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Rapid normalization of vitamin D in critically ill children: A phase II dose evaluation randomized controlled trial (VITdAL-PICU pilot)

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Investigator Agreement

Coordinating Investigators			
Name	Dr. Dayre McNally (CHEO PI)	**Signature**	
		Date	

Investigator Agreement

By signing below, I confirm that I have read this protocol and agree to conduct this study in accordance with the procedures described in this protocol, with Good Clinical Practice and with Health Canada NHP and Division 5 Regulations.

Name of Principal Investigator (Print) Dayre McNally

Signature of Principal Investigator: _____

Date _____

List of Abbreviations

- 25(OH)D – 25-hydroxyvitamin D
- AI – Adequate Intake
- ALRI – acute lower respiratory tract infection
- CCCTG – Canadian Critical Care Trials Group
- CHD – congenital heart disease
- CHEO – Children's Hospital of Eastern Ontario
- CHEO RI – Children's Hospital of Eastern Ontario Research Institute
- CHEO CRU – Children's Hospital of Eastern Ontario Clinical Research Unit
- CPB – Cardiopulmonary bypass
- CRF – case report form
- CTSI – clinical trial site information form
- DMS – Data Management Services
- DMSC – Data monitoring and safety committee
- ECMO – extracorporeal membrane oxygenation
- FDA – US Food & Drug Administration
- GCP – Good Clinical Practise
- HRQL – Health-related quality of life
- ICH – International Conference on Harmonization
- IOM – Institute of Medicine
- IU – international unit
- NICU – neonatal intensive care unit
- OHRI – Ottawa Hospital Research Institute
- PedsQL – Pediatric Quality of Life Inventory Scale
- PELOD – Pediatric logistic organ dysfunction
- PICU – pediatric intensive care unit
- QUI – Qualified Investigator Undertaking form
- RDA – Recommended Daily Allowance
- REB – Research Ethics Board
- REBA – Research Ethics Board Attestation
- RCT – randomized controlled trial
- SADR – serious adverse drug reaction
- SAE – serious adverse event
- SAUDR – serious adverse unexpected drug reaction
- SOP – standard operating procedure
- VDD – vitamin D deficiency
- VDR – vitamin D receptor
- VITdAL-PICU - Rapid normalization of vitamin D in critically ill children: A phase II dose evaluation randomized controlled trial

Contents

STUDY SUMMARY

Title	Rapid normalization of vitamin D in critically ill children: A phase II dose evaluation randomized controlled trial (VITdAL-PICU pilot)
Short Title	VITdAL-PICU
Protocol #	VITdAL-PICU 01
Phase	2
Methodology	Randomized, double-blind dose evaluation trial Experimental arm – high dose vitamin D Control arm – placebo * Patients will be randomized 2:1 (high dose:placebo)
Study Duration	Up to 2 years
Study Centre(s)	Children's Hospital of Eastern Ontario Medical University of Graz (Austria) Clinica Sanatorio Aleman
Objectives	To determine whether a weight based enteral loading dose protocol can rapidly normalize vitamin D levels in critically ill children
Number of Participants	Maximum of 67 patients total
Diagnosis & Main Inclusion Criteria	Critically ill children who: • Are admitted to ICU, • Have a corrected gestational age > 37 weeks to age < 18 years, • Have an expected ICU admission in excess of 48 hours and will have access for bloodwork at 7 days, and • Have a blood 25(OH)D less than 50 nmol/L (regardless of prior approach to supplementation)
Study Product, Dose, Route, Regimen	Vitamin D3 (Cholecalciferol) Oral Solution 50000 IU/mL Single dose on enrolment: 10000 IU/KG to a maximum of 400000IU
Duration of Administration	Single dose at enrolment
Reference Therapy	Placebo solution: This group receives placebo solution at enrolment
Statistical Methodology	The primary objective of this study is to determine whether a weight based loading protocol can rapidly normalize vitamin D status in critically ill deficient children. The primary analysis for the study will be the proportion of participants in the treatment arm achieving 25(OH)D levels above 75 nmol/L on day 7 (point estimate, 95% confidence interval).

BACKGROUND INFORMATION & SCIENTIFIC RATIONALE

Background and Rationale

Severe vitamin D deficiency is well known to cause significant childhood disease, including hypocalcemic seizures and bone abnormalities[1-3]. Although severe deficiency is now rare, many Canadian children still endure suboptimal vitamin D status (referred to as vitamin D deficiency, VDD)[4-7]. A growing body of literature suggests that VDD negatively influences body composition (bone, muscle, fat)[8-11] and may predispose to various neurologic, cardiovascular, respiratory and immune disorders (e.g. diabetes, asthma)[12-14]. Given vitamin D's potential role in the health of organs central to critical illness pathophysiology it has been hypothesized that VDD could represent a modifiable risk factor in the ICU setting[15,16]. Multiple observational studies in the adult critical care setting have tested this hypothesis, reporting both high deficiency rates and associations with organ dysfunction, health resource utilization and mortality[16-20]. Consistent with this literature, our research group recently identified that 70% of critically ill Canadian children were VDD, with multiple PICUs outside of Canada reporting similar rates (30-85%)[21-27]. In addition, both of our observational studies demonstrated relationships between VDD, illness severity and clinical course[21,22].

Although of concern, the high VDD rate in critically ill Canadian children should also be viewed as a potential opportunity to improve clinical outcomes. Approximately 10 000 children are admitted to pediatric intensive care units (PICUs) in Canada each year. These children receive interventions and prolonged period of rehabilitation to prevent death, reduce morbidity, and avoid new long-term impairments[28,29]. *Our research group, and others[30,31], believe* that *optimization of vitamin D status in deficient critically ill children has the potential to modulate illness severity, speed recovery, reduce long-term morbidity and save health care dollars*. In addition to observational study findings, there is some supportive clinical trial evidence. A recently published placebo controlled RCT (VITdAL-ICU) reported a trend towards decreased mortality in deficient critically ill adults with a 540 000 IU enteral load of vitmain D (43% vs 35%, p=0.09)[32]. This moderately sized RCT is the only phase III trial to address this question. Further, multiple small RCTs evaluating high dose vitamin D supplementation have suggested benefit in unwell stable pediatric populations with asthma, recurrent pneumonia, and heart failure[33-36].

Despite the suggestive body of basic science and clinical literature it is not yet possible or appropriate to translate the findings to the PICU bedside. Why? First, there have been no phase III trials establishing that rapid repletion of vitamin D levels improves outcomes in any medical or surgical PICU population[37]. Moreover, at this time it is not possible to either treat an individual patient, or proceed with a phase III trial as there has been no pilot work identifying a dosing regimen that will safely and rapidly normalize vitamin D in the PICU[37]. *The work proposed in this submission is the completion of a pilot multicenter dose evaluation RCT to determine whether an innovative protocol, involving weight based enteral loading therapy, can rapidly and safely normalize vitamin D levels in critically ill children.* This study is the essential next step to inform the design and conduct of a multicenter phase III trial that will determine whether rapid normalization of vitamin D improves outcome.

Research Questions

Hypotheses

Pilot study (current proposal): We hypothesize that a weight based enteral loading protocol can rapidly and safely normalize vitamin D status in critically ill vitamin D deficient children.

Eventual phase III trial: We hypothesis that a weight based enteral loading regimen will improve patient outcomes and/or reduce health care spending.

How will the results of the trial be used?

Critical illness occurs in 10 000 children each year Canada, 100 000 in North America and more than a million worldwide. In addition to death, these children are at great risk for significant suffering, prolonged periods of rehabilitation and new morbidity or chronic disease. High vitamin D

deficiency rates in PICUs and the recognized importance to the health of multiple organ systems suggest the vitamin D supplementation could represent a simple, inexpensive and safe means of improving outcomes and reducing health care spending. Unfortunately, IOM and Health Canada approved daily dosing regimens for vitamin D require months to restore levels. Loading therapy represents a more appropriate approach for restoring vitamin D status in critically ill children. Unfortunately, there have been no studies of loading therapy in the PICU setting. Consequently, despite significant literature suggesting VDD to be a modifiable risk factor in critical illness, there is no robust published evidence to inform physicians on the true benefits or risks of loading therapy. The proposed phase II clinical trial will evaluate an innovative weight based dosing regimen intended to rapidly and safely normalize vitamin D levels. Study findings will be used to inform a multicenter international phase III trial evaluating the clinical and economic benefits to rapid normalization. Technology developed and knowledge gained from this project (and overall program) will be easily generalizable to critically ill children worldwide.

Justification for this Trial

Vitamin D axis and definition of vitamin D deficiency

In order to appreciate the clinical problem described above, one must consider the basic endocrine pathway and vitamin D status. A schematic and explanation of the basic endocrine pathway is provided (Appendix A). Circulating 25 hydroxyvitamin D or 25(OH)D is the generally accepted marker of body vitamin D status[38,39]. Although thresholds and terminology vary, vitamin D sufficiency is generally accepted as a 25(OH)D concentration above 75 nmol/L, deficiency as below 50 nmol/L, and severe deficiency at 25 -30 nmol/L[40-44]. These thresholds are based on biochemical indicators of axis stress and values below which symptoms and disease predisposition rises. Briefly, when 25(OH)D falls into the 50 nmol/L range, maintenance of active hormone levels requires elevation of serum parathyroid hormone (PTH) and increased renal enzyme activity[45,46]. As 25(OH)D falls into the 30 nmol/L range, production of active hormone [1,25$(OH)_2$D] falls and healthy individuals can develop electrolyte disturbances and clinically evident disease (rickets, seizures, myocardial disease)[46-48]. Although overt clinical disease is not evident in otherwise healthy individuals until 25(OH)D values drop below 30 nmol/L, population based research has established improved bone health with 25(OH)D values over 50 nmol/L[40]. The appropriate threshold for defining deficiency as it relates to intensive care has not been defined.

