

## **PROTOCOL FOR MGUS TRIAL**

Can Vitamin B12, as Hydroxocobalamin, reverse or partially reverse Monoclonal Gammopathy of Unknown Significance (MGUS), and thus prevent progression to Multiple Myeloma and related haematological malignancies?

A multicentre, randomized, partially placebo-controlled, partially masked, 2 control group, 150 subject, clinical pilot study of high dose intravenous vitamin B12, and relatively low dose folate, in the treatment of MGUS.

### Study Title

Can Vitamin B12, as Hydroxocobalamin, reverse or partially reverse Monoclonal Gammopathy of Unknown Significance (MGUS), and thus prevent progression to Multiple Myeloma and related haematological malignancies?

### Study Objectives

#### Primary Objective

The study will investigate whether high dose intravenous vitamin B12, with low dose folate support, can produce a partial or total reversal of MGUS, and lead to a potential treatment for the prevention of Multiple Myeloma and other related haematological malignancies.

#### Secondary Objective

The study will investigate whether there is any aetiological connection between varying degrees of B12 deficiency status (from mild, sub-clinical, compartmentalized even, to general, severe) and MGUS. A possible genetic link between gastric atrophy, low B12 status and the risk for MGUS/ Multiple Myeloma will also be investigated, using both biochemical and epidemiological data.

### Design and Outcomes

A multicentre, randomized, partially placebo-controlled, partially masked, 2 control group, 150 subject, clinical pilot study of high dose intravenous vitamin B12, and relatively low dose folate, in the treatment of MGUS. There is no placebo for the IV vitamin B12 because there is currently no standard treatment available for MGUS, (for which the spontaneous regression rate is less than 4%.) Thus, given that IV is an invasive procedure and carries some risk, a placebo IV is considered unethical, and a full double-blind study impracticable. The study will explore whether high dose IV vitamin B12, with some supporting folate, can reduce the monoclonal protein in MGUS by 20% or more.

(See diagram attached for design of study. 6a attached)

### Interventions and Duration

As this is an orthomolecular medicine study, the design does not follow an orthodox drug model design which may lead to artefact results, since nutrients do not work in isolation. The 2 control groups however should clarify the role, if any, of high dose IV vitamin B12 in MGUS. The active arm

will receive 10,000 µcg IV B12 weekly and 30 mg folate daily, together with a daily multi-vitamin –mineral and ω-3 fatty acid supplement for a period of 6 months, followed by a lower weekly dose of 1000mcg B12 for 3 months, with folate and other support supplementation. The first control group will receive only a placebo supplement. The second control group will receive only the daily multi-vitamin-mineral and ω-3 fatty acid supplement. The 2 control groups will be double-blinded and masked. As explained above, because of ethical and practical considerations, this cannot be done with the active intervention group.

#### Sample Size and Population

150 male and female, largely white, subjects from approximately 25 different health regions of the UK will be studied. It is expected that the average age of the MGUS subjects will be about 60 years.

#### Duration of Study

Recruitment of subjects should take approximately 6 months. Once 150 subjects have been recruited, there will be a pre-entry screening and preparation period of 1 month, followed by 6 months active intervention, 3 months of follow-up observations with minimum interventions, and 3 months of no interventions followed by a final assessment. Thus each subject is expected to be in the study for a total of 13 months. (See schedule of evaluations following. 7a attached)

### STUDY OBJECTIVES

#### Introduction

This protocol is based on the article by C. Wheatley (D Phil Oxon), A Unified Theory of the Causes of Monoclonal Gammopathy of Unknown Significance (MGUS) and Multiple Myeloma, with a Consequent Treatment Proposal for Long-Term Control and Possible Cure Journal of Orthomolecular Medicine, 2002, Vol 17, No.1: 7, (see Appendix I) which all participating physicians should read and evaluate for themselves. (A preliminary epidemiological study organised by the registered charity, Orthomolecular Oncology, Reg. No. 1078066, (<http://www.canceraction.org.gg>), is already under way with the aim of drawing together MGUS/Myeloma and related disorder patients who may subsequently wish to take part in this pilot study, and ensuing trials. The preliminary study involves a detailed questionnaire for patients which may throw more epidemiological light on the proposed thesis. (see Appendix II) All participants are encouraged to discontinue adverse health practices, such as smoking, poor diet, high stress levels, lack of exercise etc and helped to follow the good health guidelines embodied in the '5 Rs of Cancer Recovery and Recurrence Prevention', in the Orthomolecular Oncology Patient's Guide, distributed free to each participant, and also published on the web site.)

