Irish Society for Clinical Nutrition & Metabolism

IrSPEN GUIDELINE DOCUMENT No. 1:

Prevention and Treatment of Refeeding Syndrome in the Acute Care Setting

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On behalf of IrSPEN's Standards and Guidelines Committee

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Irish Society for Clinical Nutrition & Metabolism

About IrSPEN

The Irish Society for Clinical Nutrition and Metabolism (IrSPEN) is a multidisciplinary organisation dedicated to optimising the identification and management of patients at nutritional risk, both in hospital and community settings.

Founded in 2010 with the support of the Irish Society of Gastroenterology (ISG), the Irish Nutrition and Dietetic Institute (INDI) and the Irish Section of the Nutrition Society, IrSPEN members include clinicians, dietitians, nutritionists and other health professionals from clinical practice, research and education. Together our aim is to combat malnutrition by optimising the nutritional management of patients in hospital and the community.

The Key Aims of IrSPEN

IrSPEN aims to advance Ireland as a model of best practice in clinical nutrition by:

- Ensuring early identification of those at risk of disease-related malnutrition.
- Ensuring safe, efficacious and high quality nutritional care for all patients both in hospital and the community
- Promoting research that advances our knowledge or practice of clinical nutrition in Ireland

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Abbreviations

ASPEN	American Society for Parenteral and Enteral Nutrition
ATP	Adenosine triphosphate
ESPEN	European Society for Clinical Nutrition and Metabolism
INDI	Irish Nutrition and Dietetic Institute
IrSPEN	Irish Society for Clinical Nutrition and Metabolism
ISG	Irish Society of Gastroenterology
IPNEC	Intersociety Professional Nutrition Education Consortium
MDT	Multidisciplinary team
MUST	Malnutrition Universal Screening Tool
NG	Nasogastric feeding tube
NICE	National Institute for Health and Clinical Excellence (UK)
PEG	Percutaneous endoscopic gastrostomy
RFS	Refeeding syndrome
U&E	Urea and electrolytes

Foreword

Professor Frank Murray

Risk of refeeding syndrome is a common high stakes medical condition. While it can be relatively easily prevented and treated, identification of patients at risk remains a major challenge. The personal and economic cost of failing to identify and manage such patients is substantial, yet awareness of the condition remains poor amongst clinicians, and protocols aimed at its prevention and effective management are lacking in many hospitals, both locally and internationally. This initiative by IrSPEN to highlight this area is a significant step forward for us here in Ireland.

This guideline is systematically organized and includes clearly presented sections on risk identification, prevention and management. It also provides a helpful audit tool and calls for an integrated approach to management across the important disciplines involved. There is also a useful guideline on electrolyte replacement.

The authors, Karen Boland, Damodar Solanki, and Carmel O'Hanlon deserve great credit in undertaking the production of these guidelines on behalf of IrSPEN. I commend their implementation to all hospitals.

Professor John V Reynolds – Chairman IrSPEN

Disease-related malnutrition is estimated to affect around 140,000 people in Ireland at a cost of at least €1.4 billion per year. Nearly one in three adults admitted to hospital in Ireland are at moderate to high risk of malnutrition, much of which goes undetected and untreated until advanced. A key focus of our activities in IrSPEN is therefore to promote routine nutritional screening of patients so that those in need of nutritional support can be identified promptly and treated at the earliest opportunity.

However, refeeding previously starved, malnourished patients must be done with the utmost care, whether enterally or parenterally. All healthcare staff must be made aware of the potential risk of refeeding syndrome, a potentially fatal condition if patients at high risk are not properly identified and the necessary care taken in the first days of feeding to avoid the problem.

These guidelines, and the work of IrSPEN, aim to advance the standards of nutritional care in Ireland in line with best international practice. To that end, I would urge clinicians to ensure that the recommendations in this guideline are adopted within their hospitals, so that this highly preventable but under-recognised condition can be avoided.

Executive Summary

1. Refeeding syndrome (RFS) refers to serious metabolic disturbances that can occur in starved and/or malnourished patients on recommencement of feeding, either enterally or parenterally.

2. The condition typically appears in the first days of refeeding and is potentially fatal if not recognised promptly.

3. As few hospitals audit the occurrence of RFS, the incidence of the condition is unknown and undoubtedly variable, depending on whether protocols aimed at its prevention are in place. The incidence of patients at risk of RFS has been established from one local audit in a Dublin teaching hospital at 22% of acute medical and surgical admissions, of which 9% went on to develop signs of the condition. Hence, it can be assumed that all hospitals regularly see and treat patients at high risk of the condition.

4. RFS is easily prevented if those at high risk of this condition are identified prior to the initiation of feeding. This makes it essential for all hospitals to implement protocols to ensure that a risk evaluation is conducted prior to instituting any enteral or parenteral feeding and that those at high risk are managed accordingly. (Sample protocols are provided for adaptation in the Appendices)

5. The presence or severity of one or more of the following features is used to determine a patient's risk of developing the condition:
   a. Little of no nutritional intake in recent past.
   b. Significant weight loss.
   c. Low BMI (underweight).
   d. Electrolyte disturbance, specifically low phosphate, potassium and/or magnesium prior to feeding.
   e. History of alcohol abuse or drugs including diuretics, insulin, chemotherapy and/or antacids.

   Certain conditions are more likely to be associated with RFS and should be taken into consideration in assessing overall risk.

   Note: A decision tree to determining and rating a patient's risk of RFS is provided as appendix 1.

6. This guideline document outlines a practical approach to the identification and management of patients at risk of refeeding syndrome. Through publication of this document, we hope to increase awareness of this condition, which has real and profound consequences for patients.

7. Guidelines presented here can be adapted for local protocol development in accordance with local procedures for policy and guideline development.

Key Recommendations

1. Development and implementation of local protocols – an integrated approach

Local protocols for the identification, prevention and treatment of refeeding syndrome should be part of a hospital-wide routine nutritional screening programme. An integrated approach to the prevention and treatment of refeeding syndrome is fundamental to providing high quality care to patients at risk, with access to appropriate expertise, e.g. dietetic services.