Evidence for an association of vitamin D deficiency with poor clinical outcomes

Reported roles for vitamin D in electrolyte homeostasis, cardiovascular health, muscle strength, inflammation and innate immunity lead to the hypothesis that deficiency might represent a modifiable risk factor for critical illness. Over the past 5 years, a growing number of observational studies in adult ICU and cardiovascular populations have investigated this hypothesis. These studies have reported high VDD rates and associations between hormone level and organ dysfunction, health resource utilization and mortality[7,12–15,19,29–31]. In the past 3 years, multiple pediatric studies have been published confirming the findings of adult ICU studies, demonstrating high VDD rates in the PICU setting[21-27]. Appendix B summarizes the published observational studies of vitamin D status in PICUs worldwide. Further, some have also demonstrated associations between lower levels and organ dysfunction, health resource utilization, and mortality[16-20]. More specifically, in 2012 our research group published one of two large pediatric studies documenting high deficiency rates and associations between lower vitamin D levels and worse clinical course in PICU[21,22]. Our study, the only multicentre PICU study to date, evaluated 326 critically ill Canadian children and determined that 70% had 25(OH)D levels below 50 nmol/L. Further, we demonstrated that VDD was associated with a 2-fold higher odds of heart dysfunction, longer ventilatory support, and 2 additional PICU days. We also performed a study focused on children with congenital heart disease (CHD) and demonstrated that almost all were deficient at time of admission to ICU from the operating room - mean 25(OH)D of 35 nmol/L, 85% deficient[23]. In that study, children who required greater post-operative care (catecholamine infusions, greater fluid administration) had statistically lower 25(OH)D levels at time of separation from cardiopulmonary bypass. Additionally our work has demonstrated

that the presence of VDD significantly augments the effect of adrenal insufficiency on illness severity[23].

Biological pathophysiology of vitamin D deficiency in critical illness

A role for vitamin D in critical illness has biological plausibility as there are multiple mechanisms through which deficiency could contribute to organ dysfunction.

Critical illness hypocalcemia - Calcium initiates and propagates nerve conduction, muscle contraction, and contributes to intra-cellular signal transduction. Hypocalcemia is common (30%) in the PICU and following cardiac surgery for CHD[49-51]; the need for parenteral calcium replacement is associated with morbidity and mortality[52]. Adult and pediatric ICU studies have not only shown that patients with hypocalcemia have worse clinical outcomes, but demonstrated that those with low calcium are more likely to have abnormalities of the vitamin D axis – low 25(OH)D, hypoparathyroidism, and renal dysfunction[49,50,53].

Cardiovascular dysfunction - Cardiovascular dysfunction is common in pediatric critical illness, with many patients receiving fluid boluses and catecholamine infusions to support blood pressure and cardiac output[54]. A role for vitamin D in pediatric heart health can be found in case reports and case series describing cardiomyopathy secondary to isolated severe VDD[52,55-57]. Further, approximately half of children with vitamin D related rickets have been shown to have subclinical cardiac dysfunction[58]. Recent observational studies in PICU have shown an association between lower vitamin D levels and need for fluids and vasoactive agents[21,23]. Further, a small RCT of high dose supplementation on stable children with heart failure demonstrated an improvement in a clinical Heart Function score and echocardiographic findings[36]. Vitamin D influences the cardiovascular system indirectly through body calcium stores and directly through the vitamin D receptors (VDR) present on myocytes and endothelial cells. Vitamin D metabolites influence myocyte structure and function via gene and protein expression through nuclear VDR[59]. Additional research has shown that myocyte contractility can be favorably altered within minutes by $1,25(OH)_2D$ supplementation, mediated through signal transduction pathways, enzymatic reactions and ion channels[60-62].

Immune dysfunction - Critical illness and complex surgery (e.g. cardiopulmonary bypass) frequently result in a dramatic systemic inflammatory response syndrome[63,64]. There is good evidence that vitamin D plays an important immunomodulatory role mediated through functional VDR present on all major immune cell types. Specifically, vitamin D has been demonstrated to inhibit antigen-induced T-cell proliferation, antagonize the pro-inflammatory Th1 (T-helper) response, suppress macrophage release of pro-inflammatory cytokines, and alter gene expression of adhesion factors, decreasing adherence and chemotaxis of neutrophils[65-67]. Vitamin D signaling is also known to play a role in innate immunity. For example, appropriate vitamin D signaling is known to be important for production of cathelicidins[68-70]. Cathelicidins are one major type of endogenous antimicrobial peptides that which provide protection against multiple viral and bacterial pathogens.

Muscle weakness – ICU acquired weakness is a well-recognized consequence of critical illness, and contributes to mortality, morbidity, worse functional outcomes and quality of life[71-74]. A significant body of observational research on children and adults has clearly demonstrated that severe VDD can cause muscle pathology and clinically relevant weakness[75-79]. More recently, important research conducted as part of a RCT initiated by co-applicant (Dr. Weiler) demonstrated potentially long lasting effects of high dose vitamin D on body lean muscle mass in infants and young children[9,80]. Further, the recent RCT evaluating administration of 540 000 IU to critically ill adults (published by co-applicant, Dr. Amrein) demonstrated that patients with 25(OH)D between 30 and 50 nmol/l who received study drug had improved grip strength and physical component of the SF-12[32]. The positive influence of vitamin D may be mediated indirectly or through VDR in the nucleus and plasma membrane of skeletal muscle[8].

In summary, VDD has been linked to hypocalcemia, cardiovascular dysfunction, immune and muscle dysfunction thereby leading to the possibility that rapid restoration of vitamin D in critically ill children could lead to improvement in the listed domains.

Current approach to vitamin D supplementation in PICU

Due to the negative health consequences of vitamin D deficiency, it is recommended that all children consume a minimum quantity of vitamin D. The Recommended Daily Allowance (RDA) or Adequate Intake (AI) levels suggested by the Institute of Medicine (IOM) and supported by Health

Canada are 400 IU (infants) and 600 IU (older children)[40]. Slightly higher doses have been suggested by the Canadian Pediatric Society for infants living in Northern Canada (800 IU)[81]. ***Presently, no standard of care for vitamin D supplementation has been established for the PICU setting. If ordered at all, a daily dose of vitamin D between 400 and 800 IU is generally provided enterally or with total parenteral nutrition.*** It is well recognized these doses can take 2 or more months to restore vitamin D status in deficient healthy children. Available evidence on hospitalized and critically ill patients shows that with usual care vitamin D levels generally remain constant or fall over time[82,83]. ***Given available evidence, it is clear that current approach (no treatment or RDA/AI) will not restore vitamin D status in a time frame optimal to benefit the critically ill child.*** For these reasons, a different dosing regimen is essential to rapidly normalize vitamin D levels to realize the potential health benefits of sufficient vitamin D status.

Relevant clinical trials

Pediatric trials of daily high dose and loading dose vitamin D regimens

In preparation for this study, our research group completed a systematic review of all pediatric trials reporting on the administration of high dose vitamin D[37]. This review identified 156 trials on healthy and non-critically ill children, and comprehensively evaluated the ability of different dosing regimens to rapidly normalize vitamin D levels. **It should be noted that our systematic review (updated in January 2015) did not identify any vitamin D studies on daily high dose, nor loading dose in a pediatric critical care setting**. Our systematic review results show:

1. Daily high dose vitamin D - In addition to RDA/AI, the IOM provided a higher age specific dose called the daily upper tolerable intake level (1000-4000 IU)[40]. Supported by Health Canada, the daily tolerable upper intake level is intended to gradually elevate vitamin D levels into the high normal range (while safely avoiding toxicity). In our systematic review, we evaluated pediatric studies administering doses approximating the daily tolerable upper intake level to deficient children (Appendix C). **Our findings convincingly demonstrated that normalization of vitamin D levels in unwell deficient children still require more than a month of treatment**. Correction of VDD in this time frame is unlikely to benefit most critically ill children patient.
2. Loading dose vitamin D – Ten study arms were identified that provided vitamin D supplementation to children as single or divided enteral dose between 40 000 to 600 000 IU. Visual inspection demonstrates that loading therapy can rapidly elevate vitamin D levels within 48-72 hours of administration (Appendix D). It was also evident that administration of a constant dose over a wide age range can result in both under and overdosing. Meta-regression of data from studies that reported pre and post 25(OH)D was used to create a multi-predictor model predicting vitamin D response by dosing and population characteristics**. Altogether our analysis of pediatric clinical trials of non-critically ill children suggested weight-based enteral loading therapy of approximately 10 000 IU/kg as the appropriate dosing regimen to rapidly normalize vitamin D status (in unwell VDD children).** This dosing regimen would increase a group baseline 25(OH)D of 30 nmol/L to a group mean level of 100 nmol/L (Appendix E).

Based on these findings we propose an innovative protocol that utilizes a weight based enteral loading approach to normalize vitamin D status in critically ill children. The goal is to reach a target vitamin D level of 100 nmol/L with lower and upper thresholds in the sufficient range (75 and 150 nmol/L, respectively).

Trials of high dose vitamin D in related populations

Although limited, there is evidence to suggest potential clinical benefit to vitamin D loading therapy in related populations. The VITdAL-ICU study on critically ill adults (published by co-applicant, Dr. Karin Amrein) compared 540 000 IU to placebo and suggested a mortality benefit (43% vs 35%, p=0.09)[32]. In that study, subgroup analysis suggested an interaction between outcome and baseline 25(OH)D level: (i) evaluation of those participants with baseline 25(OH)D < 30 nmol/L demonstrated a statistically significant mortality reduction with vitamin D (50% vs 35%, p=0.02), while (ii) evaluation of those participants with baseline 25(OH)D between 30 and 50 nmol/L showed improvement in grip strength and physical component of the SF-12 questionnaire. Further, two pediatric studies also suggest potential benefit. A RCT of 450 young children presenting with acute lower respiratory tract

(ALRI) infection demonstrated that a single 100 000 IU enteral dose of vitamin D reduced repeat ALRI episodes[35]. Similarly, a recent systematic review of pediatric clinical trials of vitamin D in asthma by our research group demonstrated that high dose vitamin D supplementation, including a 60 000 monthly loading regimen, can reduce subsequent asthma exacerbations by 50%[34,84].