#### PRIMARY OBJECTIVE

150 MGUS patients will be recruited with the aim of seeing whether the monoclonal component of MGUS can be reversed back to normality, and thus possibly establishing a definitive approach to Myeloma prevention, which is very desirable for a disease that currently has no cure and only rare long-term survival. The current 'spontaneous' MGUS reversal rate is only 4%<sup>1</sup>.

The study will investigate whether high dose intravenous vitamin B12 can induce a total or even partial, reversal of MGUS. The 'M' spike in MGUS is known to be very stable and rarely falls spontaneously below 10%. Thus a total reversal of MGUS is defined as a fall in the 'M' spike component to within normal clinical values for the immunoglobulin type in question. A significant partial reversal of MGUS is defined as a fall of 20% or more, occurring any time after entry, including the period of follow-up and conclusion. (It is hypothesised that the effects of high dose IV B12 on MGUS could be cumulative and delayed.<sup>2</sup> Hence the importance of close monitoring of the 'M' spike during this latter period.)

There is normally a 1 in 4 chance of malignant progression in MGUS, to Myeloma or other haematological malignancies. Such progression however can take up to a decade or more.<sup>1</sup> Given the relatively short time frame for the duration of this study, and the small numbers of patients involved, the risk of MGUS progression is likely to be less than 5%<sup>3</sup>. Whereas, if the hypothesis being tested has any validity, one might expect to see a regression rate in the active arm of 20% or more.

#### SECONDARY OBJECTIVES

The bone marrow aspirate in MGUS and in vitamin B12 deficiency states exhibits a number of chromosomal abnormalities indicative of a pre-malignant status<sup>4,5,6,7</sup>. This study will also investigate if there is any correlation between improved B12 status, a possible improved or reversed MGUS status, and such established chromosomal abnormalities. If there is any positive correlation, this may shed further light on the suspected role of hypo-methylation in carcinogenesis<sup>8</sup>, (adequate levels of B12 being essential for good methylation and DNA repair that avoids chromosomal fragility and transcriptional errors, which over time are believed to be key factors in carcinogenesis.)<sup>8</sup>

In addition, this study will collate epidemiological data from the preliminary questionnaires, to be completed by all 150 subjects, with the results of test evaluations both before, during and after the treatment. One of the key questions proposed by the underlying hypothesis, which collation of this information will address, is: whether there is a direct link between loss of B12 absorption due to age or gastric atrophy/surgery, or blockade by anti-ulcer drugs, or other B12 inactivating agents, (such as nitrous oxide anaesthesia, or metformin for diabetes), and MGUS and Multiple Myeloma; whether too it is in the predisposition of males and blacks to early gastric atrophy, (which parallels the greater incidence of Myeloma in these 2 groups), that the genetic link to MGUS and Myeloma is to be found? (It has not hitherto been found elsewhere.<sup>9</sup> Yet, our hypothesis notes there is also an exact parallel between Myeloma contracted at an increasingly younger age in succeeding generations of familial Myeloma, and the phenomenon of

inherited gastric atrophy manifesting at an increasingly younger age in descending generations. (see Appendix I)

B12 deficiency, like MGUS, increases with age<sup>10</sup>, and is thought to be directly connected with increasing frequency of other age-related pathologies, such as cardiovascular disease and Alzheimer/other dementias. Yet, though, for instance, it is known that 50% of Americans by age 65 do not have adequate B12 absorption<sup>10</sup>, the incidence of B12 deficiency in age, particularly at the chronic persistent levels that, it is hypothesised, may contribute to MGUS and MGUS progression, may not be routinely ascertained due to inadequate testing. A Schilling test which shows normal absorption can coexist with levels of methylmalonic acid, which belies the former fact<sup>11</sup>. In addition, there is a high reliance on serum B12 measurements, even by the most sophisticated researchers. Professor Robert Kyle, who finds our hypothesis interesting, reports that:

‘We have described a cohort of 1,027 patients with multiple myeloma seen at the Mayo Clinic from 1985 to 1998. All laboratory data was obtained within 30 days of diagnosis and before any treatment had been started. 284 of the patients had a serum B12 deterioration at the time of diagnosis. The values ranged from 50 ng/L to 2000 ng/L. The normal value is 200-650 ng/L. Thirty patients had a value of >200 ng/L.

The mean corpuscular volume (MCV) was determined in 983 of the 1027 patients at the time of diagnosis. The value ranged from 69-127. The normal range in our laboratory is 81-98. 17% had an MCV >98. the value was >100 in 9%.’

(Personal communication to Dr C. Wheatley, Jan 17<sup>th</sup> 2002.)

Serum B12 measurements, whilst capable of diagnosing outright B12 deficiency, are not helpful in elucidating a chronic or compartmental B12 deficiency, because serum B12 is not an adequate measure of B12 bio-availability. Our study will conduct both serum B12 measurements and measure B12 on Transcobalamin I and II, and III, the B12 transport proteins, for comparison and classification on this point. It is the 20% of B12 transported on TC II as methylcobalamin, that is most bio-available. The up to 80% B12 transported as adenosylcobalamin on TC I does not appear to have comparable bio-availability at the tissue level, whilst TC III appears to play a role in measuring cobalamin analogues which block the bio-availability of B12 from the body. Thus, as regards B12 sufficiency, it is the percentage saturation of TCII that counts<sup>12</sup>. And even here there is a twist: it has also been established that some TCII genotypes are functionally more efficient than others at delivering B12 to tissues, resulting in enhanced B12 status<sup>13</sup>. The same may also prove to be true of TCI. Thus the recently discovered phenomenon of compartmental B12 deficiency (which explains why in Pernicious Anaemia, for example, B12 deficiency can sometimes manifest neurologically, as opposed to haematologically, and vice versa), is perfectly plausible, as is the phenomenon of subtle B12 deficiency<sup>14</sup>. For all of the above reasons, this study will include in its exploration of the B12 status, testing for TCII genotype, and both total homocysteine and methylmalonic

acid. So that the exact role, if any, of B12 deficiency and treatment in MGUS will be very finely defined.

## BACKGROUND

### Rationale.

The patient population to be studied will be drawn from diverse health regions of the UK, and will comprise 150 recently diagnosed MGUS patients, likely to be 40 years and older, (as MGUS is almost unknown below the age of 40), an equal mix of male and female, with some racial diversity. (It is hoped, given the higher incidence of MGUS amongst blacks, that the population to be studied will include a representative sample of blacks.)

There is currently no known treatment for MGUS, a condition which has an increasing incidence with age, and is considered to be a pre-malignant pathology, since 1 in 4 MGUS patients will go on to develop Multiple Myeloma, or other haematological malignancies over a decade or more. In addition, patients with MGUS have a greater incidence of morbidity and mortality than comparable-age, MGUS-free populations. The hypothesis to be tested by this study suggests that both facts may be directly related to an increasing loss of B12 absorption in age and/or chronic, subtle, long-standing B12 deficiency. The overt B12 deficiency of Pernicious Anaemia, which is also frequently characterized by MGUS, carries a significantly increased risk for Myeloma, as well as stomach cancer, even when treated<sup>15</sup>. This latter fact suggests that, if the hypothesis to be tested has any value, significantly greater amounts of B12 should be used than are traditionally prescribed for the treatment of Pernicious Anaemia. The dose arrived at for the active intervention, of 10,000 µcg intravenous Hydroxocobalamin weekly, is a known safe dose used by doctors who practice orthomolecular medicine for the treatment of cancer and Myeloma over the last 15 years. It is also based on a vitamin B12 trial for children with neuroblastoma<sup>16</sup>, conducted at Great Ormond Street in the pre-chemotherapy era of the 1950s, which showed up to 40% or more remission, and survivals of up to 8 years. These children received 4,000 µcg weekly (intramuscular). Thus 10,000 µcg intravenous weekly for an adult, over 6 months, appears to be in proportion. Giving the dose as a one-off weekly intravenous infusion is seen as a practical solution, calculated to optimise the comfort and compliance of patients, (some of whom may have to travel far to the hospital for treatment).