Local protocols should be developed with multidisciplinary input and should include:

- A systematic approach to identify and rate a patients degree of risk of refeeding syndrome. *(See Appendix 1)*
- A management plan for at risk patients that highlights strategies and treatment plans that may prevent or at least reduce the risk of morbidity and mortality associated with refeeding syndrome. *(See Appendix 1)*
- Practical guidelines for the replacement of electrolytes in patients at risk of refeeding syndrome. *(See appendix 2 for sample guidelines developed in one Dublin acute teaching hospital. Note these guidelines are meant for patients with normal renal function. Issues related to nutritional care of pregnant women require specialist consideration and referral. We would recommend that each individual institution consider the implementation of their own guidelines based on the formulations available on their wards.)*

2. Nutritional screening

People admitted to hospital or attending an outpatient clinic for the first time should be screened for the risk of malnutrition using a validated screening tool. This is important to enable early and effective interventions that prevent and treat malnutrition. Routine nutritional screening should include screening for refeeding syndrome risk. Screening on admission to acute care will result in early identification of patients at risk of refeeding syndrome and will allow for appropriate implementation of local protocols to prevent and manage patients at risk.

3. Education and training

Nutrition education should be a requirement on the curriculum of medical and nursing professions, pharmacists, dietitians and other healthcare workers. IrSPEN have committed to continuing medical education in the field of nutrition and have consistently focused attention on the identification and management of refeeding syndrome. This topic should be included as part of routine continuing professional development.

4. Auditing practice and outcomes

We advocate ongoing audit of local practices and rates of refeeding syndrome in order to objectively monitor the benefits of local guidelines and improve the nutritional care of our patient population. Completion of the audit cycle with repeated practice audit is fundamental to the success of these guidelines. To facilitate this, a sample audit template is presented which can be adapted for local use. *(See Appendix 3)*

1. Introduction

1.1 Background

Refeeding syndrome refers to biochemical and clinical symptoms and abnormalities caused by shifts in electrolyte and fluid balance in malnourished patients upon recommencement of feeding, both enteral and parenteral [1]. This is a potentially fatal condition which may be successfully managed and even prevented if detected early, and if those at a high risk of this condition are appropriately identified in a prompt and efficient manner. The identification of patients at risk of, or suffering from malnutrition has become a focus for health services in Ireland and internationally as data emerge about the heavy economic burden associated with malnutrition and its clinical consequences [2]. Routine nutrition screening for all patients accessing health services in the community and in the hospital setting has been recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Union itself [3]. Growing education and support of screening for malnutrition offers an opportunity to reinforce the importance of screening for risk of refeeding syndrome among these patients at the healthcare interface.

1.2 Scope

These guidelines have been compiled as a guide to addressing the issues around refeeding syndrome in adults over the age of 18 years. Issues related to nutritional care of pregnant women require specialist consideration and referral. Guidance is offered, particularly with respect to electrolyte repletion, in the context of normal renal function, and should be interpreted within the unique clinical context presented with each patient.

1.3 Purpose

The purpose of this guideline document is to summarise current practices with regard to the identification of patients at risk of refeeding syndrome, and their subsequent management. Drawing from National Institute of Health and Clinical Excellence (NICE) guideline document CG32 [4] and other sources, we offer a template to aid the development of local hospital guidelines by clinicians and clinical nutritionists/dietitians.

Furthermore, we advocate ongoing audit of local practices and rates of refeeding syndrome in order to objectively monitor the benefits of local guidelines and improve the nutritional care of our patient population. A sample audit template has been included for this purpose. Through publication of this document, we hope to increase awareness of this condition, which has real and profound consequences for patients.

Refeeding syndrome is known to be a widely under-diagnosed illness leading to preventable morbidity and mortality in high-risk groups. Many studies based around the distribution of questionnaires to healthcare professionals have been performed to assess the attitudes of doctors and nurses to diagnosis and treatment of refeeding syndrome. Both doctors and nurses declare that their knowledge of refeeding syndrome and their ability to assess patients who are at a high risk of this condition is not satisfactory. In one study of healthcare professionals in Scandinavian countries, these findings were replicated, but the healthcare professionals were divided into two groups, internal medicine and gastroenterology. Those working within the field of gastroenterology reported more confidence with regard to the diagnosis and management of the complications of malnutrition, but still declared that they believed their knowledge was suboptimal [5,6].

Many healthcare institutions now heavily emphasise the importance of multidisciplinary management of nutritional needs of patients with greater input from nutrition and dietetic services. Indeed, studies indicate that the development of nutrition teams within hospitals improves nutritional status of patients and the management of these issues, with more successful implementation of screening and other nutritional guidelines [7]. Healthcare professionals should have an awareness of core patient groups at risk of refeeding syndrome, its manifestations and its management. Working groups have been previously established through the Intersociety Professional Nutrition Education Consortium (IPNEC) aiming to drive nutrition education, and focusing on complications of malnutrition such as refeeding syndrome through improvements in clinician knowledge [8]. These guidelines share the same core goals, of improving nutritional care through education.

2. Refeeding Syndrome Overview

2.1 Pathogenesis

Refeeding syndrome is characterised classically by deranged phosphate, potassium and magnesium balance within the body, although abnormalities in the metabolism of glucose and levels of sodium and water balance are widely recognised to contribute to the considerable morbidity and mortality associated with this condition [9]. The consumption of cofactors of metabolism, in particular thiamine, has its own associated consequences. The true incidence of refeeding syndrome is unknown and this relates somewhat to the lack of a definition that is widely accepted by the medical community [1].

The mechanism of refeeding syndrome is based on a series of interrelated biochemical changes occurring within the body as metabolism alters following a period of starvation. During starvation or prolonged fasting, physiology is altered to compensate for the profound reduction in glucose and energy intake. As insulin levels drop, glucagon levels rise, and the body derives its energy from glycogen stores and a biochemical shift to gluconeogenesis. Ketones and free fatty acids become the primary source of energy, and ketone body use is reduced peripherally in tissues so that, initially, protein and muscle breakdown is avoided. Fatty acids are enrolled as the primary source of energy and gluconeogenesis is then dramatically reduced by the liver [10]. However, prolongation of this physiological state eventually leads to catabolism and loss of lean body mass [11]. Intracellular minerals such as phosphate are depleted, although initially serum levels remain within normal limits as depletion occurs primarily of intracellular stores [12]. Other metabolic cofactors and vitamins or micronutrients such as thiamine are also lost and depleted.

During refeeding, the reintroduction of glucose induces a series of profound biochemical changes within the body, which will be briefly outlined here.