Safety Considerations

Despite significant health practitioner and public anxiety over toxicity, the overwhelming majority of studies evaluating high dose vitamin D have not reported adverse events. However, it is important to discuss and evaluate safety as evidence from case reports, case series and a few clinical trials does clearly demonstrate that inappropriate vitamin D intake leading to supraphysiological levels of vitamin D can cause toxicity[85,86]. Vitamin D toxicity is characterized by hypercalcemia or hypercalciuria, with the classic symptoms (lethargy, abdominal pain, anorexia, constipation, polyuria and nocturia) directly attributable to these abnormalities. With prolonged states of hypercalcemia and hypercalciuria children are at risk for developing nephrocalcinosis.

Although there is potential for toxicity with vitamin D loading therapy, there is also considerable evidence to suggest that the proposed dosing regimen (10 000 IU/kg enteral) will be safe.

1. Studies in healthy children receiving regimens approximating the daily upper tolerable intake level did not demonstrate toxicity with cumulative dosing approximating 10 000 IU/kg[80,87,88].
2. A review of case series of pediatric nephrocalcinosis identified that cases attributed to vitamin D occur in the context of one or more doses above 600 000 IU administered to healthy children or those with genetic abnormalities of vitamin D receptors[89-93].
3. We recently performed an adverse event analysis as part of our systematic review[37]. The analysis did not find evidence of toxicity until loading doses exceeded 400 000 IU (these studies generated group mean 25(OH)D levels above 200 nmol/L) (Appendix F)
4. The VITdAL-ICU study did not demonstrate increased hypercalcemia or hypercalciuria rates in the group of vitamin D deficient critically ill adults that received 540 000 IU[32].
5. Pediatric case reports and case series of clinical and subclinical cardiac dysfunction secondary to VDD describe improvements in patient status with both gradual and rapid restoration of vitamin D levels[52,55-58,94].
6. Pediatric RCTs evaluating loading dose therapy in healthy and stable unwell pediatric settings (e.g. ALRI, asthma) have not suggested safety concerns [34,35,84,95].

Although our literature review suggests that the proposed innovative weight based loading protocol for this study will be safe, we feel that the absence of any critically ill children in the trials prevents definitive statement. **The primary objective of the proposed study is to measure 25(OH)D response, but we will also evaluate for vitamin D related adverse events in real time**. If any participant shows significant perturbation of calcium metabolism, the patient will receive additional investigations with referral to local endocrinology and/or nephrology services (as appropriate). To assist the Site Investigators and most responsible physicians we will establish a vitamin D safety committee, separate from the Data Safety Monitoring Committee, to oversee the day to day evaluation of vitamin D related adverse events. Drs. Lawson (pediatric endocrinologist) and Geier (pediatric nephrologist) have extensive experience with measurement, interpretation and evaluation of vitamin D status and adverse events related to potential toxicity.

STUDY OBJECTIVES

Primary Objective

We propose a prospective double-blind dose evaluation phase II RCT in up to 67 critically ill children to determine whether a weight based enteral loading dose protocol can rapidly normalize vitamin D levels in critically ill children.

Secondary Objectives:

We will evaluate whether the weight based vitamin D loading protocol, when compared with usual care, results in:

1. Greater occurrence of vitamin D related adverse events (e.g. hypercalcemia, hypercalciuria)
2. Improved vitamin D axis functioning (e.g. active hormone levels, calcium metabolism)
3. Differences in blood measures of inflammation and innate immunity (e.g. CRP, procalcitonin)

Tertiary Objectives

If the dosing protocol evaluated as part of this dose evaluation RCT is successful we will subsequently undertake a multicentre phase III trial. For this reason the VITdAL-PICU pilot study will also explore a number of feasibility objectives:

1. Assess adherence and problems with our proposed treatment protocol (including blinding)
2. Assess the appropriateness of our eligibility criteria for the full trial
3. Estimate the rate of patient recruitment and understand barriers to recruitment

ELIGIBILITY CRITERIA

Inclusion Criteria

The inclusion criteria for this study are:

(i) Admitted to ICU,
(ii) Corrected gestational age > 37 weeks to age < 18 years,
(iii) Expected ICU admission in excess of 48 hours, and will have access for bloodwork at 7 days (clinical bloodwork or lines)
(iv) Blood 25(OH)D less than 50 nmol/L (regardless of prior approach to supplementation),

We have chosen to include children with a wide range of underlying diagnoses as vitamin D is a pleiotropic hormone important for the health and stress response of a many different organs and tissues[13,14]. Regardless of inciting event, secondary pathophysiology involving the immune, cardiac, respiratory and renal systems is common during critical illness. Note – Premature infants are at increased risk for nephrocalcinosis and will require evaluation as part of a separate NICU based study.

Exclusion Criteria

Patients who meet any of the following criteria will be excluded:

(i) Significant gastrointestinal disorder preventing enteral drug administration (e.g. necrotizing enterocolitis);
(ii) Hypercalcemia (excluding transient abnormalities and those related to parenteral calcium administration for hypocalcemia);
(iii) Confirmed or suspected William's syndrome**;**
(iv) Patient known to have nephrolithiasis or Nephrocalcinosis;
(v) Imminent plan for withdrawal of care or transfer to another ICU;
(vi) Physician refusal;
(vii) Previous enrollment in the study;
(viii) Patient known to have granulomatous disease (tuberculosis or sarcoidosis),
(ix) Severe liver dysfunction/liver failure;

(x) Patient know to have hypersensitivity or allergy to vitamin D or any of the non-medicinal ingredients of the formulation;

(xi) Patient on thiazide diuretics who is also receiving regular ongoing calcium supplementation above the daily recommended intake for reasons other than hypocalcemia**;**

(xii) Adolescent female of child-bearing age with a positive serum pregnancy test; or

(xiii) Patient on digoxin-therapy

At present there is no intravenous form of cholecalciferol~~,~~ preventing the inclusion of ICU patients who cannot receive enteral drugs. Patients who meet all other criteria but cannot receive enteral drugs will be followed by the study team and re-evaluated for eligibility once this exclusion criteria disappears. CHD patients with Williams syndrome have a genetic susceptibility to hypercalcemia and current guidelines recommend against any vitamin D supplementation[96]. Patients presenting with hypercalcemia, nephrolithiasis or nephrocalcinosis would be at increased risk for an adverse outcome. Until the safety of loading dose vitamin D is demonstrated in critically ill children without these risk factors, it would be prudent to exclude these high-risk groups in the RCT.

STUDY DESIGN

Trial Description

The VITdAL-PICU dose evaluation study will be performed as a multicentre double-blind phase II RCT. We will enroll up to 67 patients across all sites. Research Ethics Board approval will be obtained from the Children's Hospital of Eastern Ontario and from the local Research Ethics Board at each participating site. A Clinical Trial Application will be submitted to Health Canada (No Objection letter received on 03 July 2015). International sites will submit an application to their respective regulatory body. Prior to enrolling at other sites we will confirm with our RI that the appropriate insurance is in place and that their local authorities have approved study drug and protocol.

Study Endpoints

Primary outcome:

To determine whether loading dose therapy can rapidly normalize vitamin D status we will measure blood 25(OH)D concentration. More specifically, our primary outcome is the proportion of critically ill children who achieve blood 25(OH)D concentration above 75 nmol/L by day 7. 25(OH)D is widely regarded as the best indicator of vitamin D status[97].

Note - Two published adult studies, and our pediatric study[98] have failed to demonstrate blood concentrations of $1,25(OH)_2D$ as a superior marker of vitamin D status in critically ill patients[99-101].

Note – If bloodwork cannot be obtained on day 7 ± 48 hours (e.g. no access to bloodwork, patient discharged), the patient's 25(OH)D level from the day 3 sample will be used for the primary outcome

Other outcome measures:

1. *Vitamin D related adverse events* – A statistically measurable difference in clinically significant adverse events between the loading dose and placebo arms is unlikely in a phase II study. Therefore, we will evaluate for potential toxicity using two well accepted surrogate outcome measures.
   (i) *Hypercalcemia* – We will define hypercalcemia as an ionized calcium level above 1.40 mmol/L (children under 8 weeks as > 1.45 mmol/L) [102-104].

(ii) *Hypercalciuria* – We will identify hypercalciuria using calcium-creatinine ratios, defined using age specific norms and thresholds[104-107].

As detailed in the DSMB section we will also evaluate for and report on the occurrence of serious adverse events that could potentially be related to vitamin D.

2. *Vitamin D axis function* – Improved signaling through the vitamin D axis will be evaluated through an evaluation of blood calcium, PTH and $1,25(OH)_2D$. Change in immune function will be evaluated through inflammatory markers (C-reactive protein, procalcitonin) and antimicrobial peptide levels (cathelicidin) [68,69,105].

3. *Feasibility* - The pilot study will also allow us to evaluate protocol feasibility outcomes including protocol non-adherence, and study drop out. We will also preliminarily explore the feasibility of a subsequent multicentre phase III interventional study through an evaluation of the proposed eligibility criteria (i.e. can we predict ICU stay longer than 48 hours and the ability to obtain bloodwork at 7 days) and patient accrual rate. We will also assess our ability to maintain blinding by documenting the frequency of unblinding requests from the clinical care team and from the pharmacy.

4. *Phase III trial outcomes* - The pilot study will also allow us to assess potential outcomes for a phase III trial. These results will be used to better inform a sample size for subsequent phases of this research program. The Phase III trial outcomes that will be assessed are:
   (i) Multiorgan dysfunction: (PELOD-2 score: days 0,3,7,14, and every 30 days until discharge or 90 days)
   (ii) Readiness for PICU discharge

Measurement of Outcomes at Follow-Up

Primary outcome:

1. Vitamin D status – For the final reporting and interpretation of regimen success, we will evaluate research blood collected on day 7. Liquid chromatography-mass spectrometry technology that allows for the differentiation and reporting of all vitamin D metabolites occurring at relevant concentrations will be utilized[108]. As it is less biologically active we will report on, but not include, the C3 epimer in the final 25(OH)D concentration[21,86].