The duration of the intervention period and 2 follow-ups is determined by the following considerations. The number of patients, (50), in the active intervention arm is not great. And, whilst 3 months might be deemed a more than adequate period for total haematological renewal and a possible positive outcome, there could theoretically be some late responders. Moreover, if a positive outcome of the B12 treatment is observed in the first 3 months, it is of value to see if it persists. In the first follow-up period, (3 months), where a dose of B12 (1000 µcg weekly IM) comparable to that for Pernicious Anaemia treatment is used, it is important to observe whether there is a decline in positive outcome, or whether this dose represents a good maintenance therapy regime. It is also conceivable that positive outcomes, not seen in the 6 months' active intervention, might manifest at a later

stage. In the final follow-up period, (3 months), of no B12 treatment, it is important to note whether any positive outcomes persist, or are reversed.

Whilst the dose of B12 given in the active intervention arm will be supra-physiological, a relatively small amount of folate (30mg, oral, daily), will also be administered. The ratio of folate to B12 here is based on that used in a successful trial of B12 for squamous metaplasia in the lungs of smokers<sup>17</sup>. There is an intimate relationship between B12 and folate in DNA synthesis, and the folate is intended to ensure that the high B12 will be properly utilised.

The administration of B12 and folate may be of particular therapeutic value in cancer, not just because of enhanced DNA methylation, but because, as the late Professor Victor Herbert observed<sup>6</sup>:

Lack of either damages DNA synthesis. The primary damage is to de novo DNA synthesis, with the result that there may be secondary increment in salvage DNA synthesis<sup>118</sup>. In those tumors in which synthesis of DNA by the salvage pathway is relatively greater than in normal cells, as compared to the de novo pathway of DNA synthesis, it is theoretically possible that folic acid and/or vitamin B12, by enhancing de novo DNA synthesis, could be relatively more helpful to normal than to tumor cells and relatively more harmful to certain tumor cells<sup>15,118</sup>.

It is theoretically possible that this might apply to the transformed cell of the immunoglobulin that produces the monoclonal protein.

#### INTERVENTION RISKS.

Vitamin B12 has a supremely safe toxicity profile<sup>18</sup>. It has been used for nearly half a century in France (and the US) as a treatment for cyanide poisoning, in doses of 4 grams, often administered repeatedly over 2 or 3 consecutive days, with dramatically good response<sup>19</sup>, and no ill effects beyond a red skin rash. Whilst there are one or two cases known of anaphylactic shock in the literature, it is thought that these may have been due to microbial contamination of B12 in poor early production methods. Since the B12 in this study will be administered in a clinical setting, this possibility, however remote, can be considered and guarded against. The only other risks envisaged are those normally attached to the invasive procedure of an intravenous infusion.

There is also a school of thought that might attach a promotional effect to vitamin B12 in cancer<sup>6</sup>. Our hypothesis does not espouse this view, in part because B12 blocks both Interleukin – 1  $\beta$  and Interleukin – 6, which really do promote Myeloma, and because, additionally, B12 may down-regulate expression of C-myc. (see Appendix I article.) However, in the event that a statistically significant promotional effect were to be observed during the course of the active intervention, the study would be halted. This school of thought however is theoretical, and appears to be contradicted both by the neuroblastoma B12 trial in the 1950s<sup>16</sup>, and 2 case histories of the long term use of vitamin B12 in active Myeloma<sup>2,20</sup>.

