical evaluation
63 studies. A PROM is “a measurement based on a report that comes directly from the patient
64 about the status of a patient’s health condition without amendment or interpretation of the
65 patient’s response by a clinician or anyone else.”¹¹ The development of a PROM is a
66 continuous process of evaluating and adapting draft versions. In this study we developed the
67 construct of a novel PROM for vitamin B12 deficiency and assessed the content validity.

68

69 **Methods**

70 **Study Design**

71 Development of the B12 PROM followed the Rothrock guidance for developing a valid
72 PROM.¹² We developed the PROM in three phases: (1) Gathering input from experts and
73 literature review to define a construct and develop a conceptual model; (2) Development of
74 items and response options by reviewing the literature and processing input from health care
75 providers, scientists, and patients; (3) Item improvement by processing feedback from
76 laypersons, test interviews, semi-structured cognitive interviews with patients, and forward
77 and backward translation. All methodological decisions and versions of the B12 PROM have
78 been approved by consensus meetings in the steering board committee [KS, JV, CP].

79 *Gathering input*

80 The definition of the construct was based on answering three questions: “What do you want
81 to measure?”, “Which target population?”, and “What is the purpose?”.¹³ Researchers and
82 health care providers (n=9) provided their input to answer these questions. A literature search
83 was performed to search for existing PROMs on B12 deficiency. PROM experts (n=4) were
84 consulted to ask for advice on the usefulness of available generic PROMs to measure clinical
85 outcomes of B12 deficiency and the development of the construct and conceptual model of a
86 specific B12 PROM.

87 *Development of items and response options*

88 Item development was based on a literature review and expert opinions of health care
89 providers, scientists, and patients. The literature review was based on a literature search in
90 PubMed and Google Scholar [CP]. Search terms included Pernicious Anemia/Pernicious
91 Anaemia/Vitamin B12 deficiency and symptoms/complaints. Search results covered a time
92 frame from 1822 to 2016 and included clinical review papers, case studies, and patient
93 surveys. Snowball search methods were used until saturation of symptoms was reached.
94 Through multiple discussion rounds, the list of symptoms was reduced by (1) combining
95 related symptoms into one item, (2) discarding medical test results that are reported by health

96 care providers rather than patients, and (3) excluding symptoms that clinical experts regarded
97 as extremely rare [CP, KS, SH, JaV]. This resulted in B12 PROM version 1.

98 All five patient representatives, appointed by the B12 Institute in Rotterdam, were invited to
99 assess the acceptability and feasibility of the B12 PROM. All had received a diagnosis of
100 vitamin B12 deficiency themselves and/or within their family in combination with a career as
101 a health care provider or medical researcher. These patient representatives were invited to
102 two video focus group meetings to discuss the acceptability and feasibility of completing the
103 B12 PROM. The following subjects were discussed: (1) missing symptoms, (2) unnecessary
104 or unrecognisable symptoms, (3) the order of the symptoms, (4) comprehensibility, (5)
105 response options, and (6) the length of the questionnaire. The feedback was processed, and
106 this resulted in B12 PROM version 2. This version was discussed in a similar manner with
107 the head (n=1) of vitamin B12 deficiency patients' Facebook group ('B12 tekort, de vergeten
108 ziekte') with >16,000 members, who has extensive experience with social media platform
109 discussions on B12 deficiency. New items were included in B12 PROM version 3 if they
110 were recognised by at least two sources (literature, health care providers and/or patients) and
111 prioritised by the steering board committee as frequently reported symptoms among vitamin
112 B12 deficient patients.