Other outcomes

1. Vitamin D related adverse events - As they have the potential to be clinically relevant, blood and urine calcium values will be determined in real time.
   i. *Hypercalcemia:* Identification of persistent hypercalcemia (> 24 hours, without calcium administration) will trigger an endocrinology consult. Blood calcium will be analyzed from the research blood samples collected on Day 3, 7, 30, 60 and 90 or until hospital discharge. If ionized calcium is ordered as part of clinical care within 24 hours of these time points, a separate research sample will not be collected and the clinically-indicated calcium result will be used instead. In addition, all ionized calcium levels from clinical bloodwork will be monitored and recorded on the study case report form.
   ii. *Hypercalciuria*: Similarly, urine calcium will be evaluated after study drug administration, with measurements on day 3 and 7 and then monthly measurements as possible until discharge or 90 days. If hypercalciuria (based on calcium: creatinine ratios) is identified on two sequential urine samples (excluding the first sample drawn at enrolment) the study nephrologist will be consulted to evaluate specific patient characteristics (how abnormal results are, trends, use of furosemide, renal dysfunction, expected length of stay, etc.) and whether they should have a repeat measurement

and/or a renal ultrasound to evaluate for nephrocalcinosis. If it is not possible to collect at least day 3 and 7 study samples the study nephrologist will be contacted to determine appropriate post-hospital discharge follow-up.

iii. *Hypervitaminosis*: Current understanding is that acute vitamin D toxicity occurs in the setting of 25(OH)D well in excess of 250 nmol/L. However, there is some evidence that with longstanding (months to years) elevation of 25(OH)D toxicity may be seen with levels approaching 200 nmol/L range. For safety and scientific purposes, those patients who have a 25(OH)D level >200 nmol/L will be discussed with Endocrinology. Endocrinology will review the patient's calcium levels (blood and urine) and clinical course, and may decide that the patient should be followed as an outpatient. All perturbations will be systematically documented (see Appendix G for a summary of the safety procedures for abnormal research samples).

2. Vitamin D axis outcomes – $1,25(OH)_2D$, PTH, CRP, procalcitonin and cathelcidin levels will be determined using validated assays.

3. Feasibility –

   i. We will also document problems encountered with administration of study drug and safety monitoring (protocol non-adherence).
   ii. We will assess our ability to maintain blinding by tracking the number of times that the care team requests that blinding be broken.
   iii. We will record the impact of eligibility criteria on screening and recruitment. For example, we will evaluate the ability to predict ICU admission for > 48 hours and our ability to obtain bloodwork at 7 days to determine whether these time periods need re-evaluation.
   iv. Briefly, we will evaluate recruitment by recording the total number of patients enrolled, and the number of enrolling sites, on a monthly basis. All patients who meet the study inclusion criteria will be documented on a study screening log, which we will use to further scrutinize the appropriateness and impact of eligibility criteria.

EXPECTED DURATION OF SUBJECT PARTICIPATION

Study Duration

Study participants will receive study drug (vitamin D or placebo) at enrollment. Study participants will be followed until hospital discharge (censored at 3 months following enrollment). Three months will be an adequate period to screen for potential side effects of rapid normalization of vitamin D status (hypercalcemia, hypercalciuria, nephrocalcinosis). Patients who are discharged from hospital before 90 days will be contacted by telephone on Day 90 to determine if they have been readmitted to a hospital, have been ill, or if they have experienced any symptoms that could be related to vitamin D toxicity since discharge from hospital. In the subsequent phase III trial, patients may be followed for a longer period to better understand long-term health and resource benefits. Certain participants may need to be followed for a longer period of time. If a patient's 25(OH)D level at the last test prior to hospital discharge is >200 nmol/L (rare), they will be discussed with Endocrinology. We expect that this will be very small percentage of patients.

Frequency and Duration of Follow-Up

Study participants will have blood collected as part of the screening and enrolment process (to determine vitamin D status eligibility) and on days 1, 2, 3 and 7, at the time of the specific triggers, and

at the time of hospital discharge. Urine samples will be collected at enrolment (Day 0), on days 3, 7, and at the time of hospital discharge. To inform the analysis plan for the phase III trial we will collect clinical relevant outcome data including: fluid administration, surgical procedures, progression and resolution of organ dysfunction, occurrence of adverse events, readiness for ICU discharge, length of hospital say, survival status, and development of new morbidity at discharge (collected three times a week until discharge from hospital or 90 days). Additional information will be collected for patients who are discharged from hospital before 90 days including hospital readmission rate, and frequency of illness.

STUDY MEDICATION/INTERVENTION

Europharm® has agreed to provide both the vitamin D and placebo solutions at no cost. Post-randomization, the hospital pharmacy will provide both vitamin D and placebo solutions to the nursing staff for administration.

Study Medication Description

*It is essential to point out that the objective in the experimental group is to correct vitamin D deficiency in critically ill children. Unlike many other clinical trials of vitamin D, our goal is to achieve and maintain levels considered "*normal"* (75 to 150 nmol/l). The proposed dose is <u>not</u> designed to achieve supraphysiological levels (> 200 nmol, not attainable with diet and sunlight).

Participants randomized to the experimental arm will receive an enteral cholecalciferol load (Vitamin D3 (Cholecalciferol) Oral Solution 50,000 IU/mL) at enrolment at a dose of 10 000 IU/kg (maximum 400 000 IU).

There are no serious side effects to the actual administration of vitamin D. Some patients may experience mild gastrointestinal upset. Excessive doses of vitamin D can lead to hypervitaminosis D (25(OH)D in excess of 200 nmol/l), manifested by hypercalcemia and its sequelae. Early symptoms of hypercalemia may include: weakness, fatigue, somnolence, headache, anorexia, dry mouth, metalic taste, nausea, vomitting, vertigo, tinnitus, ataxia and hypotonia. Possibly more serious manifestations of hypercalcemia that develop with rapid elevation of 25(OH)D levels (>250 nmol/L) or prolonged exposure to supraphysiological levels (~200 nmol/L) include: nephrocalcinosis, renal dysfunction, osteoperosis in adults, imparied growth in children, anemia, metastatic calcification, pancreatitis, generalized vascular calcification, and seizures. Blood and urine samples will be monitored in real time for evidence of hypercalcemia and hypercalciuria. With the exception of the nephrocalcinosis and metastatic calcification (both of which require persistent hypercalcemia and/or hypercalciuria) the remainder of the symptoms can occur at presentation or during treatment of critical illness.

No dose adjustments will be made since this is a single-dose study. Should a study participant develop significant symptoms related to vitamin D toxicity, (potential drug-related adverse event) they will be evaluated and followed by the endocrinology or nephrology clinic. The nephrologist will decide whether unblinding is required.

Notes - (2) Current hospital practice for 25(OH)D determination can require a week or more for results to be available (due to batch testing and delays associated with reporting). Although reasonable for healthy patients, this time frame is not appropriate for the severely ill, and will not allow for the completion of an RCT evaluating the benefits of rapid normalization. Consequently, we will utilize the FastPack® IP system, an FDA and Health Canada approved device from Qualigen®, to rapidly quantify 25(OH)D levels in under an hour. This FastPack result will determine initial study eligibility. A detailed explanation of this device and the external validation performed by our group can be found in the SOP. Alternately, the screening sample may be sent to a certified laboratory (e.g. The Ottawa Hospital) for determination of 25(OH)D level.

Control Product Description

Participants randomized to the control group will receive a placebo solution at enrolment,. The placebo will be provided by Europharm® and contains: Caramel Color, Cherry Flavor, Citric Acid (Anhydrous); Glycerin, Polysorbate 80, Propylene Glycol, Purified Water, and Sucralose. We do not expect any significant side-effects associated with placebo administration. The control product will be identical in smell, taste, and appearance to the study drug in order to maintain blinding.

Note - Although the control group is not directly relevant to the primary outcome (determining response to vitamin D load), this arm is essential to addressing multiple secondary objectives, for example:

i. Without the placebo arm it will be impossible to evaluate whether loading therapy leads to differences in blood or urine calcium. Importantly, there is little data on urine calcium levels and hypercalciuria rates during pediatric critical illness. Elevated urine calcium levels may occur frequently in the ICU and it will be important to have information on children receiving usual care. For example, preliminary data from our ongoing pilot RCT of pre-operative vitamin D supplementation in stable CHD suggests approximately 1/3 have elevated urine calcium peri-operatively, with signifiant day to day fluctuations in levels.
ii. Without the placebo arm we would not be able to properly evaluate recruitment or our ability to achieve blinding.

Formulation, Packaging, and Labelling

Vitamin D3 (Cholecalciferol 50,000 IU/mL will be provided by Europharm as a pre-made solution. Each mL of the solution will contain 50,000 IU of cholecalciferol. Each dose of study drug will be dispensed by the pharmacy as a single dose in a syringe. The amount of study drug dispensed will be based on the study participant's weight. Labelling of the study drug will be as follows:

Vitamine D 50000 UI/mL (CTA# 184825)
Médicament de recherche (Investigational Drug)
Utiliser uniquement à des fins d'études cliniques
(To be used only for the Clinical Study)
Ne doit être utilisé que par un chercheur qualifié
(To be used by a qualified investigator only)
Dr. Dayre McNally, CHEO, 401 Smyth Rd, OT, ON K1H8L1
Manufactured by: Euro-Pharm International Canada Inc. (H1P 3H8)
Conserver à 15-30°C (Store at 15-30°C) **Lot: EU020-1 Exp. 2016-09**

Vitamine D 50000 UI/mL (CTA# 184825)
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Accountability and Product Storage

Standard operating procedure for receiving, storing, and accounting for clinical trial medications and supplies for pharmacy research support services will be followed to ensure compliance with good clinical practices and the applicable regulatory requirements. The following text

has been adapted from CHEO Pharmacy SOPs for *Investigational Drug Accountability and Storage* (CHEO PHARM 01_02) and *Pharmacy Staff Delegation for Research Studies* (CHEO PHARM 08-01).