#### STUDY DESIGN

This 150-subject, randomized, controlled, partially masked, partially blinded, study is unusual in that it is designed to a new non-drug testing model, consistent with the tenets of orthomolecular medicine, a field founded over 30 years ago by Linus Pauling. (In essence, orthomolecular medicine involves the treatment of disease with substances endemic to biochemistry : such as insulin for diabetes; B12 for Pernicious Anaemia.) In orthomolecular medicine specific high doses of a vitamin, or other biological response modifier, are never given in isolation, as this may lead to nutritional imbalances and poor efficacy. A base of all essential minerals, vitamins and fatty acids in moderately high dose is used alongside the specific therapeutic dose. It is this element that was missing from the Caret and ATBC vitamin trials in lung cancer, and may well have contributed to some of the noted adverse effects<sup>21</sup>. Since this is a new concept, and it can be reasonably argued that it may be hard thus to isolate the effects of B12 alone on MGUS, our study will contain 2 control groups : Control Group I will be given lactose and sunflower placebo ; Control Group II will get the same multi-mineral-vitamin- omega-3 fatty acid supplement as the active arm. These supplements and placebos will be begun one month pre-entry for Control groups I and II and the Active Intervention Arm. (see Appendix III.)

#### SELECTION AND ENROLMENT OF SUBJECTS.

1. 150 male and female subjects with MGUS in approximately even gender proportions, from all health regions in the UK, aged 40 and above, with a median age of 60 years, and some racial mix will be studied. The study will look specifically at Benign MGUS for IgG, IgA, IgD, IgM, and free light chains.
2. All study participants must have MGUS, diagnosed in the last 6 months prior to the study, using agarose electrophoresis with immunofixation, bone marrow aspirate, full blood biochemistry, kidney and liver profiles, bone scans to exclude lytic lesions and skeletal involvement, and urine tests for Bence Jones proteinuria.  
MGUS is defined according to the accepted criteria of: ` a serum M-component less than 3g/dl, none or a small amount of M-protein in the urine, less than 10% plasma cells in the marrow, and absence of lytic bone lesions, anaemia, hypercalcaemia or impairment of renal function.<sup>3</sup> This diagnosis must be confirmed in the week prior to entry. (See schedule of evaluations.)

#### EXCLUSION CRITERIA.

1. Biclinal gammopathies.
2. MGUS associated with other malignancies.
3. MGUS associated with HIV/AIDs.
4. MGUS patients with known alcohol or drug abuse, as this may interfere with compliance.
5. Heavy smokers, as the nitrous oxide and cyanide compounds in tobacco smoke respectively inactivate and use up vitamin B12.

6. MGUS patients with advanced cardiac disease such as severe atherosclerosis, heart failure, angina, bradycardia, and serious arrhythmias.
7. MGUS patients scheduled for surgery using nitrous oxide anaesthesia : which inactivates vitamin B12.
8. MGUS patients on any form of drug therapy that interferes with or removes vitamin B12 : eg, metformin for diabetes ; continuous antibiotic use ; anti-convulsant drugs.
9. Pregnancy and serious illness (requiring systemic treatment/and/or hospitalization, until subject either completes therapy, or is stable on therapy, in the opinion of the site investigator 60 days prior to study entry.
10. Inability or unwillingness of subject to give written informed consent.

### STUDY INTERVENTIONS

#### Interventions. Administration. Duration.

50 patients in the Active Intervention arm of the study will receive a weekly IV infusion of 10,000 µcg vitamin B12, as hydroxocobalamin.

(cyanocobalamin is not considered an acceptable substitute, as it is largely 'used' or inert B12 biochemically.)<sup>22</sup> The intravenous infusion via a brachial vein will be given over half an hour in a hospital setting. The infusion should be protected from the light by a foil wrap, as hydroxocobalamin has some degree of light sensitivity. No significant side-effects are expected. But blood pressure and pulse should nonetheless be monitored before, during and a half hour post, infusion. Moreover, though anaphylaxis is deemed extremely unlikely, first aid resources for such an eventuality should be in place.