113 *Item improvement*

114 Comprehensibility and readability of the B12 PROM were assessed by two laypersons
115 without B12 deficiency [KS], resulting in B12 PROM version 4. Content validity was
116 assessed by cognitive interviews with patients [KS]. A semi-structured interview guide was
117 prepared based on the International Society for Pharmacoeconomics and Outcomes Research
118 (ISPOR) PRO Good Research Practices Task Force Report.¹⁴ A test interview with one
119 layperson was performed to practice the think aloud method and probing method and identify
120 potential problems in the comprehensibility, acceptability, and feasibility of the interview
121 guide and B12 PROM. This feedback was used to improve the interview guide and create a

122 more plain and easy-to-read format of the B12 PROM. This resulted in B12 PROM version 5.
123 The test interview was repeated with the same layperson and the improved version of the
124 interview guide and B12 PROM, which revealed that all issues were resolved. The steering
125 board committee approved the interview guide and B12 PROM version 5 for initiating the
126 cognitive interviews.

127 B12 deficient patients from the B12 Institute (secondary care center) were recruited to
128 participate in the cognitive interviews. Purposive sampling was performed to ensure variation
129 in age, sex, highest completed level of education, duration of B12 symptoms, and duration of
130 B12 treatment. After receiving the participants' verbal consent, interviews were taken by a
131 trained researcher [KS] via video calls (Microsoft Teams™), and the audio was recorded. The
132 interviewer shared her screen such that each patient could see the B12 PROM with
133 instructions, response options, and items. Patients were asked to complete the B12 PROM
134 based on their own experience. The think aloud method and probing method were used
135 during the interview to assess the comprehensibility of the PROM.^{13,14} The interviewer asked
136 follow-up questions to further explore the understanding and solutions to improve the clarity
137 if a participant did not understand the instructions, response options and/or items.

138 Comprehensiveness of the B12 PROM was assessed by asking four questions: (1) Are there
139 any B12-related symptoms that have not been addressed in this questionnaire?; (2) How well
140 do you think this questionnaire covers your complaints?; (3) How would you rate this
141 questionnaire on a scale of 1 to 10? (1 is bad and 10 is excellent); (4) Do you consider this
142 questionnaire to be complete?

143 Data analysis and B12 PROM adjustments occurred after every four interviews. Audio
144 records were assessed, and the comprehensibility and comprehensiveness of the B12 PROM
145 were improved accordingly. Symptoms were added to the B12 PROM if missing symptoms
146 reported by patients were related to vitamin B12 deficiency in the literature. Recruitment of
147 participants for interviews continued until the steering board committee reached consensus

148 that saturation was achieved as no major improvements emerged from subsequent interview
149 rounds.

150 For use in future international studies, forward and backward translators translated the Dutch
151 B12 PROM emerging from the cognitive interviews into English based on the Guidelines for
152 the Process of Cross-Cultural Adaptation of Self-Report Measures.¹⁵ Minor changes in item
153 wording occurred in the final Dutch version of the B12 PROM based on the translators'
154 feedback.

155

156 **Results**

157 **Gathering input**

158 *Definition of the construct*

159 We want to measure how much burden adults (18 years of age and older) experience from
160 their vitamin B12 deficiency symptoms. We define symptom burden as a subjective measure
161 of the severity of symptoms. The aim of the PROM is screening and monitoring: (1) a
162 measurement instrument that can identify adults at risk of having a vitamin B12 deficiency by
163 providing a score that discriminates between adults with and without symptoms related to
164 vitamin B12 deficiency; (2) a measurement instrument to evaluate the effect of B12
165 deficiency treatment on symptoms related to vitamin B12 deficiency.

166 *Conceptual model*

167 No suitable clinical outcome measure was identified in the literature and experts concluded
168 no generic PROMs could be used as clinical outcome measure for vitamin B12 deficiency
169 because of the heterogeneous spectrum of symptoms related to vitamin B12 deficiency. The
170 need for a disease-specific PROM for vitamin B12 deficiency, which covers the broad range
171 of symptoms, was unanimously endorsed.