- As feeding occurs, the changes undertaken by the body during prolonged starvation suddenly shift, as carbohydrate metabolism once again becomes the primary focus, and fat metabolism rapidly declines. The introduction of glucose and hyperglycaemia induces insulin, and this precipitates a cascade of metabolic events. The Na^+ - K^+ ATPase transporter present on cells is stimulated by insulin leading to dramatic intracellular shift of potassium and water follows by osmosis [1]. Hence electrolytes such as potassium and phosphate shift from the extracellular to the intracellular compartment, causing a sudden profound drop in serum levels [12,13]. The metabolism of glucose and lipid is itself altered, with an attenuated capacity to respond to glucose loads. Consequences of this deranged glucose metabolism seen in refeeding syndrome include metabolic acidosis, ketoacidosis and hyperosmolar states [11].

- Fluid balance is similarly affected. Patients may demonstrate initial fluid intolerance with attenuated water and Na^+ excretion, most notable when refeeding occurs with a protein-heavy diet. This may lead to cardiac decompensation, pre-renal failure with metabolic acidosis and even sudden death [14].

- Intracellular micronutrients and vitamins such as thiamine (B_1) are already depleted and upon refeeding, are consumed rapidly due to the sudden switch to anabolism induced by feeding. This is most evident in the case of vitamins and nutrients acting as cofactors in metabolic enzyme cascades and can induce neurological complications, leukocyte dysfunction leading to increased susceptibility to infection and metabolic acidosis [15]. In the case of thiamine, which is a cofactor of transketolase, deficiency can manifest as Wernicke's Encephalopathy or Korsakoff's Psychosis resulting from increased consumption, driven by carbohydrate metabolism [16,17].

2.2 Consequences of electrolyte derangement in refeeding syndrome

The clinical features of refeeding syndrome arise as a consequence of these electrolyte deficiencies and the rapid change in basal metabolic rate. Many of these patients at highest risk of refeeding syndrome already have higher resting energy expenditure, meaning that they have more profound metabolic requirements [18]. There are specific features of refeeding syndrome which occur due to depleted electrolyte levels, inducing significant abnormalities of cardiac, renal, gastrointestinal, musculoskeletal and neurological function which may lead to debilitating morbidity and mortality. Interestingly, the clinical emergence of these conditions varies in timing, with cardiac signs and arrhythmias occurring often within hours, and neurological signs and symptoms occurring days to weeks later. Furthermore, evidence suggests that cardiac function is compromised in patients subsequent to prolonged periods of starvation, borne out in studies of patients with anorexia nervosa. These patients have demonstrable reductions in cardiac mass along with global loss of muscle mass, contributing to difficulties with fluid balance seen upon refeeding [19].

Hypophosphataemia

Phosphorus is a largely intracellular electrolyte with a significant role in many cellular processes within the body. Phosphate deficiency may have consequences for the cardiac, respiratory, neurological, renal, gastrointestinal, haematological and musculoskeletal systems. It is central to the normal functioning of intracellular processes and has a pivotal role in the integrity of the cell membrane. Furthermore, phosphate binding acts as a step in enzymatic cascades involved in cellular functioning and as second messengers. Energy storage is accomplished with adenosine triphosphate (ATP). More specifically, it is one of the renal buffers attributing to normal acid-base balance and drives oxygen and haemoglobin binding with 2, 3 diphosphoglycerate (2,3-DPG). Hence, the wide shifts in phosphate levels and profound depletion that occurs in refeeding syndrome affects all cellular processes and contributes to complications associated with this condition. The drive behind these shifts is multifactorial but certainly is linked with carbohydrate ingestion and acidosis [13,11].

Hypokalaemia

Potassium is an intracellular cation which is depleted by the anabolism induced by refeeding, as well as a direct depletion due to the insulin surge that occurs. Potassium deficiency is most widely associated with cardiac complications, in particular arrhythmias, and reduced urinary concentration by the kidneys. These are induced by the electrochemical derangement seen in potassium depletion within the cell membrane [20]. In tandem with other electrolyte deficiencies such as phosphate and magnesium, these lead to serious clinical consequences without prompt correction.

Hypomagnesaemia

Another predominantly intracellular cation, the importance of magnesium in the maintenance of cellular homeostasis, especially due to its role in enzyme function, oxidative phosphorylation and ATP production is often disregarded. Magnesium has also been identified as a key component in the structure of nucleic acid and ribosomes. It also is involved in the maintenance of an appropriate membrane potential. Therefore, magnesium deficiency may manifest with an array of cardiac, and neuromuscular consequences, as well as hypercapnia and respiratory failure. Furthermore, electrolytes such as phosphate and potassium are particularly difficult to replace during times of deficiency when associated with persistent hypomagnesaemia [21].

Hypocalcaemia

Hypocalcaemia is a relatively common finding among critically ill patients particularly in the ICU setting [22]. Clinical signs include tetany, seizures, prolonged QT interval, muscle weakness, and altered mental state with emotional lability. Hypocalcaemia commonly occurs in combination with other electrolyte disorders, particularly magnesium. One theory offered to explain this interaction with magnesium is that magnesium may impair the function of parathyroid hormone [23]. Some signs and symptoms associated with low electrolyte levels have been outlined in Table 1.

Table 1: Signs and symptoms associated with low electrolyte levels

System involved	Complication	Electrolyte depleted
Cardiac	Arrhythmia and sudden death	PO_4^{3-}, Mg^{++}, K^+, Ca^{++}
	Congestive cardiac failure	PO_4^{3-}
	Reduced cardiac contractility	PO_4^{3-}
	Digoxin toxicity	K^+
	Hyper/hypotension	PO_4^{3-}, K^+, Mg, K^+
	Tachycardia	Mg^{++}
Respiratory	Respiratory failure and/or ventilator dependency	PO_4^{3-}, Mg^{++}, K^+
	Pulmonary oedema	PO_4^{3-}
	CO^2 retention	Mg^{++}
Renal	Osmotic diuresis	PO_4^{3-}
	Pre-renal Failure	PO_4^{3-}
	Poor tubular concentration	PO_4^{3-}, K^+
Neurological	Paraesthesia	K^+, Mg, K^+, PO_4^{3-}, Ca^{++}, K^+
	Weakness	K^+, PO_4^{3-}, Mg, K^+, Ca^{++}, K^+
	Altered mental state and/or encephalopathy	PO_4^{3-}
	Paralysis	K^+, Mg, K^+
	Ataxia and tremor	Mg, K^+
	Tetany	Mg, K^+, Ca^{++}, K^+
	Seizures	Mg, K^+, Ca^{++}, K^+, PO_4^{3-}
Haematological	Leukocyte and platelet dysfunction	PO_4^{3-}
	Haemolysis	PO_4^{3-}
	2, 3, DPG depletion	PO_4^{3-}
Musculoskeletal	Osteomalacia	PO_4^{3-}
	Rhabdomyolysis	K^+
Gastrointestinal	Ileus	K^+

