Trace Element Supplementation for Parenteral Nutrition Guidelines
June 2014
(Final incorporating external reviewer feedback)
AuSPEN wishes to promote safe and evidence based practice in nutrition support, and is proud to produce clinical guidelines to facilitate this in the Australian and New Zealand context. These guidelines, however, may not apply in all situations, and individual patient or facility characteristics need to be considered in their application. These guidelines are not intended to substitute informed clinical judgment of a health care professional. No responsibility can be accepted by AuSPEN or the authors of the guidelines for the outcome of the application of these guidelines – responsibility for clinical care lies with the prescribing health care professional.
Synopsis

The 2014 AuSPEN Trace Element (TE) guidelines provide recommendations regarding the safe prescription and monitoring of TEs to patients receiving Parenteral Nutrition (PN) in Australia and New Zealand. These guidelines cover recommendations for both short term PN requirements (<20 days) and longer term PN requirements (>20 days and including home PN patients) as far as the available evidence allows.

The 2014 AuSPEN TE guidelines represent the first step of the staged review of the 1999 AuSPEN Micronutrient Guidelines. The recommendations contained in the present document cover the adult (>15 years) population. A review of the vitamin supplementation requirements in adults will follow in the coming year. Paediatric and preterm infant TE and vitamin recommendations will be dealt with separately to the adult population and will also follow in the coming year.

Significant changes to recommendations for the adult population compared with the 1999 AuSPEN guidelines include:

- 5-fold reduction in manganese (Mn) recommendation in acknowledgement of the increasing awareness of the possibility of Mn toxicity with the regular provision of 5µmol/d in long term PN recipients; and
- 2.5-fold reduction in the upper limit of copper dosage recommendation in long term PN patients due to concerns with accumulation in those with PN related cholestasis.

Clinicians are recommended to:

- Provide TEs with the provision of PN as standard practice;
- Recognise the limitations in many of the current methods of monitoring TEs;
- Monitor TE levels annually and only in longer term, stable patients unless otherwise clinically indicated; and
- Be alert to the potential of new patterns of TE deficiency and toxicity in long term PN patients due to the impact of changes in the way PN product components are stored and compounded (i.e. use of plastic and syringe-less injecting systems versus glass and metal syringe methods used previously).

Industry is encouraged to:

- Modify the composition of the currently available multi-TE products on the Australian and New Zealand market, particularly with relation to a reduction in Mn and Cu levels, and increase Se provision in line with the current recommendations.

Areas identified for further research include:

- Investigation into the TE contamination profile associated with contemporary PN compounding and storage practices;
- Surveillance of changes to TE deficiency and toxicity patterns in long term PN patients with the changes to storage and handling of PN components during compounding; and
- Development of reliable methods to facilitate TE assessment and monitoring in long term PN patients.
Summary of Trace Element Recommendations for PN

**Adult (>15 years)**
These recommendations represent *maintenance* doses for otherwise stable patients receiving PN. Those with elevated needs during acute illness or those with comorbidites that require higher replacement doses need to be assessed and prescribed TEs appropriate for their individual clinical situation.

<table>
<thead>
<tr>
<th>Trace Element</th>
<th>What is the safe and adequate daily supplementation for short term PN?</th>
<th>What is the safe and adequate supplementation for long term PN?</th>
<th>Are there any conditions in which higher supplementation should be considered?</th>
<th>Are there any conditions in which reduced supplementation should be considered?</th>
<th>What should be monitored and how frequently</th>
<th>Standard Assay</th>
</tr>
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<tbody>
<tr>
<td><strong>Zinc (Zn)</strong></td>
<td>50-100μmol (3.2-6.5mg)</td>
<td>50-100μmol (3.2-6.5mg)</td>
<td>Significant gastrointestinal losses (diarrhoea, short bowel syndrome, high output fistulae etc); &gt;20% total body surface area (TBSA) burns</td>
<td>Nil</td>
<td>Unreliable biochemical markers. Plasma Zn levels will be influence by the presence of acute phase response (APR), and therefore will decrease during trauma, infection and inflammation. There is insufficient evidence to recommend monitoring in long term patients, however monitoring frequency will need to be determined based on comorbid predispositions to increased losses</td>
<td>Serum Zn CRP*</td>
</tr>
<tr>
<td><strong>Copper (Cu)</strong></td>
<td>5-8μmol (317-508μg)</td>
<td>5-8μmol (317-508μg)</td>
<td>History of gastric bypass surgery; increased gastrointestinal losses, &gt;20% TBSA burns, Continuous Renal</td>
<td>PN related cholestasis</td>
<td>Serum copper and ceruloplasmin levels are commonly measured but these are not a reliable marker of Cu deficiency. Monitoring should be based on individual clinical indications – no recommendations for routine monitoring.</td>
<td>Serum Copper Ceruloplasmin CRP*</td>
</tr>
<tr>
<td><strong>Selenium (Se)</strong></td>
<td>0.75-1.25μmol (60-100μg)</td>
<td>0.75-1.25μmol (60-100μg)</td>
<td>Critical illness; &gt;20% TBSA Burns, (CRRT)</td>
<td>Nil</td>
<td>Serum Selenium; RBC glutathione peroxidise as a functional measure of Se status; erythrocyte Se concentration.</td>
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<tr>
<td><strong>Manganese (Mn)</strong></td>
<td>1μmol (55μg)</td>
<td>1μmol (55μg)</td>
<td>Nil</td>
<td>Demonstrated hypermanganesaemia</td>
<td>Serum or Blood Mn levels; Monitoring three to six monthly in HPN patients; Monitoring is unnecessary in short term PN.</td>
<td></td>
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<tr>
<td><strong>Iron (Fe)</strong></td>
<td>20μmol (1.1mg) may not be necessary</td>
<td>20μmol (1.1mg)</td>
<td>Long term PN recipients with conditions predisposing to Fe deficiency: ie Crohns Disease, menstrual losses, short bowel syndrome, those with repeated blood loss via blood tests.</td>
<td>Haemochromatosis</td>
<td>FBC; ferritin; transferrin No recommendations re frequency in monitoring – as clinically indicated</td>
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<tr>
<td><strong>Chromium (Cr)</strong></td>
<td>0.2-0.3μmol (10-15μg) may not be necessary</td>
<td>0.2-0.3μmol (10-15μg)</td>
<td>Pregnant PN recipients</td>
<td>Renal impairment</td>
<td>No reliable marker of Cr status. Monitoring generally not required, however may be prudent if supplementing with Multi-TE formulation in the presence of renal impairment.</td>
<td></td>
</tr>
<tr>
<td><strong>Molybdenum</strong></td>
<td>0.2μmol</td>
<td>0.2μmol</td>
<td>Nil</td>
<td>Nil</td>
<td>No reliable marker of Mo status.</td>
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<tr>
<td>(Mo)</td>
<td>(19μg) probably not necessary</td>
<td>(19μg)</td>
<td>Monitoring generally not required/recommended</td>
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<tr>
<td><strong>Iodine (I)</strong></td>
<td>1μmol (126μg)</td>
<td>1μmol (126μg)</td>
<td>Nil</td>
<td>Nil</td>
<td>Thyroid size, serial thyroid function tests (TSH, free T4) Monitoring at baseline and as clinical indicated thereafter.</td>
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<td></td>
<td>TSH T4</td>
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</table>