172 It was advised that the B12 PROM should be relatively short because vitamin B12 deficient

173 patients suffer from concentration problems and fatigue. Rather than covering all symptoms
174 related to vitamin B12 deficiency, it should include the most frequently reported symptoms
175 per body system involved in the clinical presentation of vitamin B12 deficiency. Furthermore,
176 it was decided to focus on adults because children and adolescents have different clinical
177 manifestations of vitamin B12 deficiency.¹⁶

178 **Development of items and response options**

179 The literature review resulted in a list of 118 symptoms related to vitamin B12 deficiency.
180 This list of symptoms was converted to a list of 37 items with 5 response options (B12
181 PROM version 1). For example, “*Difficulty falling asleep*” and “*Trouble staying asleep*” have
182 been combined into “*Problems with sleeping*”, and the items “*Abnormal reflexes*”, “*Romberg*
183 *sign*”, “*Babinski sign*”, “*Paranoia*”, and “*Osteoporosis*” have been removed as these were
184 more medical observations instead of symptoms that can be used to measure how much
185 burden patients experience.

186 B12 PROM version 2 was generated based on the feedback of patient representatives (n=5)
187 and included new items, rephrasing existing items to improve clarity, removal of items, and
188 categorisation of symptoms in groups. For example, the item “*Balance problems*” was added,
189 “*Brain fog*” was replaced by a more explanatory description, and “*Diminished sense of*
190 *vibration*” was removed. It was advised that a questionnaire for vitamin B12 deficient
191 patients should have a maximum completion time of 20 minutes.

192 Item generation was finalised in B12 PROM version 3 based on items that were frequently
193 reported in the B12 Facebook group, such as “*Frequent urination*” and “*Heavy feeling in the*
194 *legs*”. In addition, some items were adjusted to improve the clarity, readability, and
195 feasibility.

196 **Item improvement**

197 Cognitive interviews to assess the comprehensibility and comprehensiveness initiated with a
198 B12 PROM version of 53 items. Changes were made to the wording of items and categories,

199 and new items were added. For example, the item “*Clumsiness (e.g. knocking things over or*
200 *dropping them)*” was included as a simple description of the medical term ataxia but it
201 appeared that this item was not experienced as specific for vitamin B12 deficiency.
202 Participants’ responses to this item were: “I think everyone suffers from that sometimes.”,
203 “Knocking things over depends on whether I'm tired.”, and “I always do that. That's nothing
204 new.”. As ataxia refers to problems with coordination that cause clumsy voluntary
205 movements, this item was substituted by the item “*Difficulty to accurately perform*
206 *movements*”. Another example was the adjustment of the item “*Flat emotions*” as a
207 description of the medical term apathy because this description posed difficulties in
208 understanding for multiple patients (n=3). Two patients suggested the term “indifferent”,
209 which ultimately led to the new item wording: “*Less emotional (indifferent) in situations*
210 *where you would normally be sad, angry, scared or happy*”. In addition, new items
211 mentioned by patients and the literature have been added to the B12 PROM, e.g. “*Hair loss*”,
212 “*Cracking voice*”, “*Weakening and/or paralysis of limbs*”, “*Brittle nails*”, “*Involuntary limb*
213 *movements*”, “*Restless legs*”, and “*Sores in the mouth (ulcers)*”.

214

215 <Insert Table 1 here>

216

217 After 12 interviews with patients (Table 1), saturation was reached as the last four interviews
218 indicated good comprehensibility and comprehensiveness (Table 2).

219

220 <Insert Table 2 here>

221

222 The Dutch B12 PROM emerging from the cognitive interviews was translated into English
223 for international usage. The final version of the B12 PROM includes 62 items and 8

224 categories of symptoms (General, Senses, Thinking, In limbs and/or face, Movement,
225 Emotions, Mouth & Abdomen, Urinary tract & Reproductive organs) (Table 3).

226

227 <Insert Table 3 here>

228

229 **Discussion**

230 To our knowledge, we are developing the first Patient-Reported Outcome Measure for
231 vitamin B12 deficiency in adults. This PROM may be used to identify patients with B12
232 deficiency and to monitor and compare the effectiveness of B12 therapies. Consequently, this
233 may lead to a shorter time to diagnosis and better therapy evaluation. This paper outlined the
234 first steps of PROM development: definition of the construct and the development of a
235 conceptual model, development of items and response options, and item improvement.