3. Risk of Refeeding Syndrome

3.1 Background

The lack of a universally accepted definition of this condition means that the true incidence of refeeding syndrome is largely unknown [1]. Clinician confidence with regard to the identification of refeeding syndrome further compounds difficulties in obtaining a true incidence rate and epidemiological data. However, there have been studies, particularly based in intensive care units identifying rates of hypophosphataemia in critically unwell patients, with incidences of 28% and 34% in prospective studies [22,24].

3.2 Incidence of refeeding syndrome in Ireland

Referring to national rates of refeeding syndrome in Ireland, our experience is limited to hospital practice audit. The guidelines for the identification and management of refeeding syndrome at Beaumont Hospital arose following an internal audit based in this tertiary centre, in 2009. 102 charts and patient records were reviewed retrospectively from acutely admitted medical and surgical patients over 6 days. Using the widely available NICE guidelines, patients were stratified according to risk of refeeding syndrome on admission, and bloods before and during feeding were monitored. Rates of thiamine prescription, electrolyte monitoring and frequency, and dietitian referral were recorded in these patients, and outcomes recorded. According to NICE guidelines, 21.5% (n = 22) patients were at high risk of refeeding syndrome on admission to hospital, with 9% having at least 1 major risk factor. 9% of those at high risk (n = 2) went on to develop and display signs of refeeding syndrome. Only 32% (n = 7) of those at high risk were managed appropriately with electrolyte monitoring, thiamine replacement and referral to the Department of Nutrition and Dietetics. Upon review of these results, a multidisciplinary team was assembled with representation from the Department of Gastroenterology, Department of Nutrition and Dietetics, Department of Pharmacy and Nursing Practice Management. Guidelines for the safe management of high risk patients were drafted, drawing from a literature review and NICE CG32. Guidelines for electrolyte repletion were also generated for patients with normal renal function, and these were circulated throughout the wards and on the hospital intranet. This initiative was accompanied by an education programme for clinicians and nursing staff [25].

Repeated audit only 6 weeks after full implementation of the guidelines in 2013 has shown a trend of improvement. 54 acutely admitted patients were included in the replicated audit. 20% (n = 11) of patients were at high risk of refeeding syndrome according to the guidelines. 45.5% of those at high risk were managed according to the guidelines. This is a favourable outcome when compared to 32% previously managed to best practice standards. Two patients did develop signs of refeeding syndrome, with electrolyte deficiencies. These were identified and managed promptly with no recorded adverse outcome or complications [25].

3.3 Malnutrition risk

The presence of the undernutrition form of malnutrition is the single most significant predisposing factor for the development of refeeding syndrome. ASPEN (American Society for Parenteral and Enteral Nutrition) and ESPEN (European Society for Clinical Nutrition and Metabolism) define malnutrition as a subacute or chronic state of nutrition, in which a combination of varying degrees of overnutrition and undernutrition and inflammatory activity has led to a change in body composition and diminished function [26,27].

A proposed aetiology-based terminology for use in the clinical practice setting has been developed by an International Consensus Guideline Committee [27] and is endorsed by ESPEN and ASPEN. The inflammatory process is now recognised as an integral part of the aetiology and the outcome effects of malnutrition. Three categories of malnutrition are delineated (see Table 2). Patients may be diagnosed in one or more of these categories or may change from one category to another.

Table 2: Malnutrition aetiology-based terminology [27]

Malnutrition Terminology	Definition
Starvation-related	Chronic starvation without inflammation. Includes anything that limits access to food, e.g. eating disorders.
Chronic disease-related	Inflammation is chronic and of mild to moderate degree. Includes organ failure, pancreatic cancer, rheumatoid arthritis, sarcopenic obesity.
Acute disease or injury-related	Inflammation is acute and of severe degree. Includes major infections, burns, trauma or closed head injury.

3.4 Incidence of malnutrition in Ireland and across Europe

It is estimated that 30 million Europeans suffer disease-related malnutrition at a cost of €170 billion per year [28]. In Ireland, it is considered that at any one time there are 143,000 adults at high to medium risk of disease-related malnutrition, of which at least 50% are aged 65 or over [2]. The annual cost of disease-related malnutrition to Ireland is estimated to be €1.42 billion, representing over 10% of the total annual health and social care budget [2].

Nutrition Screening Week (2010 and 2011) established the malnutrition risk of Irish patients on admission to hospital and of residents in longer term care [29]:

- 1 in 3 patients admitted to Irish hospitals were considered to be at risk of malnutrition, with 75% of these considered to be at high risk.
- Up to a third of residents in Irish nursing homes were considered to be at malnutrition risk.

The presence of such a high degree of malnutrition risk in the Irish healthcare system contributes significantly to the risk of refeeding syndrome in acute care settings. ***This highlights the key need for mandatory nutritional screening in acute care in Ireland.***

4. Prevention and Treatment

4.1 Overview of prevention and treatment

Truly effective nutritional care evolves from appropriate and strong preventative measures which are implemented in a consistent manner. This should focus on identification of patients at risk of malnutrition and its complications at an early point in interaction with healthcare service, whether in the community or at the level of secondary and tertiary care. This is particularly true in the case of refeeding syndrome, where prevention and management are entwined and dependent on the early identification of at-risk patients. Indeed, the steps in identifying patients at risk of this condition are congruent with those of the MUST score (Malnutrition Universal Screening Tool), affording the opportunity to implement and encourage screening for both malnutrition and refeeding syndrome at the same point of interaction. Many cases of refeeding syndrome occur in patients who are being fed either enterally with NG and PEG feeding or parenterally. However, it has also been recognised in subjects being fed orally after a period of starvation such as patients with a history of anorexia nervosa. Widespread and routine implementation of screening programmes at the first point of contact between patient and clinician will enhance identification of patients at risk who do not require enteral or parenteral nutrition support.