* In TEs that are affected by acute phase response changes, a CRP level should be assayed concurrently with TE levels to provide a measure of context in which to interpret the TE levels obtained (ie if an APR is impacting on the TE levels assayed).
Introduction

Trace elements (TEs) are present in minute amounts in body tissues and are essential for optimum human growth, health and development¹. Recommended Daily Intakes have been established for nine essential trace elements – chromium, copper, iodine, iron, manganese, molybdenum, selenium, zinc and fluoride². The essential roles of cobalt and vanadium in humans have also been proposed, however limited data to support this presently exists.³, ⁴

Cotzias defined an essential TE as one which has the following characteristics:
- Present in healthy tissues of all living things;
- Constant tissue concentration from one animal to the next;
- Withdrawal leads to a reproducible functional and/or structural abnormality;
- Addition of the element prevents the abnormality;
- The abnormality is associated with a specific biochemical change; and
- The biochemical change is prevented and/or cured along with the observed clinical abnormality⁵.

TEs usually exist in two forms: as charged ions, or bound to proteins or complexes within molecules (e.g. metallo-enzymes). Each element has different chemical properties that become critical in its functional role in cells or extracellular compartments¹.

Many enzymes require small amounts of one or more trace elements for full activity. Minute concentrations of trace elements affect the whole body though interactions with the enzymes or hormones that regulate substrates. This ability is enhanced if the substrate has some regulatory function¹.

Generally a varied diet will provide adequate TEs, notwithstanding geographical variations in availability. In terms of clinical nutrition support, while enteral feeding products and oral supplements include sufficient TEs to ensure nutritional completeness, PN solutions do not due to chemical stability considerations. TEs need to be added to PN admixtures separately closer to the time of administration using commercially available multi-TE solutions or through compounding individual TE combinations to meet individual clinical requirements.

In 1999 AuSPEN published “Guidelines for Intravenous Trace Elements and Vitamins”⁶, an initiative that developed out of the Micronutrient workshop held during the 1996 Annual Scientific Meeting. This document aimed to provide guidance to Australian and New Zealand clinicians for the provision of micronutrients, including TEs, during times of acute illness and in patients on long term (including home) PN. Recommendations at this time were based on those contained in a contemporary review of the subject⁷.

The current revision of the 1999 guidelines has been undertaken in acknowledgment of recent research and clinical findings that calls into question the adequacy of the existing recommendations: most notably, the potential toxicity concerns with long term use of the currently recommended manganese and copper levels. This poses further clinical challenges as the currently available multi-TE preparations available in Australia and New Zealand remain based on the older guidelines and have yet to be modified to align with more recent research.

While the 1999 guidelines include both TEs and vitamins, the present review is being conducted in a staged process and the present work deals only with TEs. This is in
recognition of the need to provide timely guidance in the face of the changing evidence base underpinning the practice of long term PN patients: the review of vitamin provision in this population will follow the completion of the TE review.

The recently published “ASPEN Position Paper: Recommendations of Changes in Commercially Available Parenteral Multivitamin and Multi-Trace Element Products” addresses the changes in evidence with regards to the provision of parenteral micronutrients and eloquently outlines the historical development of the use of TEs in this population. Furthermore it makes recommendations to industry regarding the revision of currently available commercial multi-TE preparations. As this publication represents the most recent review of this topic, it has been utilised as the starting point for the current AuSPEN guideline review. The ASPEN recommendations for supplementation have been considered in the context of the unique needs of PN recipients in Australia and New Zealand, and subsequently adopted or modified to meet regional requirements, as appropriate for each individual TE.

It is anticipated these guidelines will be used by clinicians in conjunction with other resources available in the literature, however comparable units of measurement are not used consistently internationally at the present time. Therefore, to allow for ease of comparison with the international literature, these guidelines report the AuSPEN recommendations and other quoted references in both SI units (μmol) and μg.

A comparison of the revised 2014 AuSPEN recommendations against the 1999 guidelines are presented in Appendix 1.

**Guideline Review Process**

The draft guidelines review was developed by a committee of volunteers with experience in research and various aspects of PN provision, which was originally convened by the President of AuSPEN with the mandate of reviewing the 1999 guidelines document. The guideline review was conducted in accordance with the AGREE II tool for guideline development and review, and in line with AuSPEN guideline development document.

Focused clinical questions pertaining to the provision of TEs in parenteral nutrition support were formulated. The ASPEN Position Paper, as the best synthesis of the literature on this topic at the present time, was used as the basis for answering the clinical questions posed. Further literature searches for each clinical question covering 2009 to present were conducted for each clinical question to ensure any research published since the 2009 ASPEN workshop was included in the present review. Search terms including the trace element and key words from each clinical question were utilised in electronic search engines (Pubmed, CINAHL), using MeSH terms and Boolean search strategies.

The available information was interpreted for application within the Australia and New Zealand context, and recommendations appropriate to local clinical practice were made.

The strength of evidence underpinning each recommendation was evaluated using the ‘NHMRC Levels of Evidence and Grades for Recommendations for Developers of Guidelines’ 11. The level of evidence of each study was assessed as I (highest) to IV (lowest). The body of evidence for each clinical question was assessed and received a grade A, B, C or D depending on the strength of evidence available and its applicability to the Australian and
New Zealand context. While it is noted that high levels of evidence are sought to justify changes to clinical practice, this should be balanced against the realities of nutritional research in which the elements of well-designed randomised controlled trials, notably blinding and randomisation, are not always possible due to ethical or logistical reasons. As such, lower grades of evidence often represent the best level of evidence available and this does not necessarily invalidate the recommendations they are attributed to. Due to these limitations, unless otherwise indicated, the recommendations contained in this document are NHMRC Grade D recommendations.

