Protocol for excluding B12 deficiency (Megaloblastic anemia/ Pernicious Anaemia) from adult and child patient presentation

**Relevance**
This protocol is relevant to all diagnosing clinicians, ie GPs and Nurses. HCAs and other staff should be aware of the possible ‘presenting symptoms’ and suggest that patients see a diagnosing clinician for further investigation.

**Presenting Symptoms**
If a patient presents with **Tiredness, depression, hair loss, pins and needles, numbness in hands or feet, tremors and palsies, palpitations, recurrent headache or dizziness**, B12 deficiency should be considered.

**Beginning a diagnosis – presenting to GP/ Nurse**
Using Appendix A –1 Minute Health Check –
If B12 deficiency is suspected order a blood test for FBC, Serum vitamin B12, Folic Acid, TSH, U+Es, LFT, Glucose and other tests you feel are required for symptoms/exclusion/ differential diagnosis.

**Once Blood results are available**
If the serum B12 level is below 180ng/L (or local laboratory threshold) then staff should make a 15 minute appointment with the GP or nurse who requested the blood test. This meeting may reduce to 10 minutes length once Doctors and Nurses are familiar with the process.

Harrison’s “Principles of Internal Medicine” 16th Ed indicates that with signs and symptoms indicative of B12 deficiency

- <180ng/L or <200ng/L **Clinically significant/ severe B12 deficiency**
- 200-300 **Moderate deficiency**
- >300 **“Subtle” (subnormal/normal B12 but with signs & symptoms)**

🌟 Based on Harrison’s “Principles of Internal Medicine” 16 ed 2005 p606
🌟 Compare with Lab specifications from Swindon & Marlborough NHS Trust (see accompanying document “Observational analysis”)

**Therapeutic Trial:** if the patient is diagnosed as moderate or subtle deficiency (>180ng/L with signs and symptoms, other autoimmune condition or family history) then they should be clinically reviewed every 4 weeks until you reach a clinical decision whether to commence treatment – even when the B12 level does not drop below 180ng/L. A deterioration of condition demonstrated by signs and symptoms is sufficient to commence a therapeutic trial.

**Prophylactic treatment** should be given (regardless of borderline blood serum B12) following Gastro-Intestinal (GI) surgery, and for patients with sudden onset of paralysis, blindness, psychosis, Crohns colitis, early dementia etc, see below.
Other Actions to Take

- If clinical depression is suspected – complete PHQ9 and treat/refer as appropriate
- Neurological manifestation – neurological examination and refer to neurologist for further investigation
- Provisional diagnosis of any other condition – refer to appropriate speciality.

Treatment Schedule – BNF (British National Formulary) Guideline “9.1.2 Drugs used in megaloblastic anaemias” (Sept 2010) and suggested variations

Before treatment starts, patients should agree to B12 replacement therapy by signing and dating the appropriate consent form.

Megaloblastic anaemia/ Pernicious Anaemia

B12 deficiency with neuro-psychiatric signs and symptoms, with or without anaemia or macrocytosis, a multi-system, poly-glandular, multi-point poisonous syndrome.

Hydroxocobalamin¹ by intramuscular injection:

Pernicious Anaemia (B12 deficiency) and other macrocytic anaemias without neurological involvement. Initially 1mg 3 times a week for 2 weeks then 1mg every 3 months

*Clinically review every 2 months with or without serum B12 and if clinically indicated increase the frequency to every 2 months or every month

Pernicious Anaemia (B12 deficiency) with neurological signs and symptoms. Initially 1mg on alternate days until no further improvement (maximum reversal of neuro-psychiatric signs and symptoms are achieved), then 1mg every 2 months.

*Clinically review every 2 months with or without serum B12 and if clinically indicated increase the frequency to every month or more frequently

Prophylaxis of vitamin B12 deficiency

In the following instances B12 replacement therapy should be instituted as a prophylactic measure even when the blood serum B12 is higher than the local laboratory threshold (>180ng/L or >200ng/L):

1- Specific medical history renal imbalance, diabetes, >65 years old, or following GI surgery, Crohn’s colitis, early onset dementia: initial loading doses followed by 1mg every 1, 2 or 3 months

2- Moderate/ subtle B12 deficiency with mild signs & symptoms: initially use oral (OC²) B12 1mg per day. The patient’s blood serum B12 should rise. If the patient’s signs and symptoms do not respond then review and consider injections (SC/IM) of hydroxocobalamin on the same basis as for Pernicious Anaemia.