NICE guidelines have been published identifying those at greatest risk of refeeding syndrome, and are easily applied to the wider inpatient base. Clinical Guidelines 32 (CG32), were designed as a guide to nutrition support in adults. They offer concise and clear recommendations with regard to daily calorie intake in those at high risk of refeeding syndrome. They reference the recommended rate of nutrition support in terms of kcal/kg/day, and advise continued attention to fluid and electrolyte balance as well as micronutrient supplementation. We have relied heavily on these guidelines as a template for our recommendations, but have placed a renewed focus on the issue of electrolyte supplementation for patients with deficiencies induced by refeeding syndrome [4].

Our guidelines for the management of refeeding syndrome focus on the identification of at-risk patient populations, prevention, and management of this condition with appropriate fluid balance, micronutrient replacement and feeding, and finally, management of complications with electrolyte repletion and monitoring.

4.2 Identification of patients at risk of refeeding syndrome

The NICE guidelines have outlined an easily implemented system based on major and minor criteria for this purpose. These criteria include Body Mass Index (BMI), recent weight loss, recent oral intake, and drug history and baseline electrolyte levels (see Figure 1). We advise the use of these criteria by clinical staff and healthcare workers to identify at-risk patients. In addition, we recommend that certain patient groups at particular risk of this condition as previously discussed be highlighted. These include patients with a history of:

- Current or recent history of cancer [30]
- Eating disorders [18]
- Chronic debilitating disease [31]
- Patients post gastrointestinal or head-and-neck surgery [32,33]
- Alcohol Dependence Syndrome
- Elderly patients living alone
- Chronic gastrointestinal symptoms
- Chronic dieting [11]

4.3 Nutritional screening

People admitted to hospital, attending an outpatient clinic for the first time or having care in a community setting should be screened for the risk of malnutrition using a validated screening tool [34]. One such screening tool recommended by the Department of Health and Children in Ireland since 2009 is the Malnutrition Universal Screening Tool (MUST) [35]. Screening is important to enable early and effective interventions that prevent and treat malnutrition. Routine nutritional screening should include screening for the risk of refeeding syndrome. Screening on admission to acute care will result in early identification of patients at risk of refeeding syndrome, enabling the immediate implementation of a refeeding syndrome protocol, and effective nutritional intervention.

4.4 Initial management and monitoring of patients at risk of refeeding syndrome

We have adapted an algorithm (See Appendix 1) developed initially for use at Beaumont Hospital, but which can be applied easily to any institution. Following the identification of patients at high risk of refeeding syndrome, electrolytes should be checked, particularly Na^{+}, K^{+}, Ca^{++}, PO_4^{3-} and Mg^{++}. Given the known cardiac complications of such electrolyte deficiencies, particularly arrhythmias, we advise ECG monitoring or telemetry where severe low levels are recorded or where appropriate according to clinical judgement. These electrolytes should be assayed serially and on a daily basis for 5 days and then 3 times weekly until stable with prompt replacement when required. These patients should be reviewed by a clinical dietitian as soon as possible in order to advise a safe rate of feeding. We advise an initial rate of 10 kcal/kg/day or 5 kcal/kg/day in extreme risk.

Management should be accompanied in all cases by a multivitamin preparation and thiamine replacement immediately before and during the first 10 days of refeeding to prevent the onset of neurological complications such as Wernicke's Encephalopathy. According to the NICE guidelines, thiamine replacement is sufficient orally at a dose of 200 - 300 mg/day [4]. The benefits of these levels of thiamine supplementation for the prevention of neurological complications in critically ill patients has been published previously [19]. In critically ill patients for whom oral treatment is not feasible and in those with a recent history of alcohol abuse, parenteral thiamine is a more appropriate choice for prescription. High dose parenteral thiamine can be given once daily for 3 days for RFS as per NICE guidelines. More frequent administration may be needed if alcohol abuse is suspected.

4.5 Electrolyte repletion

The nature of our hospital system is such that Non-Consultant Hospital Doctors (NCHDs) often are responsible for the initial phase of electrolyte repletion. Questionnaire-based audits have identified this as an area requiring further education and a cause of low levels of confidence among this group of clinicians. According to one audit of 730 consultant surgeons in Great Britain and Ireland, 70% of consultants believed that not all patients received adequate fluid and electrolyte support, and only 16% felt that clinical staff were appropriately trained to manage patients electrolyte balance [36]. We have identified this as an area which would best be addressed with guidelines for the repletion of electrolytes, and subsequent monitoring.

Beaumont Hospital guidelines were formulated after a thorough literature review with involvement of the Department of Pharmacy, dealing with electrolyte replacement for patients with normal renal function, and were reviewed by consultant clinicians at this institution (see Appendix 2). We would recommend that each individual institution consider the implementation of such guidelines based on the formulations available on their wards.

The most profound electrolyte abnormality associated with refeeding syndrome is hypophosphataemia. Repletion of this electrolyte in particular can be difficult, as studies have consistently shown that repeated boluses are required in the initial stages of refeeding syndrome to achieve persistent normal phosphate levels [13,37]. This electrolyte is largely intracellular, and serum levels may not be used as a definitive guide to replacement. There are no prospective randomised control trials in the literature which focus on traditional weight based bolus phosphate repletion led by serum levels, versus a calculated continuous infusion. Following a review of the literature, it is clear that patients with hypophosphataemia in the context of refeeding syndrome have higher phosphate requirements to achieve normal serum levels. In a small prospective study including 30 patients with normal renal function and who had been diagnosed with refeeding syndrome, 93% achieved phosphate levels > 0.5 mmol/L with a more aggressive approach and repletion with 50 mmol PO_4^{3-} [38]. Reviews of phosphate repletion largely refer to the ICU setting, and studies have determined that a dosage of 45 mmol PO_4^{3-} at an infusion rate of 20 mmol/h is safe. In the general ward setting, such rates would be inappropriate given the lower levels of monitoring available [37].

Therefore, we have advised that in the context of refeeding syndrome and normal renal function, bolus treatment of hypophosphataemia with 1 vial Phosphate Polyfusor® (50 mmol phosphate in a 500ml solution), or an equivalent formulation be prescribed. See Appendix 2 for administration guidelines. However, each patient must be considered individually, being particularly mindful of renal function and drug history when using these as a guide to repletion.