The draft version of the guideline was piloted and reviewed using a non-structured approach within the guidelines review committee and peer-reviewed using groups within AuSPEN (Clinical Practice Committee, AuSPEN council). Internationally recognised experts in the field of micronutrients were sought for their critical appraisal of and input into the guidelines through feedback and application of the AGREE II tool9. Local end users with experience in PN provision also provided peer review using the AGREE II framework9. Feedback was incorporated into a further revision of the guidelines. The final guideline was approved by members of the guideline development group and AuSPEN Council. A more detailed description of this process can be found in Appendix 2.

A planned review these guidelines is scheduled in 5 years time.

Scope and Purpose of the TE guidelines

The guidelines are primarily designed for Australian and New Zealand clinicians prescribing and monitoring PN: This includes but is not limited to Medical Officers including Gastroenterology specialists, pharmacists, and dietitians. These guidelines are intended to provide guidance in the prescription of maintenance doses TEs to primarily clinically stable patients receiving PN. They include short term PN (such as during acute illness) to long-term PN. Longer term PN patients for the purpose of these guidelines are defined as patients with chronic intestinal failure (over 20 days PN provision12), and may be medically stable and receiving PN in the community, or during an acute and prolonged hospital admission. These patients may maintain some level of oral intake, however the adequacy due to limitations on amount tolerated or secondary to altered anatomy necessitate the need for PN to maintain their nutritional status.

While these guidelines attempt to cover the majority of situations in which PN may be provided as part of medical or life sustaining treatment as far as the currently available literature allows, additional TE requirements precipitated by acute or critical illness and/or comorbid conditions that predispose the PN recipient to higher needs will require replacement in excess of the recommendations contained herein. This spectrum spans from

The secondary purpose of this guideline is to provide a base from which to inform industry to modify the currently available multi-TE preparations to reflect the best available evidence and ensure patient safety. This is an important and necessary step required to enable safe and evidence based PN practice in Australia and New Zealand.

These guidelines do not attempt to address the enteral requirements for TE supplementation, nor are they intended to provide a comprehensive review of the biological roles, dietary sources or deficiency and toxicity states of each TE: An excellent summary of these are presented as Appendix 1 of the ASPEN position paper8.
Trace Element Recommendations for Adults

Zinc

How should Zinc requirements be assessed, prescribed and monitored for patients on short term and long term PN to ensure adequate intake to meet individual patient needs and minimise metabolic complications?

Zinc (Zn) is essential for wound healing, immune function, growth and fertility, maintenance of plasma protein integrity and regulation of gene expressions\(^2,13\). It is widely distributed in a variety of foods and deficiency symptoms are rare\(^2,13\).

Zn deficiency has a significant effect on nucleic acid metabolism which influences the protein and amino acid metabolism. Other deficiency symptoms include delayed wound healing, decreased immune function and hair loss\(^13\).

Zinc requirements in PN patients with and without abnormal losses have been reported extensively\(^13\). In stable patients, 45-60\(\mu\)mol (2.9-3.9mg)/day Zn supplementation has been recommended\(^7,8,13,14\). In PN patients without diarrhoea, 38\(\mu\)mol/day has been proposed as a minimum safe level\(^13\). Patients with significant gastrointestinal losses, such as those with short bowel syndrome or high output enterocutaneous fistulae, may require increased Zn provision of up to 183\(\mu\)mol (12mg)/d per litre of gastrointestinal fluid loss\(^15\). Patients with poor wound healing or significant burns\(^8,13,14\) have elevated Zn requirements and have been shown to tolerate Zn supplementation of up to 550\(\mu\)mol (36mg)/day without toxicity\(^16\).

Zn toxicity is rare and has only been documented in cases of large dosage errors in amounts >765\(\mu\)mol (>50mg)/day\(^17\).

Whilst acutely ill patients in hospital may require extra Zn due to increased losses, long term established home PN patients will require lower dose of Zn except in very hot months in Australia where there could be significant losses through sweating and the requirements will increase. Hence it is important to provide Zn according to the patient’s physiological status and requirements.

AuSPEN recommends routine Zn supplementation of 50-100\(\mu\)mol (3.2-6.5mg)/day in both short and long term PN recipients in recognition of the broad variation of requirements within this population.

Measuring plasma Zn is inaccurate and can be influenced by acute phase response where it appears to decrease in trauma, infection and stress\(^13,16\) and therefore levels should be interpreted in context of CRP levels. Deficiency is rare and only seen in patients with prolonged Zn deprivation\(^16\).

There is insufficient evidence regarding the frequency of monitoring Zn in long term PN patients. Each patient should be assessed taking into consideration their clinical symptoms and comorbid physiological state (ie gastrointestinal loses, hypercatabolism)\(^13\).
Copper

How should Copper requirements be assessed, prescribed and monitored for patients on short term and long term PN to ensure adequate intake to meet individual patient needs and minimise metabolic complications?

As an essential component of many enzymes, Copper (Cu) is an important TE in humans and plays a significant role in connective tissue synthesis and iron metabolism through its role in a number of metalloenzymes. Deficiency symptoms include anaemia (hypochromic and microcytic), leukopenia, bone and joint disorders as well as neuropathy, myopathy and myeloneuropathy. Deficiency has been described in patients with gastric bypass surgery and through effluent in those requiring prolonged continuous renal replacement therapy (CRRT) place some groups of critically ill patients at additional risk of deficiency.

Cu deficiency is rarely seen outside of prolonged PN provision in the absence of Cu supplementation, however those with increased losses may benefit from increased Cu prescription. Patients with gastrointestinal losses including diarrhoea may be given 6.3-7.8 µmol (400-495 µg)/day.

Cu toxicity is rare in humans however excess Cu, which is concentrated in brain, kidney and liver, can cause harmful effects in long term PN patients in the presence of PN associated cholestasis. In these patients the dose may be reduced to 2.4 µmol (150 µg)/day.

AuSPEN recommends Cu supplementation of 5-8 µmol (317-508 µg)/day in keeping with the current ASPEN position paper. The recommendation brings a significant reduction from the 1999 AuSPEN recommendations in acknowledgement of excessive Cu in current parenteral TE solutions.