The Sponsor/Investigator or Principal Investigator (JDM) is responsible for ensuring that investigational drugs are managed according to all of the applicable regulatory International Conference on Harmonization (ICH), Good Clinical Practice (GCP), and local requirements. Any or all parts of this procedure are delegated to appropriately trained study team members, but remain the ultimate responsibility of the Principal Site Investigator. The following tasks will be delegated to pharmacy: study drug accountability tracking, ordering and receiving study drug, dispensing study drug, study drug dose preparation, and disposal of study drug.

Receipt of Investigational Drugs

Pharmacy staff will review the shipping documentation upon receipt of the investigational drugs, and will record the drugs received to ensure that the information on the shipment invoice corresponds to the products sent and received, including the quantity, lot number, and expiry or retest date. Pharmacy staff will document any damages and/or discrepancies, and retain the documents and shipping records. If any inconsistencies are noticed between the invoice and drug received, pharmacy staff will communicate this to the sponsor/investigator as soon as possible. Pharmacy staff will retain all documentation related to transportation and receipt of the investigational drugs throughout the study with the essential study documents. These documents will be kept at the pharmacy until study close out, at which time they will be stored with the rest of the essential study documents.

Sponsor Labeling of Investigational Drugs

Labelling of the study drug will comply with applicable regulatory requirements (see above sample label). Pharmacy staff will ensure that the label on the investigational drug is not hidden, covered, withdrawn, or modified without the authorization of the Principal Investigator. If required by the institution, pharmacy staff will apply an additional label (i.e. subject label) in such a way that is does not cover the original label of the investigational drug.

Storage of Investigational Drug

Pharmacy staff will store the study drug in a secure environment with controlled access restricted to authorized personnel, and with controlled temperature (15-30°C). Pharmacy staff will monitor the temperature and record regularly, either manually or by an automatic device. If problems arise, pharmacy staff will move the drug to an alternate storage area. Any storage issues will be documented. Storage records and will be kept within easy access of the investigational drug and be available for monitors, auditors, etc. if requested. Temperature records will be filed in such a way so they are easily accessible to research staff, monitor, auditors, etc. if requested.

Distribution of Investigational Drug

The investigational drug will only be used only in accordance with the approved protocol. Any use outside of the protocol will be documented and reported to the Principal Investigator. Pharmacy staff will maintain a dispensing log to document assignment of investigational drugs to specific study subjects. This log will be stored in pharmacy until study close out.

Accountability of Investigational Drug

Pharmacy staff will document the return of all investigational drugs and/or containers, and maintain this documentation with the essential study documents. Study drug that has been assigned to a subject and not used will not be given to another study subject, to a subject outside the study, or to another site

Return/Destruction of Investigational Drugs

All IP bottles/syringes will be kept during the study and returned to pharmacy until all drug accountability is monitored and verified. IP bottles will be destroyed once all IP is reconciled upon study completion. At study completion, pharmacy staff will obtain written authorization from the Principal Investigator for destruction of drug. Destruction will be carried out in accordance with institution/pharmacy procedures. Defective or outdated drugs will be returned or destroyed in the same manner, unless otherwise requested by the Principal Investigator. The return and/or destruction documentation will be filed with the essential study documents stored in the pharmacy until study close out.

Randomization

Pharmacy staff will follow the randomization procedures as described in the protocol, and document subject allocation. Pharmacy staff must ensure that the randomization code is broken only in accordance with the unblinding procedures described in the study protocol. Randomization documentation will be filed with the essential study documents stored in the pharmacy until study close out.

Subject Compliance with Study Medication/Intervention

We do not anticipate problems with compliance for the following reasons: (i) Patients are hospitalized, will be followed closely by the research staff, and study drug will be ordered and administered by nursing; (ii) Further, the primary outcome is initial response to the loading protocol. As the study drug is to be given on the day of enrollment we would anticipate near 100% compliance for receipt of at least one load of cholecalciferol. Adherence to the protocol will be recorded as an outcome measure of our pilot study.

Concomitant and Prohibited Meds

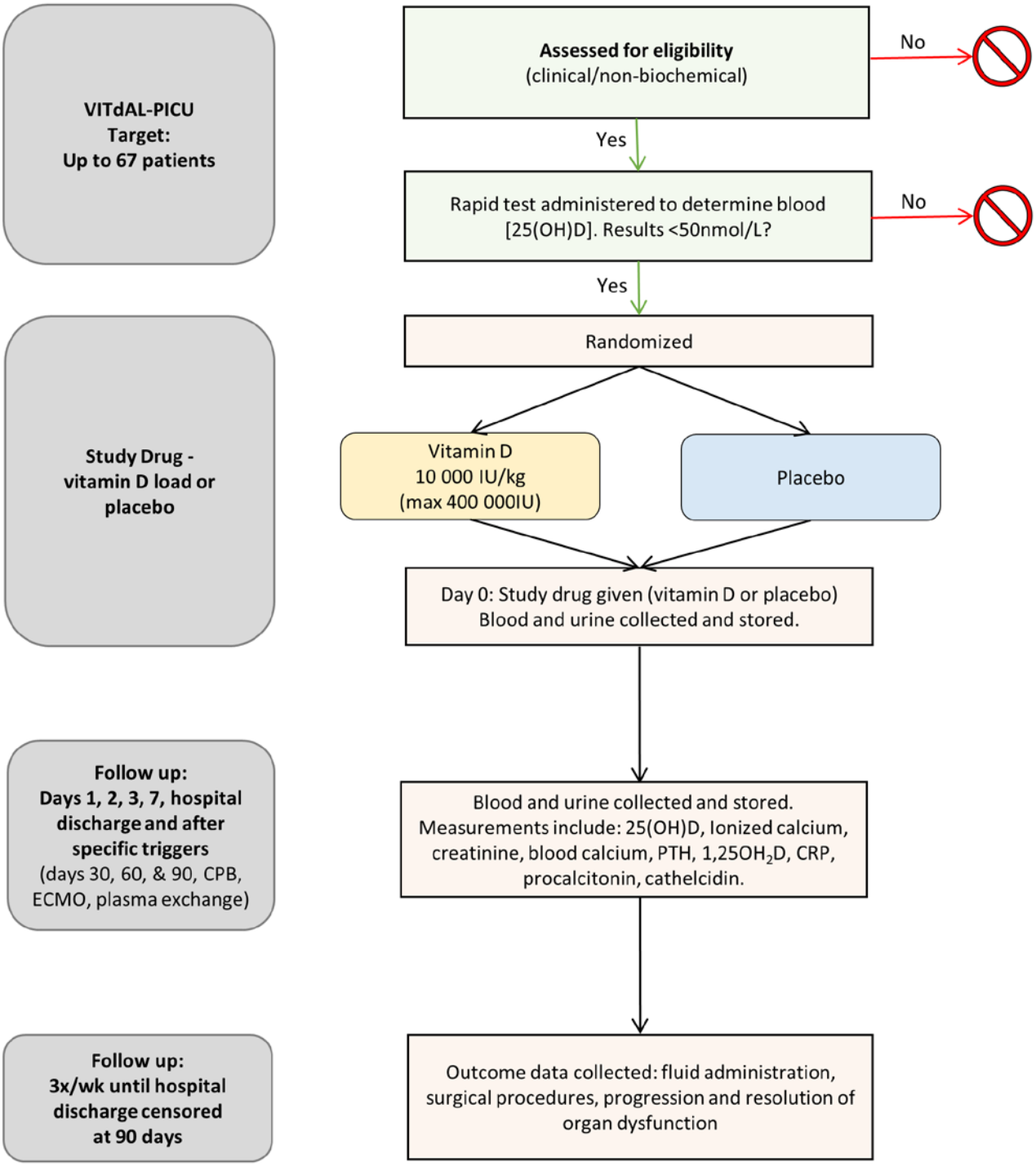
As per the exclusion criteria, children on digoxin therapy will not be permitted to take part in the trial because of potential interactions with cholecalciferol. Vitamin D administration can increase the risk of hypercalcemia if given to patients on thiazide diuretics and calcium. Therefore, patients who are on thiazide diuretics and also receiving regular, ongoing calcium supplementation above the daily recommended intake will not be permitted to take part in this study (except for those patients who are receiving the calcium supplementation for hypocalcemia).

Both Arms

At the discretion of the health care team, study participants in either arm can receive routine or standard of care daily vitamin D administration (400-800 IU/day). With the exception of study drug administration (enteral cholecalciferol or placebo) there will be no other changes to clinical management. Co-interventions will not be protocolized as the study is blinded and any differences should relate to either random chance or effects from the study drug. Additional vitamin D administration and other major co-interventions will be captured on the case report form.

STUDY PROCEDURES/EVALUATIONS

Schematic of Study Design



Identification of patients, Screening, and Randomization

Eligible patients will be identified in the intensive care units. Patients will be screened on a daily basis (Monday through Friday) by study staff. The ICU staff including physicians, nurses, pharmacists, dieticians, respiratory therapists as well as patient families will be made aware of the study through information sessions, posters, bi-monthly emails and monthly pamphlets providing study updates (see Appendix H for integrated knowledge translation and consumer engagement plan). Once a patient is determined to meet the study eligibility criteria, with the exception of vitamin D status, a member of the patient's circle of care will ask the legal guardian (and patient where appropriate) if study staff can come and speak to them about a research study. Once permission has been obtained through the circle of care, research staff will approach the family about study participation. If informed consent is obtained, blood will be acquired to determine if the patient meets the eligibility criteria of being vitamin D deficient. Study staff will first call the laboratory to determine if sufficient discard blood is available for the patient. If no discard blood is available, the study team will provide a blood sample package to the bedside nurse, and the blood sample will be collected with the patient's next clinically indicated bloodwork or through existing lines. Research staff will determine vitamin D status using the Qualigen® FastPack IP system (results should be available in approximately <2h), or by sending the sample to a certified laboratory for analysis of 25(OH)D levels. If the 25(OH)D is less than 50 nmol/L the patient will be considered fully eligible and will be randomized into the study.