3- Moderate/ subtle B12 deficiency with severe signs & symptoms: patient presenting with strong family history, presence of other auto-immune conditions, major signs and symptoms which could become irreversible if treatment is not commenced urgently eg optic neuritis/ neuropathy, sudden onset blindness, subacute combined degeneration, ME, CFS, MS-like presentation, single limb

¹ methylcobalamin is used in USA, Canada, India, Japan and other countries. Pharmacists in Wales also report that they can prescribe methylcobalamin. Methylcobalamin is considered superior to hydroxocobalamin by many people because it is one of the natural body forms of B12

² OC – Over the Counter. B12 can be purchased as oral lozenges from health food shops and the internet. Use methylcobalamin for preference
paralysis, sudden loss of muscle mass (Motor Neurone Disease-like presentation), non-epileptic seizures, dysphagia, Bell’s Palsy/ Ramsey Hunt syndrome, Parkinson’s like presentation, dementia, total alopecia, migrainous headache, temporal arteritis, recurrent miscarriages, dysfunctional uterine bleeding, or psychosis: initial loading dose followed by 1mg every 1-3 months.

Note: treatment should be tailored to patient need; some people need injections more frequently than once per month.

**Therapeutic Trial** should be used where B12 deficiency is suspected because of signs and symptoms, but B12 deficiency is subtle or subclinical on the basis of blood serum results. 1mg IM or SC (hydroxocobalamin or methylcobalamin) should be given alternate days for 2 – 3 weeks (6 to 9 doses) followed by 1mg IM or SC³ per week for 3 months. Signs and symptoms should be monitored, and frequency varied if required. If there is no improvement in signs and symptoms after 3 months (13 weeks) then B12 deficiency can be excluded. A therapeutic trial will not interact with other medication given and other treatment can be started at the same time.

**Cyanide poisoning** (victims of smoke inhalation who show signs of significant cyanide poisoning) hydroxocobalamin (or methylcobalamin in some countries) the usual dose is 5g (or 70mg/kg in children) by intravenous infusion, given once or twice according to severity.

NOTE THAT cyanocobalamin is licensed for 1mg IM injection monthly; because of reduced retention in the body in comparison to hydroxocobalamin and methyl-cobalamin (not licensed). Cyanocobalamin is excreted by the kidney preferentially which is why Cobalamin is used to treat cyanide poisoning.

**Nitrous oxide anaesthesia.** Nitrous oxide inactivates Vitamin B12 in the body including brain cells. Therefore a B12 deficient patient (or her GP) should alert the surgeon and anaesthetist so that an alternative anaesthetic agent will be used during surgery.

**Mother & Foetus, Neonate, Child**

**B12 deficiency: prevention, early diagnosis and treatment**

An undiagnosed, untreated B12 deficient mother receiving only folic acid supplement could deliver her child with neuromuscular damage, sub-acute combined degeneration of the spinal cord, congenital abnormalities, tumours including brain damage and spina bifida. This can be avoided with B12 replacement before and during pregnancy (treat as for PA with neurological signs and symptoms).

The neonate 0 – 1 month born to an untreated B12 deficient mother should receive intensive IV B12 replacement treatment in the hospital neonatal department.

**Child 1 month – 13 years**

If an untreated B12 deficient mother opts to breast feed, mother and infant will require B12 replacement and regular monitoring as per BNF guidelines. Please note, baby milk powder fortified with vitamin B12 may not be sufficient to correct the moderate to severe deficiency in a new-born.

A child, whether born to a known B12 deficient mother or not, who presents with delayed development, hyper activity, behavioural problems, dyspraxia, learning disability, autistic spectrum disorder like presentation, should initially be screened by blood test, to exclude B12 deficiency, underactive thyroid, inborn errors of metabolism, and any other condition suspected.

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1 Injections Intra-Muscular (IM, into the muscle of the shoulder or thigh) or Sub Cutaneous (SC, stomach, buttock etc).
   IM injections will be released into the blood more quickly giving faster effects but lasting less time, whereas injections into fatty tissue will be released more gradually.
Treatment as per BNF guidelines for children. Review the signs and symptoms and vary the frequency according to the child’s needs (following the loading doses of alternate day injections); 1mg weekly, fortnightly, monthly, 2 monthly or 3 monthly. When required, refer to appropriate paediatric speciality.

**Cessation of treatment**
In most cases, treatment should continue for life. Treatment should be varied as follows:

- If the patient shows signs of improvement or is stable for 2 years, then the frequency of injections can be extended from monthly to every 2 months, or from every 2 months to every 3 months
- If the patient suffers symptoms before the next scheduled injection, then the GP should consider injections closer together to minimise suffering
- Blood serum B12 is not considered a good measure of the effectiveness of injections; relief from signs and symptoms is the best measure. It should be noted that the majority of B12 in blood serum is in the inactive form, and that the serum B12 test measures all forms of Cobalamin including the less biologically active cyanocobalamin form.