There is no definite recommendation on the frequency of supplementation as Cu deficiency is very rare. It is recommended that requirements be reassessed periodically and adjustments made based on individual clinical requirements.

Assessing Cu deficiency or toxicity is difficult as serum values will be low only in very severe deficiency. Serum Cu and ceruloplasmin levels are often elevated in APR, pregnancy, liver disease, malignancy and post myocardial infarction, therefore cannot be considered as a reliable marker of Cu deficiency. CPR levels should be measured concurrently with Cu levels in order to provide a context for interpreting the presence of APR. Low plasma levels, on the other hand, can be considered a reliable measure of deficiency in the absence of APR.
Selenium

How should selenium requirements be assessed, prescribed and monitored for patients on short term and long term PN to ensure adequate intake to meet individual patient needs and minimise metabolic complications?

Selenium (Se) functions as an antioxidant and in redox reactions and thyroid metabolism. It is a component of selenoproteins such as glutathione peroxidise. Prior to 1990 low levels of Se in soils in New Zealand and in certain parts of Australia meant that dietary intakes and Se status were lower than in many other countries. This has since improved but Se status remains lower than in many other countries\textsuperscript{2,26}. The importance of this in relation to provision of Se in PN remains unclear.

Observational studies of Home PN (HPN) patients have shown biochemical and clinical evidence of Se deficiency. A recent review by Shenkin concluded that an intake of 1 \( \mu \text{mol/day} \) (80\( \mu \text{g/day} \)) is adequate to maintain tissue concentrations in most patients\textsuperscript{27}. Short term PN requirements are less certain but many patients will have increased requirements if they have ongoing or concurrent disease or are post-surgical because of increased metabolic and antioxidant needs\textsuperscript{28}.

Patients who are critically ill, septic, are receiving CRRT and/or have major burns may benefit from higher doses of Se as IV/PN supplementation alone or in combination with other antioxidants\textsuperscript{30}. This however remains a weak recommendation in the Canadian Clinical Practice Guidelines and European Society for Parenteral and Enteral Nutrition guidelines, and the dose remains uncertain\textsuperscript{29,30}.

The currently available parenteral trace element PN additives in Australia and New Zealand deliver Se in a range from 0.4 – 0.5\( \mu \text{mol/day} \) (32 – 40\( \mu \text{g/day} \)) when given at the recommended dose. These doses are almost certainly too low and AuSPEN endorses the ASPEN recommendation that the adult daily parenteral Se requirement should be increased to 0.75 – 1.25\( \mu \text{mol/day} \) (60-100\( \mu \text{g} / \text{day} \)) for short-term and long term patients (including HPN)\textsuperscript{8}. This should be an industry standard for locally formulated trace element additives and be part of a multi-trace element additive. (NHMRC Grade C.)

Serum Se has been the preferred measure of nutritional status but is still biased by short term intake and levels correlate imperfectly with tissue levels. Levels may fall by 20-30\% with acute illness and if being measured should be interpreted in context of a simultaneous CRP level.

Measurement of RBC glutathione peroxidise is a defacto measurement of Se status but it should be noted that RBC glutathione peroxidase activity can be maintained for up to 6 months in patients receiving Se deficient PN\textsuperscript{31}. A promising new development recently reported suggests the use of erythrocyte Se concentration as a marker of Se status\textsuperscript{32}. The assay method appeared robust and was unaffected by the systemic inflammatory response. Local laboratory availability of tests and expertise should be considered. (NHMRC Grade C). There is insufficient evidence to recommend frequency of monitoring but once a year may be sufficient for most\textsuperscript{8}. 

Manganese

How should Manganese requirements be assessed, prescribed and monitored for patients on short term and long term PN to ensure adequate intake to meet individual patient needs and minimise metabolic complications?

Mn is an essential trace element required for various enzymatic reactions essential to the metabolism of macronutrients. However, Mn deficiency in humans has only been documented in experimentally-induced cases, suggesting that Mn is present in all diets in adequate amounts. In patients receiving HPN, it appears that Mn toxicity is a greater concern than Mn deficiency and supplementation could represent adverse health effects without evidence of health benefit. Small cohort studies report variable Mn toxicity in New Zealand and Australia but data is lacking of any wide-ranging systematic toxicity in HPN patients in Australia and NZ.

Two reviews have collated case reports of Mn toxicity in patients on long term PN (about 500 adult patients). Most patients had no clinical symptoms but a small number developed neurological signs including confusion and irritability and Parkinson Disease like symptoms. Elevated whole blood Mn has been shown to correlate with MRI signal intensity in part of the brain (globus pallidus), both of which decrease after cessation of parenteral Mn supplementation.

In a dose finding study of 12 HPN patients, Takagi et al showed that normal Mn levels were maintained when patients were supplemented with 1 μmol/day of Mn (55μg/d). They also reported that six participants showed moderate MRI intensity for Mn in the globus pallidus when supplemented with 2μmol/d (110μg/d) of Mn. This small study suggested that higher supplementation may lead to increased Mn deposition. Conversely no supplementation in this group caused a fall in RBC Mn but the clinical consequences of this remain uncertain.

AuSPEN supports the ASPEN position paper recommendation of supplementation of 1 μmol/d (55μg/d) of Mn and is of moderate strength evidence. (NHMRC Grade C).

Mn may be a contaminant of all PN solutions but there is limited evidence regarding the formulations used in Australia and New Zealand. Even low level contamination such as reported by Takagi of 0.25μmol/L PN (14μgs/L) may contribute to Mn status significantly but the relevance of this to patient care in Australia and New Zealand remains uncertain. There is an urgent requirement for local contamination studies to be reported in a clinically meaningful way together with a labelling requirement for allowable Mn contamination.

Whole blood Mn is the preferred test for Mn levels as it elevates and normalises again within 3 months of provision and discontinuation of supplementary Mn and it also correlates with MRI measurements of any brain deposition.

Three to six monthly monitoring of Mn in HPN patients may be prudent if high dose Mn supplementation within a trace element formulation is used. Short term monitoring may be unnecessary. Patients who have stable levels and who receive 1μmol/d (55μg/d) may only need yearly monitoring.
Iron

How should Iron requirements be assessed, prescribed and monitored for patients on short term and long term PN to ensure adequate intake to meet individual patient needs and minimise metabolic complications?

Iron (Fe) is a component of a number of proteins including haemoglobin, myoglobin, cytochromes and enzymes involved in redox reactions.