236 All participants involved in the definition of the construct acknowledged the need to develop
237 a B12-specific PROM, as there is no specific presentation of vitamin B12 deficiency. As
238 symptoms may vary, it is difficult for health care providers to recognise patients who benefit
239 from B12 testing. In addition, it is essential to assess the clinical outcome of B12 deficiency
240 to evaluate the treatment, as laboratory testing of vitamin B12 and holotranscobalamin is not
241 recommended for this purpose⁵ and elevated homocysteine and methylmalonic acid levels
242 may already fall towards normal within one week of B12 treatment.¹⁷ In contrast, the
243 recovery of clinical symptoms is slower, e.g. neurological symptoms subside over weeks to
244 months.¹⁸

245 The current version of our B12 PROM has several limitations. Firstly, the PROM was
246 developed in the Dutch language. However, the initial literature search was performed in the
247 English language, and all added symptoms were checked with English literature. In addition,
248 this study was supervised by an international research committee that included native English

249 speakers [CS, NW, DJ], and the B12 PROM was translated in a scientific manner. Secondly,
250 the participating health care providers and patients were all linked to a single medical center,
251 the B12 Institute in Rotterdam, specialising in diagnosing and treating vitamin B12
252 deficiency. This may lead to a bias towards more complex cases of B12 deficiency and cases
253 not easily recognised by primary care doctors. In addition, several patients from the cognitive
254 interviews had comorbidities with symptoms that overlap with vitamin B12 deficiency.
255 Thirdly, this PROM has been focused on symptoms experienced by adults with B12
256 deficiency, as children and adolescents may present with different age-specific symptoms of
257 B12 deficiency¹⁶, and these symptoms were not included in this B12 PROM. Age-specific
258 PROMs should be developed for children and adolescents. Fourthly, the development of a
259 user manual with a scoring guideline and the evaluation of measurement properties are
260 necessary before the implementation of the B12 PROM. Future studies need to assess the
261 measurement properties (e.g. reliability, discriminative validity, and responsiveness) of this
262 PROM.¹⁹

263 This B12 deficiency PROM could have a significant impact on clinical practice and research
264 in the future. This is the first step towards the development of (1) a screening tool to identify
265 patients with symptoms of B12 deficiency, (2) a monitoring tool for both patients and health
266 care providers to assess the severity of B12-related symptoms, and (3) a validated clinical
267 outcome measure for vitamin B12 deficiency to be used in clinical trials to compare and
268 evaluate effects of B12 treatments.

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277 digital version of the B12 PROM used during the interviews.

278 **Declaration of Conflicting Interests**

279 The Authors declare that there is no conflict of interest.

280

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339

340

341 **Table 1.** Characteristics of participants in interviews (n=12)

Age	Range 18 – 73 years 18 – 20 years (n=1) 20 – 30 years (n=3) 30 – 40 years (n=1) 40 – 50 years (n=2) 50 – 60 years (n=3) 60 – 70 years (n=1) >70 years (n=1)
Sex	Female (n=6) Male (n=6)
Highest education level	Secondary education (n=2) Vocational education and training (Dutch: MBO) (n=3) Higher professional education (Dutch: HBO) (n=4) University education (Dutch: WO) (n=3)
Duration B12 symptoms	Range 1.5 – 35 years 1 – 2 years (n=1) 2 – 5 years (n=2) 5 – 10 years (n=3) 10 – 15 years (n=2) >15 years (n=3) Difficult to estimate* (n=1)
Duration B12 treatment	Range 10 days – 12 years 0 – 6 months (n=5) 6 months – 1 year (n=1) 1 – 2 years (n=2) 2 – 5 years (n=2) 5 – 10 years (n=1) >10 years (n=1)
Comorbidities**	None (n=5) 1 (n=6) 2 (n=1)

342 *One participant said “Complaints since childhood. I cannot say from what age I remember these
343 complaints.”