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GP, Shinwell Medical Centre, Horden, Co Durham

**Hugo Minney, PhD**  
B12 deficiency Patient Support Group
Appendix A – 1 Minute Health Check – B12 Deficiency

signs and symptoms

A quick score will reveal if B12 deficiency, underactive thyroid or iron deficiency anaemia are possible diagnoses, and if the physician should order further tests.

Name ______________________________________ Date ________________________

Where will you grade these symptoms 1-10? 1 indicates that this symptom is mild and infrequent. 10 indicates the patient has it all the time and it is severe and debilitating. A score of 5 indicates that the patient has the symptom and it affects their daily life to a moderate extent.

<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
<th>Score 1-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy/ haemopoetic</td>
<td></td>
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<tr>
<td>Weariness, Lethargy, tiredness, fatigue, faints</td>
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<tr>
<td>Sleepy, tired in the afternoon</td>
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<tr>
<td>Nervous system</td>
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<tr>
<td>Tremor, foot drop</td>
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<tr>
<td>Loss of balance (ataxia), seizures, falls</td>
<td></td>
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<tr>
<td>Tingling or numbness in hands and/or feet, burning sensation</td>
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<tr>
<td>Facial Palsy</td>
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<tr>
<td>Spastic movements, Crampy pain in limbs</td>
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<tr>
<td>Stiffness of limbs, muscle wasting</td>
<td></td>
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<tr>
<td>Weakness or loss of sensation in limbs, shooting pain in back/limbs, paralysis</td>
<td></td>
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<tr>
<td>Migrainous headache</td>
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<tr>
<td>Psychiatric</td>
<td></td>
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<tr>
<td>Irritable, snappy, disturbed sleep</td>
<td></td>
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<tr>
<td>Confused, Memory disturbance/ forgetful, fogginess</td>
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<tr>
<td>Tension Headaches</td>
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<tr>
<td>Mental slowness, Mood swings, Anxiety/ Panic Attacks, depression</td>
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<tr>
<td>* Psychosis, hallucinations, delusion</td>
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<tr>
<td>Eye Ear Throat</td>
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<tr>
<td>Blurred vision/ double vision/ drooping of eyelid (lid lag), orbital pain</td>
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<tr>
<td>Dizziness, tinnitus</td>
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<tr>
<td>Difficulty swallowing, persistent cough</td>
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<tr>
<td>Immune System</td>
<td></td>
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<tr>
<td>Prone to recurrent URTI, UTI, Respiratory infections</td>
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<tr>
<td>Other auto-immune conditions</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
<th>Score 1-10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular/ Respiratory</td>
<td></td>
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<tr>
<td>Shortness of breath, wheeziness</td>
<td></td>
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<tr>
<td>Palpitations, chest pain</td>
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<tr>
<td>Pallor, lemon yellow complexion</td>
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<tr>
<td>Bruising, Vasculitis</td>
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<tr>
<td>Gastro-Intestinal (GI)</td>
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<tr>
<td>Sore tongue, bleeding gums</td>
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<tr>
<td>Red beefy tongue</td>
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<tr>
<td>Cracking the angles of mouth</td>
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<tr>
<td>Metallic taste, unusual taste, loss of appetite, loss of weight</td>
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<tr>
<td>Gastric symptoms- acidity, heartburn</td>
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<tr>
<td>Intermittent diarrhoea, IBS</td>
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<tr>
<td>Skin hair nail skeletal</td>
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<tr>
<td>Premature greying</td>
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<tr>
<td>Alopecia, Unexplained hair loss</td>
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<tr>
<td>Joint inflammation, swelling, pain</td>
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<tr>
<td>Dry skin, brittle nails</td>
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<tr>
<td>Genito-Urinary (GU)</td>
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<tr>
<td>Heavy painful periods, irregular periods, infertility &amp; frequent miscarriages</td>
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<tr>
<td>Loss of libido</td>
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<tr>
<td>Shooting pain from groin to perineum</td>
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<tr>
<td>Incontinence</td>
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<tr>
<td>Personal &amp; Family History</td>
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<tr>
<td>Family history of pernicious anaemia (B12 deficiency), underactive thyroid, diabetes, vitiligo, depression</td>
<td></td>
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<tr>
<td>Vegetarian, vegan, poor diet</td>
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<tr>
<td>Alcoholism, Smoking</td>
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</table>

PHQ9 Patient Health Questionnaire to be completed

* Neurological examination and appropriate referral if indicated

Physician should also order routine blood tests including serum B12 in the following cases:

- ME, CFS, MS-like presentation
- Children born to B12-deficient mothers, presenting with behavioural problems, learning disability, dyspraxia, dyslexia and autistic spectrum disorders

Before making a provisional diagnosis of B12 deficiency, exclude all other possible diagnoses, with appropriate blood tests as clinically indicated.
B12 Consent Form

Dear patient

Your blood test shows that you have low levels of Vitamin B12 in the body, and your signs and symptoms indicate that you have a deficiency of Vitamin B12.