Dietary Fe is absorbed in the duodenum and this route may be unavailable for patients requiring PN. Short term PN patients may have sufficient iron stores to overcome lack of provision of Fe or be given blood products as a therapeutic measure if there are significant blood losses. Longer term PN patients require Fe supplementation, especially in short bowel syndrome or Crohn’s disease where there may be additional iron loss. Menstrual losses and repeated blood tests may represent additional losses. Although there is no direct supportive evidence base for intravenous Fe in pregnancy the additional requirements in second and third trimesters must be considered in pregnant women who are HPN dependent. Clinicians caring for HPN patients should consider carefully if all requests for blood tests are necessary for patient care.

HPN patients who become Fe deficient maybe given additional Fe as part of the PN admixture but Fe has poor compatibility with multi-nutrient “all-in-one” bags. Additions of 10μmol (558μg)/L elemental Fe to “all-in-one” bags in addition to the standard Fe containing trace element has been a standard practice in some Australian and New Zealand centres for many years (ref). Oral Fe may also be prescribed where functional proximal small bowel remains but may be poorly tolerated by many HPN patients. Fe deficiency may be treated by a separate Fe parenteral infusion (iron polymaltose [FerrumH ®] or iron sucrose [Venofer ®]). Local preferences and administration guidance should be sought including managing the risk of adverse reactions.

The comorbidity of haemochromatosis may also constitute a contraindication to iron administration in PN. Fe overload as a consequence of PN has rarely been reported with long term PN but nonetheless iron status needs regular monitoring. Claims that Fe infusions stimulate bacterial growth during infection have limited evidence in the context of contemporary therapy and modern practice in stable patients.

Some of the currently available parenteral TE additives in Australia and New Zealand contain Fe (20μg or 1-1.1mg /dose) and there is an absence of reports of toxicity over the past decade associated with this dose. AuSPEN continues to recommend this as a safe level of supplementation and that it should continue to be an industry standard for locally formulated trace element additives and be part of a multiple trace element additive.

Inadequate Fe intake can lead to varying degrees of deficiency. Low Fe stores may be indicated by low serum ferritin and a decrease in Fe binding capacity. It should be noted, however, that ferritin is an acute phase response protein and will increase during illness even in the presence of iron deficient anemia. Early Fe deficiency may be indicated by decreased serum transferrin saturation whereas Fe deficiency anaemia is indicated by a low haemoglobin and haematocrit as well as reduced mean corpuscular haemoglobin and volume. (NHMRC Grade B) In critically ill patients hepcidin represents a newly identified means of distinguishing true Fe deficiency from the effects of inflammation.
Chromium

How should chromium requirements be assessed, prescribed and monitored for patients on short term and long term PN to ensure adequate intake to meet individual patient needs and minimise metabolic complications?

Trivalent Chromium (Cr) is the biologically active form of Cr and functions as a coenzyme in a variety of metabolic reactions and as component of metalloenzymes. It is recognised for its importance in optimising glucose tolerance.\(^45\)

Cr is absorbed in the small bowel, but with low bioavailability (0.4% to 2.5%)\(^46\). Patients with some functional small bowel receiving supplemental PN may receive adequate chromium from their oral diet and/or chromium contamination through their PN solutions.

While concerns are frequently cited that high serum Cr levels detected in both short and long term PN patients may result in toxicity and/or kidney damage,\(^8,46,47\), it should be noted there have been no reports of Cr toxicity in adult patients associated with elevated serum levels either from PN or hip implants\(^3,8\).

Four case reports in the literature describe the development of Cr deficiency in patients receiving long term PN provision without or with inadequate Cr provision. In these cases, symptoms manifested between 6mths and 2 years of PN commencement\(^48-51\). Cr depletion during pregnancy has been described\(^46\), and therefore may need to be considered in the event of providing PN during pregnancy\(^46\).

Some older evidence suggests Cr contamination of PN solutions may provide up to 0.3 µmol/d (15µg/d)\(^8,47,52\), however no Australian and New Zealand data is presently available and the effect of routine omission of Cr from long term PN provision has not been assessed\(^8\).

AuSPEN recommends that Cr should be routinely supplemented in patients receiving short and long term PN at levels of 0.2 to 0.3µmol/d (10-15µg/d). This represents a reduction in the upper recommendation from the 1999 AuSPEN Micronutrient guidelines in recognition of Cr as a possible contaminant of PN solutions.

Due to the absence of reliable methods for assessing Cr status, Cr levels are often not monitored in Australia and New Zealand. For patients receiving Cr as part of their PN multi-TE supplementation in the presence of renal impairment (not receiving dialysis), monitoring serial serum concentrations as clinically indicated may be advised. Plasma Cr levels are reduced during acute illness\(^46\). Both short and long term PN patients receiving PN supplemented with Cr have demonstrated elevated circulating serum Cr levels\(^8,46,47\). It is not clear how long Cr needs to be withheld from PN solutions to get an accurate reflection of tissue status from serum or plasma samples\(^46\). Red blood cell concentrations will not reflect levels of trivalent Cr and should not be used to assess Cr status\(^46\). Urinary Cr excretion is a poor indicator of Cr tissue status\(^46\). The only reliable way to diagnose a Cr deficiency is by demonstrating resolution in insulin resistance or abnormal glucose clearance that resolves with chromium supplementation, and reappears if supplementation is discontinued\(^46\).
Molybdenum

How should molybdenum requirements be assessed, prescribed and monitored for patients on short term and long term PN to ensure adequate intake to meet individual patient needs and minimise metabolic complications?

Molybdenum (Mo) is required as a cofactor in enzymes involved in the catabolism of sulphur amino acids and purines, including xanthine oxidase, sulphite oxidase and aldehyde oxidase.

In the likelihood of reasonable premorbid Mo status in the Australian region, those receiving PN for a short period of time may not require Mo supplementation due to adequate body stores. Similarly those receiving supplemental PN in the presence of a functional stomach and proximal small bowel with continuing on an oral/enteral intake may absorb adequate amounts of Mo to avoid the need for parenteral supplementation.

Australia and New Zealand routinely supplements Mo in their multi-TE solutions although Mo is thought to be a contaminant of PN solutions. However the last published Australia and New Zealand investigation into Mo contamination occurred over 30 years ago, and the levels obtained at this time (<5 to 15μg/d [<0.5-16μmol/L]) cannot be generalised to the present time due to changes in compounding practices in the ensuing years. Given the absence of reported toxicity or deficiency concerns with the currently provided levels in the presently available multi-trace element solutions, AuSPEN supports maintaining the current level of supplementation in the Australia and New Zealand PN practice (0.2μmol/d [19μg/d]).