In certain cases, it may be possible to verify the patient's eligibility and obtain consent prior to PICU admission. Patients scheduled for cardiovascular surgery will be screened before surgery. If the patient meets study eligibility criteria, the study team will try to obtain informed consent either at the pre-operative appointment in the Cardiovascular Surgery (CVS) Clinic, or on the day or surgery while the legal guardians are waiting in the CVS parent room. The CVS nurse (part of the circle of care) will first ask the legal guardian if the study team can come to speak to them about the study. If informed consent is obtained, the study team will try to obtain discard blood from the laboratory. If no discard blood is available, a blood sample will be collected to determine vitamin D status at the time of PICU admission. If the patient meets the vitamin D criteria for enrolment (25(OH)D <50 nmol/L), the patient will be randomized into the study.

Alternate Consent Procedures for Measurement of Vitamin D Status during Screening

An important inclusion criteria for this study is that the patient will still be in ICU for 48 hours from the time of screening and enrolment, and is expected to be in hospital, with access for bloodwork, at Day 7. This criteria is important not only for our primary outcome, but also to properly monitor patients for symptoms of vitamin D toxicity through the collection of blood and urine samples. In order to reduce the number of patients excluded by this criteria, it is important that patients are screened and enrolled as close to the time of PICU admission as possible. To improve our ability to do this, we will employ two alternate consent processes for measurement of vitamin D to determine eligibility. These alternate consent processes will be used solely for screening. Written consent will be obtained prior to administration of study drug.

Telephone Consent for Screening

A member of the circle of care will first speak with the legal guardian and get permission for the study team to phone them. A member of the study team, in the presence of an impartial witness, will then contact the family by telephone and explain the study using the VITdAL-PICU Script for Telephone Consent. The study team will discuss all elements of the approved consent form during the phone conversation. They will explain in detail the purpose, risks, benefits, and study related procedures. The legal guardian will be provided time to ask and have their questions answered. The study team will offer to email or fax a copy of the consent form to the legal guardian. The legal guardian will be reminded that consent is voluntary and that they are free to withdraw at any time

without explanation and without affecting the care their child receives at CHEO. If the legal guardian agrees to participate, the study team member and impartial witness will both sign the consent form and will arrange a time for the legal guardian to sign the consent form (i.e. at their next visit to the hospital). The study team will then measure the patient's vitamin D status to determine if they are eligible for the study (as described above). If the patient is eligible, the study team will inform the legal guardian, confirm that they still wish to participate in the study, and have the legal guardian sign the consent form prior to enrolling and randomizing the patient. The only study procedure that will occur before the legal guardian signs the consent form is the measurement of the patient's vitamin D status. After the legal guardian has provided their signature, enrolment will occur as described above. If the patient does not meet the vitamin D criteria and is not eligible for the study, the legal guardian will still sign the consent form at their next visit to hospital indicating that they provided consent for the screening process via telephone.

Consent for screening through the care team

Consent for screening will also be obtained through the care team using a simple permission form. This form will be provided to legal guardians at PICU admission and will ask the legal guardian to indicate it they give permission to have their child's vitamin D status measured to see if their child is eligible for a research study on vitamin D. If the legal guardian agrees, the study team will measure the patient's 25(OH)D level as described above. If the patient meets the eligibility criteria, the study team will seek written informed consent for the trial as outlined above. If the patient is not eligible, the study team will let them know that their child did not meet the eligibility criteria for the study.

Randomization and Allocation Concealment:

The Methods Centre at the Ottawa Hospital Research Institute (OHRI) will generate a computer-generated randomization list. Patients will be randomized 2:1 using random variable block sizes (2-4 patients/block) to avoid major imbalances. Randomization will be stratified by: (i) by patient age (above or below 30 days of age); (ii) site (Austria, Chile, CHEO NICU or CHEO PICU) in order to account for site-specific practice variation. We have decided to stratify by age as neonates can respond uniquely to medications due to different water/fat content, hepatic and renal functioning. Further calcium homeostasis and the definition of abnormal for both hypercalcemia and hypercalciuria are difference for neonates. Stratification by neonatal status will ensure that these differences are equally distributed between the groups.

Randomized allocation will be achieved using a hard copy randomization list: when an eligible patient is identified, study staff will confirm each eligibility and exclusion criteria, and record the next available study ID number within the correct stratification group on the drug order form. The pharmacist will match the study ID number assigned to the hard-copy randomization list to determine treatment allocation and will dispense the dose of study drug. The study drug will be sent to the patient's bedside and administered by the bedside nurse. Administration of the study medication will be recorded in the patient's medical chart.

Blood and Urine Sampling

Blood measurements will be performed on samples collected during screening and on days 1, 2, 3, 7, and at hospital discharge. If discard blood is used for screening, a separate enrolment sample will be collected from randomized patients to have sufficient quantity for analysis of vitamin D metabolites. If a fresh sample is collected at screening, then a separate enrolment sample will not be required. If routine blood work is not planned for these specific days, and arterial or central venous line access is not available, research blood samples will be collected at the time of the next clinically indicated venipuncture. Urine samples will be collected at enrolment and on Day 3, 7 and at discharge. The amount of urine that will be collected during each sample is approximately 5mL. In order to comply with the CHEO REB guidance for blood sampling, the volume collected for each blood

sample will vary depending on the patient's weight. There are 6 planned blood samples for this study. However, since blood will only be drawn through existing lines or with clinically indicated bloodwork, patients may have less than 6 samples collected. In addition, patients may have additional bloodwork done following specific interventions or triggers. We anticipate that ~15-20% of patients will require an additional sample within the first 30 days for this reason. For low-weight patients, we will evaluate the amount of blood collected to date and if needed, adjust the volume or not collect the trigger sample to remain within the total volume 30 days limit in the CHEO REB guidelines.

Patient Weight	Volume per Sample	Total Volume Collected from Planned Samples
2-3 kg	1.5 mL/sample	9 mL
3-4 kg	2 mL/sample	12 mL
4-5 kg	2.5 mL/sample	15 mL
>5 kg	3 mL/sample	18 mL

Blood samples at each time point will be analyzed for 25(OH)D levels at study close out. Sub-sites will store collected samples and they will be shipped to the Coordinating Centre for analysis (see Appendix I for further detail). Ionized calcium will be measured in the research sample collected on Days 3, 7, 30, 60 and 90 unless ionized calcium has been measured through clinical bloodwork in the preceding 24 hours, or a clinical calcium sample is planned for that day. Since blood samples will only be drawn through existing lines or with clinically-indicated bloodwork, we will not consider it a protocol deviation if a research blood sample cannot be collected. Similarly, if a patient cannot produce urine for a urine sample, we will not consider this a protocol deviation. Since we will be timing bloodwork with clinical bloodwork, we have established acceptable time windows for research samples (i.e. if the Day 3 sample is collected on Day 2 or 4, we will consider this acceptable and still include the sample in the analysis).

Research Sample Target	Acceptable Range
Day 0 (Enrolment)	n/a
Day 3	+/- 1 day
Day 7	+/- 2 days
Day 30	+/- 7 days
Day 60	+/- 7 days
Day 90	+/- 7 days

Additional Blood Sampling After Specific Triggers

Clinical interventions: Specific interventions are known to significantly reduce 25(OH)D concentrations, including: cardiopulmonary bypass (CPB), extracorporeal membrane oxygenation (ECMO), plasma exchange[23,109,110]. Study patients who receive specific interventions after administration of study drug will have their blood concentrations of 25(OH)D determined post intervention. We anticipate that one or more of these interventions will occur in less than 20% enrolled in the study. Similarily, if a patient is consented and the screening 25(OH)D level is >50 nmol/L (patient not eligible), but the patient subsequently undergos an above-mentioned intervention, a new blood sample (discard whenever possible) will be collected to re-screen the patient. If the 25(OH)D level in the post-intervention screening sample has fallen to <50 nmol/L, the patient will be randomzied into the study.
Time in hospital: Our systematic review found that blood 25(OH)D concentrations begin to fall within one week of loading dose administration[37]. Meta-regression determined the average fall in 25(OH)D to be 5 nmol/L per week (upper confidence interval was 8 nmol/l/week). Further, available data also suggests that hospitalized children and adults experience a decline in 25(OH)D concentration over

time[82,83]. If the participant remains in hospital, they will have blood 25(OH)D evaluated every 30 days. This will inform us as to whether to include a repeat test and load approach in the ultimate phase III trial for those children who remain in hospital for > 30 days.

Scenarios for Re-Screening

As mentioned above, an additional screening sample may be collected in consented patients who do not have a 25(OH)D level under 50 nmol/L but then undergo an intervention known to lower 25(OH)D levels. Additionally, if a screening sample 25(OH)D result is abnormal, an additional screening sample may be collected and re-analyzed. This is the same process that is followed in clinical care for an abnormal laboratory result (new blood sample collected and re-analyzed). An abnormal sample result could suggest a problem with sample collection, sample processing, or performance of the Qualigen® assay. An abnormal 25(OH)D result will be defined as a result that is inconsistent with what is known about vitamin D levels in critically ill children. Most children in the PICU are deficient in 25(OH)D and only a small percent have levels above 80 nmol/L. Interventions frequently used in the PICU are known to further reduce 25(OH)D levels. For example, a patient who underwent cardiac surgery with cardiopulmonary bypass who had a screening sample 25(OH)D result of 80 nmol/L at PICU admission would be considered abnormal since our previous research on over 50 patients undergoing cardiopulmonary bypass did not identify a single patient with a value even close to this.