Vitamin B12 is essential for life. Vitamin B12 deficiency can result in damage to every system and gland in the body

- it is needed to make new cells in the body, including red blood cells, and for enabling genes (DNA) to switch on and off
- it is needed for maintenance of the myelin sheath around nerve cells, and deficiency can result in numbness, paralysis, or shooting pains, as well as confusion and memory loss
- it is a vital catalyst in the body’s energy pathways, so without it you may suffer lethargy and tiredness, and at the same time disturbed sleep
- It helps maintain cell membranes, which means it is important for a normal immune system, for hormone production, and for the production of digestive juices.

Vitamin B12 is found in meat, fish, eggs and milk but not in fruit or vegetables. The medical view is that a normal balanced diet contains enough B12. However, failure to absorb Vitamin B12 from food will cause B12 deficiency resulting in many forms of illnesses and disabilities.

Treatment – Vitamin B12 can be administered by either injection or taken by mouth. This is an ongoing treatment and your Doctor will advise you on how this will be given. You will be monitored and have further blood tests, to check on progress.

Risks – Although injectable B12 is completely non-toxic, some people report a little local discomfort after injection.

The practice has explained:-

About the condition

Treatment required and ongoing monitoring

I fully understand and I accept the above:

Signature: ........................................................................................................................................

Date: ........................................................................................................................................

For Surgery Information:

Diagnosis

Clinically significant B12 def <180/<200 (lab threshold) (with signs & symptoms) ...................................[ ]
Subclinical / subtle B12 Def >180/>200 (lab threshold) (WITH signs & symptoms) .................................[ ]

Additional Requirements

Signs & Symptoms sheet completed ....................................................................................................[ ]
Consent form signed ............................................................................................................................[ ]
Patient Information Leaflets given .......................................................................................................[ ]
Appendix B – Vitamin B12 deficiency and direct or indirect causation of disease

Deficiency of vitamin B12 is a multi-system, polyglandular, multipoint poisonous syndrome. B12 is required for proper function of most of the body’s systems, so deficiency leads to disease in these systems.

This appendix lists some of the common conditions that can be treated successfully by using Vitamin B12 replacement therapy, and a causative mechanism can be described.

Haematological
- Unexplained recurrent anaemia
- Myelodysplasia
- Pancytopenia / bruising

Psychiatric
- Depression
- Memory loss / confusion
- Anxiety
- Psychosis
- Angry / moody / snappy

Gastro-intestinal
- Recurrent gastritis
- Mouth ulcers, bleeding gums
- Pernicious anaemia
- IBS / diverticulosis
- Unexplained diarrhoea
- Crohn’s Colitis

Cardio-Vascular / Respiratory Systems
- Cardiac failure – artherosclerosis, stroke
- Temporal arteritis
- Vasculitis
- Exacerbation of angina – palpitations, breathlessness
- Asthma exacerbation

ENT (Ear, nose & throat)
- Tinnitus / vertigo
- Glossopharyngeal neuropathy (swallowing difficulties)
- Dizziness / falls

Endocrine / Immune systems
- Post Viral Immune Deficiency Fatigue Syndrome (ME)
- Poor wound healing / susceptibility to infection
- Auto-immune conditions such as vitiligo, myositis, diabetes coexisting with myoderma

Neurological
- Dementia
- Alzheimers’
- Optic Atrophy / blindness
- Doublevision, Ptosis
- Loss of sensation in limbs, trunk, face, genitalia
- Pseudo seizures, non-epileptic seizures
- Blackouts and faints
- SubAcute Combined Degeneration (SACD)
- Single limb paralysis
- Multiple sclerosis like B12 deficiency syndrome
- Neuropathic pain / myopathy
- Cramps / crampy pain
- Babies with neuromuscular damage may be born to mothers who are B12 deficient during pregnancy
- Tension / migraine headaches
- Parkinson’s like presentation
- Motorneurone like presentation with limb muscle atrophy
- Bell’s palsy
- Ramsay Hunt syndrome

Bone
- Osteoporosis, suppressed activity of osteoblasts
- Inflammatory polyarthritis

Dermatology
- Alopecia
- Dry scaly skin / dermatitis
- Brittle nails

Genito-Urinary
- Dysfunctional Uterine Bleeding
- Repeated miscarriages
- Polycystic ovarian disease
- Dysmenorrhoea, menorrhagia
- Recurrent UTI
- Loss of libido
- Double-incontinence

If treatment is delayed, this may cause irreversible damage, or fatality. Always exclude vitamin B12 deficiency before making a final diagnosis and deciding treatment options.

If vitamin B12 deficiency co-exists with other causes, B12 therapy compliments other treatments rather than interferes.