Mo is not routinely monitored due to the limitations of biochemical markers of Mo status. Serum and plasma are difficult to obtain due the low circulating levels of Mo. Plasma levels do no correlate with Mo status. Urinary Mo levels reflect dietary intake of Mo and do not correlate with Mo status.

In the absence of routine laboratory data, clinicians should be aware of the cluster of symptoms and biochemistry presented in the Abumrad case report, and consider Mo deficiency should these present together: these included generalised oedema, lethargy, disorientation and coma in the presence of elevated plasma methionine levels (4 to 5 fold of normal controls), low serum uric acid (<20% of normal controls) and low urinary uric acid excretion.
**Iodine**

How should iodine requirements be assessed, prescribed and monitored for patients on short term and long term PN to ensure adequate intake to meet individual patient needs and minimise metabolic complications?

Iodine (I) is an essential trace element that facilitates normal growth and development through its role in the thyroid hormones thyroxine (T\(_4\)) and triiodothyronine (T\(_3\)).\(^{57}\)

Patients receiving PN in Australia and New Zealand may be at higher risk of low baseline I levels due to the region’s relatively low soil I levels, particularly if fortified foods such as bread and salt\(^{58}\) have not been routinely consumed.

In patients with adequate baseline stores, thyroid stores of I may be sufficient to meet metabolic requirements for short term PN provision or for <3mths\(^{59,60}\). Short term PN (28 days) with or without I did not affect T3 and T4 levels in patients receiving cisplatin based chemotherapy for the management of oesophageal cancer\(^{61}\). However it should be noted that this data has been sourced from countries with good I sufficiency: no comparable data on the Australian or New Zealand population is available at the present time.

As I is absorbed in the duodenum and is highly bioavailable\(^{59}\) patients on PN with a functioning duodenum and maintaining some oral intake may not require additional I supplementation. A Brazilian study showed that patients with intestinal failure or short bowel syndrome maintained their I status and thyroid function while consuming a normal diet and receiving long term PN without I supplementation\(^{62}\). One case of I deficiency while on long term PN has been described in an 18 year old with SBS consuming a limited oral intake, in the absence of PN I supplementation\(^{59}\).

Regular administration of amioderone or iodinated contrasts are the only likely sources of coincidental I provision in patients receiving PN in Australia and New Zealand since chlorhexidine antiseptics have replaced povidone-iodine antiseptics in routine practice\(^{59}\).

AuSPEN recommends a daily maintenance dose of 1.0μmol I per day (126μg/d) for adult patients on short or long term PN.

Monitoring of I status through monitoring of thyroid size and thyroid function tests (thyroid stimulating hormone (TSH), free T4) should be conducted at baseline and routinely thereafter as clinically indicated.\(^ {59}\) Thyroid function tests – TSH,T3 and T4 – are the most commonly used biochemical tests in Australia and New Zealand to monitor I status in patients receiving PN, however it should be noted these are not reliable measures as they do not consistently fall below normal ranges in the presence of I deficiency\(^{59}\). Furthermore, the interpretation of levels of T3, T4 and TSH may be further affected in acutely unwell patients who experience ‘euthyroid sick syndrome’\(^ {59}\). However long term serial thyroid function tests may be useful to monitor general trends in I status and may assist in guiding clinical decision making with relation to supplementation needs in long term PN patients\(^{60}\).
**Recommendations for Clinicians**

TEs are essential components of human nutrition and should be provided daily with PN provision from the time of commencement as standard practice in both short and longer term PN provision.

All PN patients require appropriate nutritional monitoring, including consideration about adequacy or excess of TE provision specific to their individual clinical circumstances. However, it should be highlighted that biochemical assessments of TE are expensive, many TEs do not have reliable biochemical tests available at the present time, and those that do will often not yield clinically relevant information when patients are in an acute phase of illness. For this reason, unless otherwise clinically indicated, monitoring of TE levels should be reserved for clinically stable, longer-term PN patients. In cases where monitoring is being performed in more acute patients, a CRP level in which to provide context the level of inflammation or presence of acute phase response that may be impacting results should be performed. In stable HPN patients, annual TE monitoring should be sufficient.

**Recommendations for Industry**

The current commercially available multi-TE products available in Australia and New Zealand are outlined in Appendix 1. These products, having been developed to align with former guidelines and recommendations, will require reformulation to enable evidence based TE provision in the Australia and New Zealand.

A new multi-TE product in which the TE doses mirror the recommendations contained in this document would represent the ideal commercial product to meet the clinical needs for Australia and New Zealand PN practice, based on the evidence available at the current time.

Alternatively, modifying existing formulations to accommodate the following would provide clinicians with safer multi-TE preparations for practice:

- Mn provision decreased to 1μmol/d (55μg/d)
- Cu provision decreased to 5μmol/d (315μg/d)
- Se provision increased to the higher end of the recommendations (~1.2μmol/d [~100μg/d])

**Implications of recent changes in PN practices on future TE provision:**

**Recommendations for Surveillance and Future Practice in PN**

All recommendations regarding TE provision in PN to date are based upon four decades of PN practice that has relied almost exclusively on PN formulations compounded from component solutions packaged in Type 3 Borosilicate glass bottles and glass ampoules, and components drawn up and compounded using metal syringes.

Extraction of TE from glass bottles in which PN components were sterilised and stored, along with their rubber closures, have long been recognised as a source of metallic contamination. In 1986 Shike observed that “contamination of PN solutions with ultratrace elements was widespread and variable”, and as well as the intentionally added TE (Zn, Cu, Cr, Mn and Se), boron, molybdenum, nickel, vanadium, aluminium and cadmium were detected in amounts in several cases exceeding the daily estimated absorption from the gastrointestinal tract. Of particular concern was aluminium contamination, detected at levels from 4-9 times daily gastrointestinal absorption.⁶³.
The use of metal needles both to draw up and administer additions and medications into parenteral fluid systems have been replaced by the use of plastic needle-less systems. Verseik reported: "Four passages of a volume of Sod. Chlor 0.9% through a metal needle increased Ni content from 10\(\mu\)g.L\(^{-1}\) to 45\(\mu\)g.L\(^{-1}\)." \(^{64}\) In this setting, trace element deficiencies in stabilised PN patients are relatively rare.