90 Day Follow-Up

Study participants are followed until hospital discharge (censored at 90 days). Patients who are discharged from hospital before 90 days will be contacted by telephone on Day 90 to determine if they have been readmitted to a hospital, have been ill, or if they have experienced any symptoms that could be related to vitamin D toxicity since discharge from hospital. This phone call is expected to take approximately 10 minutes. Prior to contacting the family, study staff will first consult the patient's medical record to determine if the patient has been re-admitted to hospital or if the patient is deceased. If the patient is deceased, the family will not be contacted and the study staff will notify the Principal Site Investigator.

Quality of Life Assessments

Health-related quality of life (HRQL) is increasingly becoming an outcome of interest in critical care research Preliminary analysis of our research outcomes questionnaire supports this, with ~80% of caregivers identifying "Qualify of life following hospital discharge" as one of their top three most important research outcomes. In order to determine the suitability of HRQL as a research outcome for subsequent trials, we will collect pilot HRQL data from VITdAL study participants and their caregivers using the Pediatric Quality of Life Inventory 4.0 Generic Core Scales and Infant Scales (PedsQL). The PedsQL has demonstrated responsiveness and construct validity in the PICU population. The questionnaire will be used according to the 2009 PedsQL™ Administration Guidelines™ (see Appendix J).Questionnaires may be administered in person, by telephone, or by email survey through REDCap. Participants and their caregivers will be asked their preference of survey administration methods.

The questionnaire takes approximately 5-7 minutes to complete and will be administered at the following time points:

Time of Questionnaire Administration	Recall Period
Baseline – Administered within 48 hours of PICU admission or as soon as possible following enrolment if patient is enrolled into the study >48 hours after PICU admission	Last 30 days before PICU admission, specifically time before patient became ill

PICU Discharge – Administered within 24 hours of PICU Discharge or at day 7 of PICU stay, whichever occurs first	PICU admission to PICU Day 7/PICU discharge
Hospital Discharge – Administered within 24 hours of hospital discharge *Only applicable for patients with a hospital stay of at least 10 days	PICU discharge to time of questionnaire (or last 30 days, whichever is shorter)
Day 30 – Administered 30 days from the date of enrolment *If hospital discharge falls within 5 days of this time point, separate Day 30 and Hospital Discharge questionnaires will not be administered	7 days prior to the date of questionnaire administration
Day 90 – 90 days from the time of enrolment *If hospital discharge falls within 5 days of this time point, separate Day 90 and Hospital Discharge questionnaires will not be administered	7 days prior to the date of questionnaire administration

The objective at this time is to determine the feasibility of administering the questionnaire at each time point, and to collect pilot data for planning of subsequent trials. Therefore, we will not consider it a protocol deviation if the questionnaire is not completed at a certain time point or is administered early/late. All instances of non-completion will be documented.

Blinding and Allocation concealment:

The randomization lists will only be accessible to the Data Management Services (DMS) of the Ottawa methods centre at the OHRI and to the research pharmacist(s). Prior to initiation of the study, the DMS will send the randomization list directly to the research pharmacist where it will be stored for use during randomization. Further, the active drug and placebo will be identical in appearance, consistency, volume, taste and smell (no threat).

All study personnel (the Study Coordinator, Research Assistants, Principal Investigator, Site Investigators, Co-Investigators, data management personnel and statisticians), members of the health care team (treating physicians, bedside nurses, clinical pharmacists) and patients/families will be blinded to the study group assignment. Blinding is necessary, as we would like to evaluate the feasibility of a phase III trial that will evaluate clinically relevant outcomes that are subjective in nature. The assigned intervention will not be revealed until all patients have been discharged from hospital (censored at 90 days), determination of research related biochemical testing is complete, and the research database has been finalized.

In the event of an emergency, blinding can be broken at the request of clinical service. The randomization code and list of randomized participants will be stored at the pharmacy. If unblinding is required, clinical service will first contact the Principal Site Investigator, who will then contact the pharmacy to unblind the participant. Any instances of unblinding will be documented as a protocol violation.

Caregiver-Initiated Withdrawal

Caregivers are free to withdraw their consent for their child's participation at any time during the clinical trial, with or without a stated reason. Caregivers will be provided with contact information for the Study Coordinator and Assistants, and the Principal Site Investigator and instructed to contact a member of the study team should the wish to withdraw.

STATISTICAL PLAN

Sample Size

The goal of our weight based loading protocol is to achieve target 25(OH)D concentrations above 75 nmol/L in 75% of the participants who receive loading dose vitamin D. Further, the minimal acceptable proportion achieving target where we would consider proceeding with a phase III trial is 50%. Assuming that the true proportion achieving target is 75% a random sampling of 36 patients has ~90% power to return an estimate in excess of 66% (two thirds of participants achieving target 25(OH)D). Given an estimate in excess of 66% and a sample size of 36 the lower 95% confidence interval will exclude 50%. To account for 5% drop out or missing samples we will recruit up to 40 patients into the high dose arm (20 in the placebo arm).

Why expect 75% to achieve target?

Based on our systematic review and meta-regression we anticipate that 10,000 IU/kg will raise the vitamin D level by 70 nmol/l. Assuming a group average value of 40 nmol/L in the intervention arm, this will result in a post-load group 25(OH)D level of approximately ~110 nmol/L. Given a standard deviation of no more than 35 nmol/L we would anticipate that 16% of the group will not achieve a post-load value of 75 nmol/L (z-score of -1). However, given that some of the older children (weight above 40 kg) will receive less than 10,000 IU/kg, we have reduced our estimate of proportion achieving target to 25%.

Why select 50% as the lower allowable confidence interval?

The VITdAL-ICU trial suggested a 7% absolute risk reduction in mortality with 52% achieving target 25(OH)D of 75 nmol/L.

What if the loading dose approach works better than expected?

This was discussed at our September 8th Steering Committee Meeting. The decision was made to retain the maximum sample size of 40 for the high dose arm, but allowing for the trial to stop early if certain targets were met (an adaptive design, see DSMB section).

Analyses

Analyses will be performed using SAS® software (Cary, NC, USA) and a p-value less than 0.05 will be considered statistically significant.

Primary outcome – **The primary objective of this study is to determine whether a weight based loading protocol can rapidly normalize vitamin D status in critically ill deficient children. The primary analysis for the study will be the proportion of participants in the treatment arm achieving 25(OH)D levels above 75 nmol/L on day 7 (with its 95% confidence interval). We expect 0% of the control arm to achieve the target 25(OH)D level of 75 nmol/L.** The analysis will evaluate the data using both intention to treat (primary) and per protocol (secondary) approaches. The 7 patients who received two doses of study drug will be included in the intention to treat analysis. In addition, we will also report on: (i) the distribution of 25(OH)D levels on day 7 using means/medians with the appropriate measure of distribution (standard deviation, IQR), and (ii) the number of study participants who developed 25(OH)D levels in excess of 200 nmol/L. Altogether the above analysis will provide the information required to determine whether the weight based loading protocol is satisfactory for a phase III trial, and what minor modifications may further improve the intervention.

Descriptive statistics - Treatment arms will be described using: (i) means with standard deviations or medians with inter-quartile range values for continuous variables or (ii) frequencies with percentages for categorical variables.

Vitamin D axis, adverse events and clinical outcomes – Secondary analyses will be evaluated between groups based on data type. Outcome measures that are continuous will be evaluated using the t-test or Wilcoxon sign rank test (where appropriate). Binary secondary outcome measures (e.g.

hypercalcemia, hypercalciuria, nephrocalcinosis) will be compared between the two treatment groups using Fisher's exact or Chi-square. For the analysis of outcome measures that represent time to event (extubation, ICU discharge) we will apply the log rank test and generate Kaplan-meier curves. If randomization does not lead to equal distribution of important variables (e.g. weight) the above analysis will be expanded to regression modeling to allow for adjustment.
Notes – (1) Some uncertainty exists as to the appropriate 25(OH)D threshold for an ICU study of rapid normalization of vitamin D status. For example, the VITdAL–ICU trial by Amrein and colleagues identified a statistically significant difference in mortality in the subgroup of patients with severe vitamin D deficiency (<30 nmol/l)[32]. Although there was no mortality benefit for the group of patients with 25(OH)D between 30 and 50 nmol/L these patients appeared to benefit in other ways (e.g. greater grip strength, perceived physical abilities). As literature could emerge further supporting either of these cut-offs, we will determine the proportion of eligible patients with 25(OH)D under 30 and 50 nmol/l. This will allow us to determine the feasibility of a phase III trial using either threshold. (2) It is also unclear how many patients will be ineligible as a result of their inability to take drug enterally. The study by Amrein and colleagues[32] report approximately 25% of screened patients were excluded due to gastrointestinal dysfunction. We have approached Europharm® about creation of an intravenous form of cholecalciferol. They have expressed a willingness to discuss, but only if further data could be provided demonstrating need.
Acceptance of question and feasibility of study - Information collected on screening, eligibility, baseline vitamin D levels, protocol non-adherence and blinding failures (i.e. requests to unblind by t clinical care team) will be used to evaluate the feasibility of a phase III study evaluating rapid normalization of vitamin D in critically ill children. Accrual rate will also be reported, but given that this is a dose-evaluation pilot it will not be formally assessed as a feasibility outcome (with predefined targets defining acceptable).

Frequency of Analyses

As there is little experience with weight based enteral vitamin D loading therapy in critically ill children we will plan for interim safety analysis after 15, 30 and 52 patients. After review of the 25(OH)D levels and adverse event data, the Data and Safety Monitoring Committee will be empowered to provide recommendations on stopping the trial or adjusting both the dosing regimen.