4.6 Implementation of guidelines

We strongly believe that successful implementation of guidelines can only be achieved through education of all healthcare staff including clinicians, and a widely available template or algorithm for institutional use. Where possible, this should be available on the wards, in the accident and emergency department and also electronically on hospital intranet. We advocate development of local guidelines using these as a base, with easily followed steps and ideally with accessible and step-by-step guidelines for electrolyte repletion and monitoring.

5. Developing an Improved Model of Care

5.1 Audit template as a tool to monitor quality of local practice

An ideal initial step in assessing the quality of this aspect of nutritional care is through audit of current practices. A template previously successfully implemented involves inclusion of acutely admitted medical and surgical patients for chart review, ideally one day following their admission. This allows use of patient records and charts to stratify their risk of refeeding syndrome according to the NICE guidelines, and monitor management at admission and over subsequent days. Of particular interest is the assessment and frequency of electrolyte assays, thiamine administration, referral to the dietitian and documentation of any signs or symptoms or refeeding syndrome.

We advocate development of local guidelines and widespread publication of these, focusing particularly on NCHD staff involved directly in patient admission, and staff nurses who may also identify patients at high risk of malnutrition and refeeding syndrome. Completion of the audit cycle with repeated practice audit is fundamental to the success of these guidelines. See Appendix 3 for sample audit tool.

5.2 Focus on education

IrSPEN have committed to continuing medical education in the field of nutrition and have consistently focused attention on the identification and management of refeeding syndrome. This topic has been, and continues to be discussed and included on Nutrition Study days, which are a core part of the curriculum for Higher Specialist Training within the Royal College of Physicians of Ireland (RCPI). We continue to support and advocate for education at a national level, but encourage local participation through medical grand rounds and continuing medical education at individual institutions.

Refeeding syndrome identification, prevention and treatment should be a requirement on the curriculum of medical and nursing professions, pharmacists, and other healthcare workers.

5.3 Integrated approach

An integrated approach to the prevention and treatment of refeeding syndrome is fundamental to the delivery of high-quality care to at risk adults. It is important that nutrition support services are multidisciplinary and are overseen and led by senior level staff from across settings, for example through nutrition steering groups or committees. Access to appropriate expertise, e.g. dietetic services, will promote the application of individualised nutritional interventions. This in turn will improve the effectiveness, safety and experience of care for people who need nutrition support and are a refeeding risk.

Appendix 1:

IrSPEN Identification & Management of Patients at Risk of Refeeding Syndrome (RFS) initially developed for Beaumont Hospital

High risk: 1 or more major risk factors
- BMI < 16kg/m²
- Unintentional weight loss of >15% in the previous 3-6 months
- Little or no nutritional intake for >10 days
- Low levels of potassium, phosphate and magnesium prior to refeeding

Extreme risk: one of the following
- BMI <14 kg/m²
- Very little or no nutrient intake for >15 days

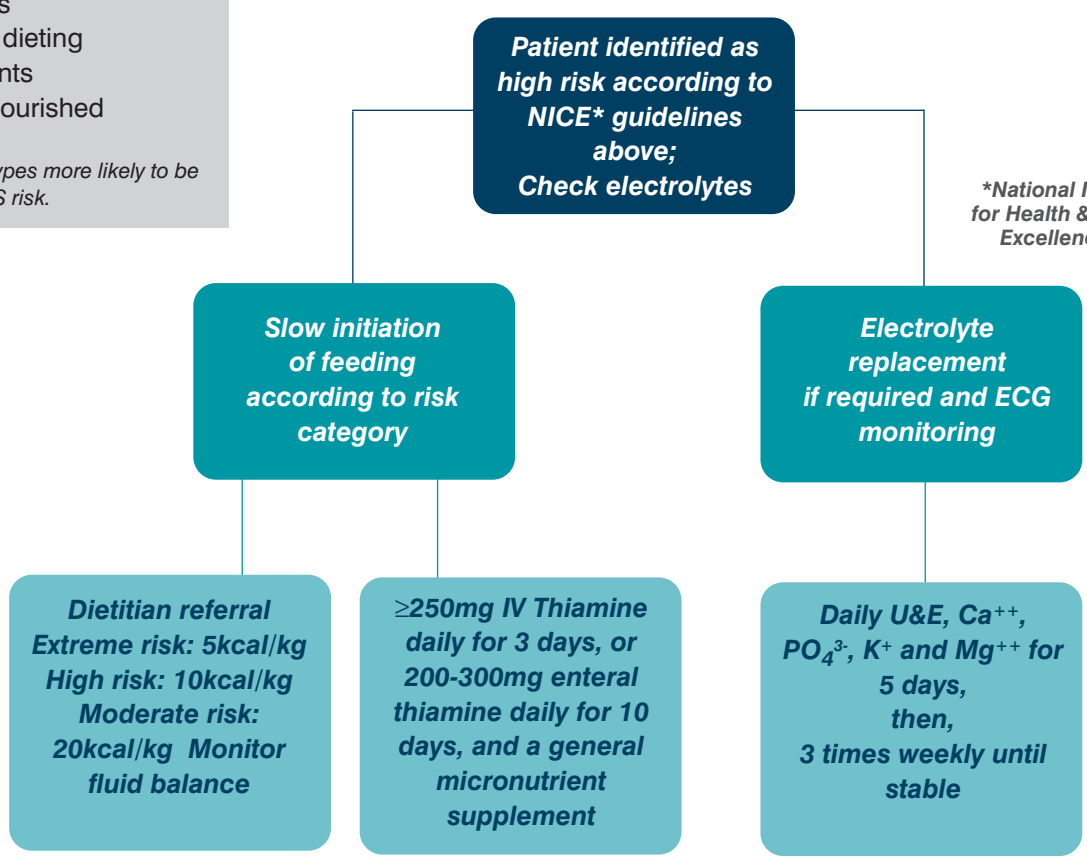
High risk: 2 or more minor risk factors
- BMI <18.5kg/m²
- Unintentional weight loss of >10% in the previous 3-6 months
- Little or no nutritional intake for >5 days
- History of alcohol abuse* or drugs including insulin, diuretics, chemotherapy or antacids.