However in recent years there has been a widespread change from glass to plastic container systems and to syringe-less systems. With this the pattern of previously assumed contamination of TEs in PN provision has changed, the impact of which is yet to be described in clinical practice.

While plastic containers are much less likely to contribute trace metals to PN solutions than glass, some level of contamination may be expected to continue. However a different range and extent of extracted TE may be anticipated and may be revealed by future studies. For example, analysis of aluminium in glass bottles with rubber closures revealed 1.57% in glass, 4.54% in rubber, compared with 0.05% recovery from an (unspecified) plastic container.\(^{55}\) Similarly, Pluhator-Murton reported plastic syringes as containing 22 elements in addition to the carbon and hydrogen of the base plastic and significant amounts of Mn, Cr, Fe, Zn, nickel in the rubber tip of the plunger that is not present in the two-piece syringes coming from some manufacturers today.\(^{66}\)

In view of the potential impact of alterations to unintentional TE contamination brought about by these changes, practitioners should now be alert to the heightened possibility of TE deficiencies amongst long-term and HPN patients. While this may suggest more frequent monitoring is warranted, the limitations on assessing TE status are acknowledged and outlined throughout this document.

We are now in uncharted waters with relation to TE provision in contemporary PN practice. It highlights the need for a further research and surveillance in this area of PN to inform clinicians and industry with regards to the provision of adequate and safe PN now and into the future.

**Recommendations for Research in Parenteral Nutrition Support**
There is a paucity of research in the area of TE provision in PN. The majority of the available literature is 20 to 40 years old, and due to the changes in PN practices described above it is currently unknown to what degree it can now be generalised to the modern PN context. Furthermore, with few exceptions, the research has been conducted outside of Australia and New Zealand and therefore the impact of different solutions, practices and this region’s vulnerability to lower baseline TE levels, such as Se and I, limit the degree to which these results can be applied to our population.

As such, further research in this area of PN provision is required. These include but are not limited to:

- Investigation into the TE contamination profile associated with contemporary PN compounding and storage practices;
- Surveillance of changes to TE deficiency and toxicity patterns in longer term patients with the changes to storage and handling of PN components during compounding;
- Development of reliable methods to facilitate TE assessment and monitoring in long term PN patients; and
• Validation of earlier poor quality studies into safe and adequate provision of TE in short and long term PN patients.
Appendix 1 – Comparison of the AuSPEN 2014 recommendations with 1999 recommendations for daily Trace Element provision

Adults (>15yrs)

<table>
<thead>
<tr>
<th>Trace Element</th>
<th>1999</th>
<th>2014</th>
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</thead>
<tbody>
<tr>
<td>Zinc</td>
<td>50-100 µmol (3.3-6.5mg)</td>
<td>50-100 µmol (3.3-6.5mg)</td>
</tr>
<tr>
<td>Copper</td>
<td>2-20 µmol (0.12-1.2mg)</td>
<td>5-8 µmol (317-515μg)</td>
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<tr>
<td>Selenium</td>
<td>0.4-1.5 µmol (35-120μg)</td>
<td>0.75-1.25 µmol (60-100μg)</td>
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<tr>
<td>Iron</td>
<td>20 µmol (1.1mg)</td>
<td>20 µmol (1.1mg)</td>
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<tr>
<td>Manganese</td>
<td>5 µmol (275μg)</td>
<td>1 µmol (55μg)</td>
</tr>
<tr>
<td>Chromium</td>
<td>0.2-0.4 µmol (10-20μg)</td>
<td>0.2-0.3 µmol (10-15μg)</td>
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<tr>
<td>Molybdenum</td>
<td>0.4 µmol (38μg)</td>
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<tr>
<td>Iodine</td>
<td>1.0 µmol (126μg)</td>
<td>1.0 µmol (126μg)</td>
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### IV TRACE ELEMENT ADDITIVES PER RECOMMENDED ADULT DOSE (Adults)

<table>
<thead>
<tr>
<th>Supplied by</th>
<th>Trace Element</th>
<th>Zn</th>
<th>Cu</th>
<th>Mn</th>
<th>Cr</th>
<th>Se</th>
<th>I</th>
<th>Fe</th>
<th>Mo</th>
<th>F</th>
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<tbody>
<tr>
<td>Baxter (Aus/NZ)</td>
<td>MTE FE μmol</td>
<td>100</td>
<td>20</td>
<td>5.0</td>
<td>0.2</td>
<td>0.4</td>
<td>1.0</td>
<td>20</td>
<td>0.2</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>μgram</td>
<td>6500</td>
<td>1300</td>
<td>270</td>
<td>10</td>
<td>32</td>
<td>130</td>
<td>1200</td>
<td>19</td>
<td>-</td>
</tr>
<tr>
<td>Baxter (Aus/NZ)</td>
<td>MTE CC μmol</td>
<td>61.6</td>
<td>15.74</td>
<td>5.82</td>
<td>0.19</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>μgram</td>
<td>4000</td>
<td>1000</td>
<td>320</td>
<td>10</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Fresenius Kabi</td>
<td>Addamel μmol</td>
<td>100</td>
<td>20</td>
<td>5.0</td>
<td>0.2</td>
<td>0.4</td>
<td>1.0</td>
<td>20</td>
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<td>50</td>
</tr>
<tr>
<td>(NZ only) Not presently licensed in Aus</td>
<td>μgram</td>
<td>6500</td>
<td>1300</td>
<td>270</td>
<td>10</td>
<td>32</td>
<td>130</td>
<td>1200</td>
<td>19</td>
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</tr>
<tr>
<td>Biomed (NZ only)</td>
<td>Biomed TE adult μmol</td>
<td>45.9</td>
<td>6.29</td>
<td>1.46</td>
<td>0.23</td>
<td>0.51</td>
<td>1.10</td>
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</tr>
<tr>
<td></td>
<td>μgram</td>
<td>3000</td>
<td>400</td>
<td>80</td>
<td>12</td>
<td>40</td>
<td>140</td>
<td></td>
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</tbody>
</table>

*Information in this table was supplied and checked by the relevant pharmaceutical companies.*
Appendix 3 – Membership of Guidelines Review Committee

Trace Elements Working Group - Convened by Ibolya Nyulasi, President of AuSPEN
Lyn Gillanders - Dietitian
Azmat Ali - Dietitian
Elizabeth Isenring - Dietitian
Emma Osland - Dietitian
Patrick Ball - Pharmacist
Mel Davies – Pharmacist