Rashes, which may indicate some sensitivity, should not be an undue cause for concern, and the patient should be reassured that they will clear up spontaneously without eventuality. The 50 patients in the active arm will additionally receive oral 30mg daily folate for the 6 months active study period, and 3 months follow-up period, as well as an oral multi-vitamin-mineral omega-3 fatty acid daily supplement for a period of 10 months. Control Group II will also receive this latter supplement for a period of 10 months. Control Group I will receive lactose and sunflower placebo for 10 months.

#### Handling of study interventions.

The pharmaceutical companies supplying the intravenous hydroxocobalamin, vitamin-mineral omega-3 supplement and placebo will deliver those in full to the participating clinical sites 1 month prior to the commencement of the study. The IV hydroxocobalamin must be stored in a dark place, at temperatures of less than 25° C.

The supplement and placebo will be dispensed in full to each patient at the commencement of the study, and patients will be asked to return any unconsumed supplements and placebo at the end of the 10 month period, as a way of monitoring compliance. Alternatively, it may be thought more

prudent to hand out supplements and placebos on a monthly basis, at the time of monthly testing.

As far as possible, the placebos should mimic the colour and appearance of the chosen supplements, (eg a sunflower oil-filled gel capsule may be a good substitute for the omega-3 fatty acid 'Cardiozen' capsule).

#### Adherence Assessment.

A registry of attendance for IV B12 infusions will be kept. Patients will be contacted by phone if absent and substitutes will be offered for any missed appointments. A pill count can be taken at the monthly testing appointment, before the next month's supply of pills is given, additional to a simple adherence questionnaire. This information will all be stored electronically as the study proceeds. Good adherence will be assiduously encouraged. We expect nonetheless that any patient who commits to this study will have a high level of motivation, in view of the aim of preventing progression to malignancy, which will be explained in the informed consent document.

#### CLINICAL AND LABORATORY EVALUATIONS.

(See schedule of evaluations.)

##### Timing of Evaluations.

##### Pre-Randomization Evaluations.

##### Recruitment.

Patients' MGUS must be properly staged in the 6 months recruitment period prior to the study. Immunoglobulin type should be noted, and a firm distinction observed between MGUS and Indolent or Smouldering Myeloma. Each MGUS patient's complete medical records should be scanned for inclusion/exclusion criteria.

##### Screening and Pre-entry.

This takes place in the month prior to study commencement. A complete physical examination should confirm inclusion/exclusion criteria suitability, together with thorough MGUS assessment. The monoclonal protein spike will be assessed twice – ie once a fortnight during this month, by high resolution agarose electrophoresis with immunofixation, to confirm a baseline reading. Full blood chemistry, liver and renal profiles will confirm there is no anaemia, hypercalcaemia or other exclusion criteria. The MCV will be noted with respect to the B12 status, though this is thought to be a late marker in B12 deficiency. True B12 sufficiency/ deficiency status will be assessed by a complex of 5 different tests. Serum B12, which is not deemed reliable with respect to true B12 bio-availability, will be included for confirmation, or refutation of the latter suppositions. A gastric atrophy test will be performed on all patients to see if it bears any significant relation to B12 status. Red cell folate will also be measured, prior to supplementation. The epidemiological questionnaires are also expected to shed light on the nutritional status of the MGUS patients, as well as revealing any obstacles to B12 absorption, or utilization. (eg. Long-term use of anti-ulcer medication, anti-diabetes drugs, poor gastric function, exposure to nitrous oxide etc.) A bone marrow aspirate will be taken to re-confirm MGUS status, and to look for chromosomal

abnormalities. Though levels of interleukin-6 are likely to be low in the pre-malignant phase of MGUS, IL-6 will be tested for in all subjects, as our hypothesis posits that one of the ways vitamin B12 may impact on malignancy is through an anti-inflammatory effect achieved by the down-regulation of NF/LB and the consequent blocking of Interleukins-6 and 1 $\beta$ . Interleukin-6 is a key promoter of Myeloma, and its presence in MGUS might be expected to herald imminent progression to Myeloma. If this is the case, an effect of vitamin B12 on IL-6 levels would be of particular interest. The addition of Bradwell's antibody test for free light chains to electrophoresis will enable any positive or negative changes during the study to be followed with greater refinement.