**See local guidelines on management of alcohol withdrawal for guidance on thiamine supplementation.*

Moderate risk: 1 of the top 3 factors above

Risk by patient category*
Chronic alcohol abuse
Elderly living alone
Chronic GI symptoms
Chronic debilitating disease
Eating disorders
Chronic severe dieting
Oncology patients
Obviously malnourished

**Indicates patient types more likely to be associated with RFS risk.*



Appendix 2:

Sample Electrolyte Replacement Guidelines for Refeeding Syndrome in Acute Care

These guidelines must be adapted for local products and protocols.

Guidelines for Potassium Replacement

Initial potassium infusions should not use glucose if possible as this may cause an intracellular shift in potassium and further depletion.
Cardiac monitoring is required if the rate exceeds 10mmol K^+ /hour or concentration greater than 40mmol K^+/L. *Concentrations exceeding 40mmol K^+/L should be given via a central line to avoid pain, phlebitis and extravasation injury.(39)
Baseline ECG is necessary if serum K^+ <3mmol/L (39,40). If serum K^+ <3.3mmol/L, magnesium level should be checked [41].

Serum potassium level	Guideline for repletion
Critical deficit K^+ <2mmol/L or K^+ <2.5mmol/L with ECG changes characteristic of hypokalaemia	Likely to require replacement in intensive setting, seek specialist advice
Severe deficit K^+ 2 - 2.5mmol/L without critical conditions or ECG changes	Intravenous replacement via peripheral line [39,40] 1. 40mmol K^+/ 1L premixed solution of potassium and fluid, given at 125mL per hour dependent on fluid status of patient. 2. Check serum potassium after 8 hours of commencement of infusion. 3. If serum potassium not corrected to normal levels, repeat step 1. Correct serum potassium to normal levels. Total supplementation of 80mmol K^+ often required in cases of severe deficit.
Moderate deficit K^+ 2.5 - 3.0mmol/L	Intravenous replacement via peripheral line [39,40] 1. 40mmol K^+/ 1L in premixed solution at 125mL per hour, dependent on patient fluid status. 2. Check serum potassium level after 8 hours. 3. If not corrected to normal levels, give further 20mmol K^+/500mL fluid. 4. Check serum potassium level 4 hours after last dose. Repeat infusion at step 3 as necessary to correct serum potassium to normal level.
Mild deficit K^+ 3.1 - 3.5mmol/L	Oral replacement [40]: Slow K® – 2 tabs tds (8mmol K^+/ tablet) Sando-K® – 2 tabs bd (12mmol K^+/tablet) Kay-Cee-L® – 10mL bd (1mmol K^+/mL) or Intravenous replacement with premixed solution of 20mmol K^+/ 500mL.

#Guidelines for electrolyte replacement are for use in the context of normal renal function, and no current dialysis treatment. Fluid balance and serum sodium level of patients should be taken into account when treatment is being undertaken.

Guidelines for Calcium Replacement

NB: correct for albumin in low albumin states

Corrected Ca^{2+}(mmol/L) = Serum Ca^{2+}(mmol/L)+ 0.02x(40 - patient albumin(g/L))[42]

- Determine potassium, phosphate and magnesium levels which will affect ability to appropriately correct calcium – hyperkalaemia and hypomagnesaemia potentiate cardiac effects of hypocalcaemia [43].
- In the presence of hypomagnesaemia, it is essential to correct magnesium deficits in order to successfully correct hypocalcaemia [44].
- Hyperphosphataemia should be corrected before giving calcium supplements [43].
- The specific regimen for calcium supplementation is dependent upon the clinical presentation of the patient. Oral supplementation should be used unless the patient is suffering from acute hypocalcaemia or tetany.

Serum calcium (corrected) level	Guideline for repletion
Acute severe hypocalcaemia Symptomatic hypocalcaemia and Ca^{2+} <2.12mmol/L or Ca^{2+}<1.9mmol/L	1. 10mL Calcium gluconate injection 10% (1g in 10mL) in 50mL glucose 5% infused over 20 - 30 minutes. Then 2. Solution of ~10mg/mL calcium gluconate made by diluting 11g calcium gluconate in 1 litre glucose 5% or normal saline and infused at a rate of 50mL/hour. This can be adjusted to maintain the calcium level at the lower limit of normal.[44] Serum calcium level should be closely monitored during infusion.
Acute mild hypocalcaemia Asymptomatic hypocalcaemia 1.9mmol/L < Ca^{2+}< 2.12mmol/L	1500-2000mg elemental calcium daily in divided doses between meals [45]. Calcichew® (Calcium 500mg) - 2 tablets bd Sandocal 400® (Calcium 400mg)- 3 tablets bd

- Oral calcium reduces the absorption of a number of other medicines, and should not be taken concomitantly with these drugs [40]. Seek advice from pharmacy.
- Excessively rapid administration of intravenous calcium may lead to vasodilation, hypotension, bradycardia and cardiac arrhythmias [39].
- If extravasation occurs, calcium gluconate can cause severe necrosis [39].

Chronic Hypocalcaemia (44)

- If due to vitamin D deficiency can use an oral calcium carbonate preparation with cholecalciferol (eg Ideos® 1 tablet bd). If renal or hepatic impairment seek specialist advice.
- Chronic hypocalcaemia requires full assessment and an expert opinion should be sought.

#Guidelines for electrolyte replacement are for use in the context of normal renal function, and no current dialysis treatment. Fluid balance and serum sodium level of patients should be taken into account when treatment is being undertaken.

Guidelines for Magnesium Replacement

Serum magnesium level	Guideline for repletion
Acute or severe hypomagnesaemia Mg^{2+} <0.7mmol/L + symptoms or Mg^{2+} <0.4mmol/L	10mL magnesium sulphate 50% injection (5g in 10mL) diluted in 500mL Sodium Chloride 0.9%. Infuse over a minimum of 5 hours for 3 to 5 days, depending on serum levels [45,46]. Often requires oral magnesium to maintain at normal serum levels.
Mild hypomagnesaemia Mg^{2+} 0.5 – 0.7mmol/L no symptoms	Give by mouth 20 to 24mmol Mg^{2+} per day in divided doses for 5 days [40]. Magnesium Verla® 2 sachets bd 1 sachet (5g) = 5mmol Mg^{2+}.