344 **The interviewer asked the participants about comorbidities. Participants mentioned the following
345 comorbidities: cardiac arrhythmia, Hashimoto's disease, hip dysplasia, delayed sleep phase syndrome,
346 hereditary motor and sensory neuropathy (HMSN) type 1, chronic fatigue syndrome (CFS), irritable
347 bowel syndrome (IBS), and functional neurological disorder (FND).

348

349 **Table 2.** Responses from patients (n=4) in the last four cognitive interviews (interview
 350 numbers #9-12)
 351

Question	Response
How well do you think this questionnaire covers your complaints?	<p>#9: “Pretty good. I really think everything is discussed that is possible and what I experience myself.”</p> <p>#10: “Yes, good. It feels like a celebration of recognition.”</p> <p>#11: “Very good overall. It does give a first impression into what my complaints are. Of course, you go into more detail during the consultation with a physician.”</p> <p>#12: “Yes, good.”</p>
How would you rate this questionnaire on a scale of 1 to 10? (1 is bad and 10 is excellent)	<p>#9: 9</p> <p>#10: 8.5</p> <p>#11: 8</p> <p>#12: 9</p>
Do you consider this questionnaire to be complete?	<p>#9: “Yes.”</p> <p>#10: “Yes.”</p> <p>#11: “Yes, I think so if there is a question where you can add complaints not mentioned in the questionnaire.”</p> <p>#12: “There is the item ‘fatigue’ in the questionnaire, but I think ‘extreme fatigue’ is insufficiently highlighted. I think it's complete after my additions.”</p>

353 **Table 3.** Items and categories of symptoms from the final B12 PROM version after cognitive
 354 interviews. Instruction: “Indicate whether you have suffered from the following complaints in
 355 the past 7 days”. Response options: “Not, Little, Moderate, Much, Very much”.

General	Movement
1. Fatigue	32. Unstable walking
2. Waking up tired after a night's sleep	33. Difficulty to accurately perform movements
3. Problems with sleeping	34. Loss of strength
4. Need for afternoon naps	35. Muscle cramps
5. Heavy, fast and/or irregular heartbeat	36. Muscular pain
6. Pain or pressure on the chest	37. Pain in joints
7. Shortness of breath	38. Involuntary limb movements
8. Headache	39. Shaky hands
9. Dizziness	40. Heavy feeling in the legs
10. Limited energy	41. Restless legs
11. Hair loss	Emotions
12. Cracking voice	42. Mood swings
Senses	43. Gloomy
13. Less smell and/or taste	44. Quick to (almost) cry
14. Blurred vision (despite using glasses or lenses)	45. Easily irritated
15. Tinnitus (ringing in the ears)	46. Anxiety and/or panic
16. Cold hands and/or feet	47. Less emotional (indifferent) in situations where you would normally be sad, angry, scared or happy
17. Balance problems	Mouth & Abdomen
Thinking	48. Decreased appetite
18. Difficulty concentrating	49. Sores in the mouth (ulcers)
19. Slow thinking	50. Painful and/or thick tongue
20. Unable to think clearly and/or foggy in the head	51. Stomach problems
21. Forgetful	52. Nausea
22. Difficulty finding a particular word	53. Bloating feeling
23. Easily overstimulated by light, sound and/or busy environment	54. Abdominal pain
24. Confused in thinking and speaking	55. Heartburn and/or acid reflux
In limbs and/or face	56. Diarrhoea
25. Tingling, burning and/or stabbing sensation	57. Constipation
26. Less sensation in limbs and/or skin	Urinary tract & Reproductive organs
27. Skin is painful when touched	58. Having a frequent urge to urinate
28. Numbness in certain spots	59. Undesirable urine loss
29. Skin and/or muscle twitching	60. Painful vaginal wall
30. Weakening and/or paralysis of limbs	61. Menstruation problems (past 3 months)
31. Brittle nails	62. Erection problems (past 3 months)

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