#### Entry

Randomization should be done in the last week of the Screening/Pre-entry months. Entry evaluations should be performed on Day 1 of Week 1, or within the 4 days following at the latest. These evaluations should precede the active intervention.

#### On-Study Evaluations

See Schedule of Evaluations 7a.

Ideally these should be performed at regular weekly intervals, on the same day as the active intervention where relevant. If a patient is on occasion unable to comply with such a schedule, the active interventions and evaluations must be done within 4 days at most of the due date.

#### Post-Intervention Evaluations

See Schedule of Evaluations 7a.

#### Final Evaluations

See Schedule of Evaluations.

#### PROTOCOL SECTIONS TO BE ADDED:

1. MANAGEMENT OF ADVERSE EXPERIENCES.

2. STATISTICAL CONSIDERATIONS.

3. DATA COLLECTION, SITE MONITORING AND ADVERSE EXPERIENCE REPORTING.

#### **CRITERIA FOR INTERVENTION DISCONTINUATION.**

The B12 MGUS active intervention study will be discontinued if a promotional effect of B12 on MGUS is seen in the active intervention arm. A promotional effect is defined as a rise of 25% or more in the 'M' spike over a period of 3 months in 25% of the active arm, in the absence of any positive effect, defined as a drop of 20% or more in the 'M' spike of patients in the active arm. Though the active intervention study would be discontinued, all MGUS patients involved in the active arm would be carefully monitored over the period of a year originally proposed for the study, using the tests and timetable listed on the schedule of evaluations. Whilst the IV and the IM B12

and oral folate would be discontinued, the multi-vitamin/mineral,  $\omega$ -3 supplements and placebos would not, as it is just conceivable that there may be some benefit to MGUS patients from this aspect of the study.

## HUMAN SUBJECTS

### 1.1 MREC and Informed Consent

This protocol and the informed consent document (Appendix III) and any subsequent modifications will be reviewed and approved by the ethics committee responsible for oversight of the study. A signed consent form will be obtained from the subject. For subjects who cannot consent for themselves, a parent, legal guardian, or person with power of attorney, must sign the consent form; additionally, the subject's assent must also be obtained if he or she is able to understand the nature, significance, and risks associated with the study. The consent form will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. A copy of the consent form will be given to the subject, parent, or legal guardian, and this fact will be documented in the subject's record.

### 1.2 Subject Confidentiality

All laboratory specimens, evaluation forms, reports, video recordings, and other records that leave the site will be identified only by the Study Identification Number (SID) to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using SIDs only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the MGUS B12 trial committee, the MREC, the sponsor, or the sponsor's designee.

### 1.3 Study Modification/Discontinuation

The study may be modified or discontinued at any time by the MREC the sponsor, or other government agencies as part of their duties to ensure that research subjects are protected.

## 2 PUBLICATION OF RESEARCH FINDINGS

Publication of the results of this trial will be governed by the policies and procedures developed by the Executive Committee. Any presentation, abstract, or manuscript will be made available for review by the sponsor, the B12/MGUS trials committee and Orthomolecular Oncology prior to submission.

## REFERENCES

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- Melphalan, and then received subsequent orthomolecular treatment which included short courses of 10,000 µcg IV B12 from Dr Patrick Kingsley MB, MRCS, LRCP, FAAEM, DA, D.Obst.RCOG. Detailed medical records and responses to treatment are both in Dr Patrick Kingsley and Dr Carmen Wheatley's possession, thanks to the assiduity as a chronicler of this very remarkable survivor.
3. This figure has been arrived at from the overview of the Mayo Clinic and other studies of MGUS progression reviewed by John Bladé and Robert Kyle in James S. Malpas, Daniel E. Bergsagel, Robert Kyle, and Ken Anderson Eds. Myeloma: Biology and Management, Chapter 22, Monoclonal Gammopathies of Undetermined Significance. (pp 515 – Evolution of MGUS), Oxford University Press, 1998.
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