Intravenous administration:

- Symptomatic hypomagnesaemia is usually associated with a deficit of 0.5-1mmol/kg Mg^{2+}. Since 50% of the administered dose is excreted in the urine, even in severe deficiency, up to 160mmol over 5 days may be required [40]. The maximum dose per day should not exceed 40mmol [47].
- Serum magnesium levels should be checked daily, 6 to 8 hours following intravenous doses [46].
- Magnesium sulphate available as 50% solution (1g in 2mL, 2.5g in 5mL, or 5g in 10mL). 1g magnesium sulphate = 4mmol Mg^{2+}.
- Maximum concentration for infusion is 20% (200mg/mL or 0.8mmol/mL) and can be given peripherally or centrally [39].
- Maximum rate of infusion is 150mg (0.6mmol) per minute [39], rapid infusion of intravenous magnesium may lead to respiratory depression and reduced tidal volume.

Chronic hypomagnesaemia:

- If losses are ongoing consider oral maintenance therapy, 4 – 12mmol Mg^{2+} per day.

#Guidelines for electrolyte replacement are for use in the context of normal renal function, and no current dialysis treatment. Fluid balance and serum sodium level of patients should be taken into account when treatment is being undertaken.

Guidelines for Phosphate Replacement

Serum phosphate level	Guideline for repletion
Severe hypophosphataemia with refeeding syndrome	Intravenous therapy 50mmol PO_4^{3-} over 6 – 12 hours. (i.e. Phosphate Polyfusor®)[48]
Severe deficit PO_4^{3-} <0.4mmol/L	Intravenous replacement via peripheral line. 1. Calculate phosphate requirement of 0.16mmol/kg [49] and administer over 6 hours in patients who are unwell or have multiple risk factors for hypophosphataemia. e.g. in 70kg patient, give 20mL potassium phosphate or sodium phosphate injection diluted in 500mL Sodium Chloride 0.9% or Glucose 5% over 6 hours [39]. 2. In critically unwell patients, increase to 0.24mmol/kg [50] over 6 hours. e.g. in 70kg critically ill patient, give 28mL sodium phosphate injection diluted in 500mL Sodium Chloride 0.9% or Glucose 5% over 6 hours [39]. 3. Recheck serum phosphate after 6 – 12 hours following infusion and repeat if necessary. Maximum of 50mmol PO_4^{3-} in 24 hours [48]. 4. Check serum phosphate levels daily for 48 hours following infusion. 5. Stop infusions when serum phosphate levels > 0.8mmol/L.
Moderate deficit PO_4^{3-} = 0.41- 0.6mmol/L	Intravenous replacement via peripheral line. 1. Calculate phosphate requirement of 0.08mmol/kg [49] over 6 hours in patients who are unwell or have multiple risk factors for hypophosphataemia. e.g. in 70kg patient, give 10mL of potassium phosphate or sodium phosphate injection diluted in 500mL Sodium Chloride 0.9% or Glucose 5% over 6 hours. 2. Recheck serum phosphate after 6 – 12 hours following infusion and repeat if necessary. Maximum of 50mmol PO_4^{3-} in 24 hours [48]. 3. Check serum phosphate levels daily for 48 hours following infusion. 4. Stop infusions when serum phosphate level > 0.8mmol/L.
Mild deficit PO_4^{3-} = 0.61- 0.79mmol/L	Oral replacement therapy 1000mg phosphorus /day (32.2mmol/day) Phosphate -Sandoz® 1 tablet bd can go up to 6 tablets daily in divided doses [40].

Intravenous solutions containing phosphate:

a) Phosphate Polyfusor® (Fresenius Kabi®) (48)
50mmol PO_4^{3-}, 9.5mmol K^+ and 81mmol Na^+ in 500mL solution.

b) Potassium phosphate injection (B.Braun®) (51)
One 20mL ampoule has 20mmol K and 12mmol PO_4^{3-}. Must be diluted and administered as per hospital guidelines for Strong Potassium Solutions [34].

c) Sodium Phosphate injection (B.Braun®) (52)
One 20mL ampoule has 20mmol Na and 12mmol PO_4^{3-}.

Oral phosphate

- **Phosphate-Sandoz® :**
  16mmol Phosphate per tablet, (20mmol sodium and 3mmol potassium per tablet) [40].

Cautions (48)

- Excessive doses of phosphates may cause hypocalcaemia and metastatic calcification.
- I.V. phosphate must not be given to a patient who is hypercalcaemic (due to potential for intravascular precipitation).
- I.V. phosphate therapy may cause arrhythmias and hypotension and is related to rate of administration. For faster administration in general ward areas, ECG monitoring is essential.
- Avoid mixing phosphate injections with infusion solutions containing calcium as there is a high risk of precipitation.
- A total maximum daily dose of 50mmol phosphate should not be exceeded.

#Guidelines for electrolyte replacement are for use in the context of normal renal function, and no current dialysis treatment. Fluid balance and serum sodium level of patients should be taken into account when treatment is being undertaken.

Appendix 3:
Sample Audit Tool

Aim	To identify the incidence and risk of refeeding syndrome among admitted patients at secondary and tertiary care centres. To analyse local practices and adherence to NICE guideline.
Standards	Local practice should be benchmarked against accepted guidelines such as the IrSPEN guidelines for the identification of patients at high risk of refeeding syndrome or the NICE Guidelines CG32.
Methodology	Following submission and clearance by the clinical governance committees, acutely admitted patient notes are reviewed to document the risk of refeeding syndrome based on clinical history, drug history, examination, and Body Mass Index (BMI). The patient population should be representative of the inpatient group as a whole, including medical and surgical patients. Patients should be categorised according to presence of risk factors. Serum electrolyte analysis should be recorded, and thiamine prescription noted. Patient outcomes should be noted. We recommend the inclusion of approximately 100 patients admitted over a minimum of 5 days to achieve a representative sample of medical practices and the patient population.
Results	Results should include the percentage of admitted patients at risk of refeeding syndrome according to the guidelines. Results should also address whether their serum electrolytes were assessed, and if thiamine and micronutrients were prescribed. Where recorded, the proportion of at risk patients referred for dietitian review should be noted, and finally, the percentage of patients who developed refeeding syndrome and their outcomes should be published.
Conclusion	Conclusion should identify areas needing improvement in order to comply with best practice.
Recommendations and Action Plan	In addition to guidelines for the identification of patients at risk of refeeding syndrome, we advise that local service providers consider implementing of guidelines for electrolyte repletion to maximise patient benefits.
Re-audit	Analysis of the effect of guideline implementation and identification of any further deficiencies to be addressed. Further recommendations may be made based on findings.

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Notes

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