Authors of the Guidelines and contributions to the process

<table>
<thead>
<tr>
<th>Authors</th>
<th>Contributions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emma Osland</td>
<td>Synopsis, Introduction, Guidelines Review Process, Scope of Guidelines, Adult Chromium, Adult Iodine, Adult Molybdenum, Recommendations to clinicians, Recommendations to industry, Appendices 1, 3, 4, 5. Collation and formatting of document and manuscript. Facilitation of the guidelines review. NHMRC Grading.</td>
</tr>
<tr>
<td>Lyn Gillanders</td>
<td>Adult Selenium, Adult Iron, Adult Manganese Appendix 2. Draft content review and checking.</td>
</tr>
<tr>
<td>Azmat Ali</td>
<td>Adult Zinc, Adult Copper, NHMRC Grading.</td>
</tr>
<tr>
<td>Elizabeth Isenring</td>
<td>Adult Manganese, NHMRC Grading. Draft content review and checking.</td>
</tr>
<tr>
<td>Patrick Ball</td>
<td>Implications of recent changes in PN practices on future TE provision: Recommendations for Surveillance, Research and Future Practice in PN. Draft content review and checking.</td>
</tr>
<tr>
<td>Mel Davies</td>
<td>Implications of recent changes in PN practices on future TE provision: Recommendations for Surveillance, Research and Future Practice in PN</td>
</tr>
</tbody>
</table>

Invited Reviewers
Mette Berger – Intensivist and Trace Element Expert, Switzerland
Alan Shenkin – Biochemist, Trace Element Expert, United Kingdom
Truc Nguyen – Pharmacist, New Zealand
Katerina Angstmann – Clinical Nurse, Australia
Ra’eesa Doola – Dietitian, Australia

Other Acknowledgements
Many thanks to Mette Berger and Alan Shenkin for their expert and detailed feedback on the guidelines.

Many thanks to Liz Purcell for coordinating the external review.
Appendix 4 – Process Report

Writing
For the development of each TE recommendation, the following process was undertaken:

- The ASPEN position paper and relevant appendix sections were consulted and the original papers cited within these were reviewed.
- For new publications from 2009 onwards, a literature search using PICO questions were conducted. These included consulting electronic search engines, using relevant synonyms for the PICO question wording.
  For example, for Iodine in Adults:
  PICO 1: For adult patients receiving short and long term PN, what level of iodine supplementation, compared to no supplementation, is required to avoid deficiency and toxicity?
  PICO 2: For adult patients receiving short and long term PN, what methods (compared with other alternative methods available) are most effective for monitoring iodine status?

  Search terms below were utilised in Pubmed and CINAHL:

  - Terms: (iodine) + “parenteral nutrition”; synonyms including ‘TPN’, ‘PN’, ‘intestinal failure’ and ‘home parenteral’
  - Limits: 18yrs +, 1/1/2009-31/12/2013
  - Hits = 6, 1 not relevant as related to catheter line care

  Further searches using combination so the same search terms were used in Google Scholar, though did not yield further studies.

- New articles were sourced and information synthesised with those obtained from the ASPEN paper, and these were used to answer the clinical questions posed.
- Information specific to the unique geographical environment that may impact baseline TE status in Australian and New Zealand were considered. These included but were not limited to the FSANZ Total Diet Survey and the background information underpinning the Australian and New Zealand Nutrient Reference Values.
- Face to face (8 March, 14 November 2013) and teleconference (9 September, 22 October, 17 December 2013) meetings were utilised to determine geographically appropriate TE recommendations and to facilitate the completion of the draft guidelines.

Review
In the first instance the draft in its entirety was peer reviewed by the TE Working Group. Subgroups of the TE Working Group reviewed the content of the draft and compliance with AGREE II (EO, PB, LG, IN) and the NHMRC grading of recommendations and levels of evidence contributing to the recommendations (EO, LI, AA). These were conducted through teleconferences and face to face meetings respectively. The final outcome of this process was subjected to external review.

The external review process was coordinated by AuSPEN’s Clinical Practice Committee, excluding those on both this committee and the TE Working Group (EO, PB, LG). Recognised experts in the field of micronutrients, PN and/or guideline development were
contacted with a request to review the draft guidelines by a member of the AuSPEN Clinical Practice Committee. An online survey (via Survey Monkey®) that contained the elements of AGREE II was forwarded to those who agreed to participate. The results were scored as per the AGREE II tool.

Feedback from reviewers was incorporated into the final document. This final version was reviewed by AuSPEN council for final approval prior to publication on the AuSPEN website.
## Appendix 5 – Glossary of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>ASPEN</td>
<td>American Society for Parenteral and Enteral Nutrition</td>
</tr>
<tr>
<td>APR</td>
<td>Acute Phase Response</td>
</tr>
<tr>
<td>AuSPEN</td>
<td>Australasian Society for Parenteral and Enteral Nutrition</td>
</tr>
<tr>
<td>Cr</td>
<td>Chromium</td>
</tr>
<tr>
<td>CRP</td>
<td>C Reactive Protein</td>
</tr>
<tr>
<td>CRRT</td>
<td>Continuous Renal Replacement Therapy</td>
</tr>
<tr>
<td>Cu</td>
<td>Copper</td>
</tr>
<tr>
<td>Fe</td>
<td>Iron</td>
</tr>
<tr>
<td>HPN</td>
<td>Home Parenteral Nutrition</td>
</tr>
<tr>
<td>I</td>
<td>Iodine</td>
</tr>
<tr>
<td>IV</td>
<td>Intravenous</td>
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<tr>
<td>Mn</td>
<td>Manganese</td>
</tr>
<tr>
<td>Mo</td>
<td>Molybdenum</td>
</tr>
<tr>
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<td>Magnetic Resonance Imaging</td>
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<tr>
<td>RBC</td>
<td>Red Blood Cell</td>
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<tr>
<td>Se</td>
<td>Selenium</td>
</tr>
<tr>
<td>TBSA</td>
<td>Total Body Surface Area</td>
</tr>
<tr>
<td>TE</td>
<td>Trace Elements</td>
</tr>
<tr>
<td>Zn</td>
<td>Zinc</td>
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10. CLINICAL PRACTICE GUIDELINES POLICY FOR GUIDELINE DEVELOPMENT AND ENDORSEMENT. [4 November 2013 2013].
11. National Health And Medical Research Council. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. In; 2009.