Subgroup Analyses

We will evaluate biochemical and clinical outcomes within three different subgroups. First, we will evaluate initial 25(OH)D response in the group of patients under and over 40 kg. Second, we will evaluate and compare changes in biochemistry and clinical measures separately for the groups with starting 25(OH)D above and below 30 nmol/L. Third, we will evaluate and compare 25(OH)D response and clinical measures separately for newborns (age < 30 days) versus older children (age > 30 days).

Feasibility of Recruitment

The planned recruitment rate is up to 67 patients. At CHEO we have between 500 and 600 PICU admissions per year. Of these, we anticipate that up to 50% of patients will either not be eligible, the physician will refuse, or the parents/caregivers will be unavailable or not willing to speak with research staff. Based on both our experience with vitamin D RCTs and previously published work on factors affecting consent in PICU studies in Canada, we anticipate that 50% (n=125, 10/month) of those approached will agree to participate[111]. Of those that choose to participate we anticipate that approximately 50% (n=67, ~5 per month) will be eligible for randomization based on a 25(OH)D under 50 nmol/L. Recruitment rates are difficult to predict, and are frequently slower than expected. Consequently, we will allow up to 2 years for recruitment into this dose evaluation study. The recruitment rate will be enhanced with expansion of the study to the international sites and to the

NICU at CHEO. Recruitment through CVS, and alternate consent procedures for measuring vitamin D during screening will also improve recruitment rate (see Appendix K and Appendix L for Gantt timeline of this study and of the overall research program).

Loss of Follow-Up

Follow up for the VITDAL-PICU ends at 90 days, hospital discharge or death (with the exception of those patients that are followed by nephrology or endocrinology after hospital discharge). Consequently, loss to follow-up will primarily relate to participant withdrawal or drop out and is anticipated to be negligible (< 5%). As most critically ill ICU patients have regular blood work (daily) we anticipate that in the absence of death there will be research blood and urine collected for 25(OH)D and calcium determination on the vast majority (> 95%) of patients on days 3 and 7. For our ongoing RCT of pre-operative supplementation in children with CHD, post-operative collection of research blood for the primary outcome is 100%.

Role of the Data Safety Monitoring Board

The Data Safety Monitoring Board (DSMB) will be comprised of two clinical experts and a biostatistician or clinical epidemiologist. Terms of Reference will be created for the DSMB and approved by all DSMB members and the Principal Investigator before recruitment commences. The DSMB will function independently and at arm's length from the Study investigators and the Steering Committee. The primary responsibilities of the DSMB are to: periodically review and evaluate the accumulated study data for participant safety; make recommendations to the Steering Committee based on these reviews regarding the continuation, modification or termination of the trial; and comment on the relevance of new external published data from other trials that may impact on patient safety or efficacy of the study treatments. The DSMB will meet and review 25(OH)D and safety data after 15, 30 and 52 participants have reached Day 7 of study enrolment. Alternatively, reviews will be conducted at least yearly. Specifically, the DSMB will review the percentage of participants meeting target 25(OH)D, those exceeding 200 and 250 nmol/L, and the occurrence of vitamin D related adverse events (hypercalciuria, hypercalcemia), and serious adverse events potentially related to study drug. With the exception of the 25(OH)D results, the DSMB will initially be blinded to study group allocation for safety data and any clinical or biochemical outcome data requested. However, the DSMB will also be provided with the group identity codes under separate cover so that they can evaluate the data with knowledge of treatment group if desired. If safety concerns arise, more frequent meetings will be initiated, and the trial may be terminated. The DSMB Chair can also request a full meeting at any time. The DSMB Chair will receive immediate notification and reports of serious adverse events determined to be related to the study drug. In addition, the DSMB Chair will receive a report for all deaths and all requirements for renal replacement therapy, regardless of whether they are thought to be related to the VITdAL-PICU study.

Adaptive design and stopping rules

To ensure that we are not enrolling patients unnecessarily, it was decided at the Sept 8, 2015 Steering committee meeting that the DSMB also review the 25(OH)D primary outcome data after 30 and 52 patients have completed all study procedures (primary outcome data will not be reviewed after 15 patients). The following criteria will be used to determine whether the trial should be stopped early for the primary outcome.

- Proportion achieving 25(OH)D ≥ 75 nmol/L
    - After 30 participants: Point estimate of ≥ 90% (lower confidence interval would be approximately 75%)

- After 52 participants: Point estimate of >75% (lower confidence interval would be approximately 60%)

*If the DSMB was to see a signal in the SAE or vitamin D related adverse event data and felt that enrolling another 15 participants would help resolve whether the difference could be real they could recommend against stopping.

- Participants achieving potentially toxic levels
  - If more than 10% of study participants achieved 25(OH)D above 250 nmol/L, even in the absence of clinical sequelae, we will consider modifying the loading dose downward (these cases would be reviewed for signs of biochemical or clinical toxicity by the DSMB).

COST-EFFECTIVENESS SUB-STUDY

As part of the full phase III VITdAL-PICU trial we do intend to perform a cost effectiveness sub-study. A recently funded and active research project (DEMAND-PICU Study) by one of our co-applicants, Dr. Kusum Menon, seeks to determine the costs associated with critical illness. These costs have not been previously documented in Canada, and will include those related to hospital (base rate, nursing ratios, etc.), patient (ECMO, dialysis, surgery, imaging, etc.) and family factors (distance from home, travel, hotel expenses). We anticipate the results of this study to be available well prior to the phase III trial. If funding for our pilot is secured and additional information is required, we will collect data as part of the VITdAL-PICU.

During the current phase II study, resource utilization data collected as part of the REB approved DEMAND-PICU study (REB no. 14/211X and 14/191X) will be linked to patients enrolled in VITdAL-PICU at CHEO to perform a pilot cost effectiveness sub-study. Data collection for the DEMAND-PICU study will run until February 2016, after which time we will continue to collect the same resource utilization data for VITdAL-PICU patients (if funding permits).

PARTICIPATING CENTRES

VITDAL-PICU will be performed as a multi centre study: Participating sites include the Children's Hospital of Eastern Ontario (study coordinating centre), University of Graz, Clinica Sanatorio Aleman, and London Health Sciences Centre (London, Ontario, Canada)).. The study coordinating centre will work with the CHEO Research Institute to ensure that appropriate insurance is in place to expand to non-Canadian sites. The site investigator at the Austrian site will be collaborator Dr. Karin Amrein, who was the principal investigator on the VITdAL-ICU adult study[32]. We have teamed with this non-Canadian site as they have established research infrastructure and have completed the only phase III trial of loading dose vitamin D in an ICU setting.

Study sites include:

Site	Site Investigator	Status
University of Graz, Austria	Dr. Karin Amrein	Confirmed site
London Health Sciences Centre, London, ON	Dr. Anna Gunz	Confirmed site
Clinica Sanatorio Aleman, Concepcion, Chile.	Dr. Raul Bustos	Confirmed site

SAFETY, SERIOUS ADVERSE EVENTS, ATTRIBUTION AND REPORTING

Serious adverse events (SAEs) will be reporting according to the Canadian Critical Care Trials Group (CCCTG) Standard Operating Procedures for SAE reporting. This SOP complies with the Canadian Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS), the International Conference on Harmonization (ICH) Guidelines (E6) for Good Clinical Practice (GCP) and Health Canada (HC) Food and Drug Regulations. The CHEO site will also comply with the CHEO Research Institute N2 SOP 012_06 Serious Adverse Reaction in Clinical Trials. The following text under the headings "Definitions" and "Documentation, Monitoring, and Reporting of Adverse Events" has been adapted from the CCCTG SOP for SAE Reporting.

Adverse Event Definition and Attribution

Adverse event clinical severity is classified as:

- Mild: Signs and symptoms that can easily be tolerated or ignored.
- Moderate: Symptoms that cause discomfort but are tolerable; they cannot be ignored and affect concentration.
- Severe: Symptoms that affect usual daily activity.

Serious Adverse Event (SAE):
Any event that is fatal or immediately life threatening, permanently disabling, severely incapacitating, results in birth defect or requires prolonged inpatient hospitalization,
OR…
Any event that may jeopardize the patient and requires medical or surgical intervention to prevent one of the outcomes listed above,
Serious Adverse Drug Reaction (SAR) is defined as:
An adverse drug reaction that requires hospitalization or prolongation of hospitalization, that results in persistent or significant disability or incapacity, or results in birth defect, that is life-threatening, or results in death.
Serious Unexpected Adverse Drug Reaction (SUADR) is defined as:
Serious adverse drug reaction that is not identified in nature, severity or frequency in the risk information in the Investigator's Brochure or on the label of the drug.

Adverse Event Attribution

Serious adverse events and drugs reactions will be placed into one of the following 5 categories:

Unrelated to investigational agent/intervention

- Not related The AE is clearly not related to the intervention
- Doubtful The AE is not likely to be related to the intervention

Related to investigational agent/intervention

- Possible: The AE may be related to the intervention
- Probable: The AE is likely related to the intervention
- Definite: The AE is clearly related to the intervention.

REB and Health Canada Reporting Parameters

Health Canada provides the following statements to help define a SAE that requires expedited reporting:

- Expedited reporting of reactions which are serious but expected will ordinarily be inappropriate.

- Expedited reporting is also inappropriate for serious events from clinical investigations that are considered not related to study product, whether the event is expected or not
- Similarly, non-serious adverse reactions, whether expected or not, will ordinarily not be subject to *expedited* reporting.
- As per International Conference on Harmonization (ICH) E2A Guidance Document: "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" adopted by Health Canada, only serious and unexpected ADR reports that have been assessed by either the Investigator or the sponsor as having a reasonable suspected causal relationship to the drug, should be reported."
- As per the N2 CHEO RI SOP Serious Adverse Drug Reaction Reporting in Clinical Trials, 5.4.1 "The sponsor or Sponsor/Investigator must comply with the regulatory requirements of Health Canada regarding prompt reporting of unexpected serious adverse reactions, and for which a causal relationship with the investigational product cannot be ruled out."
- CHEO REB SOP-005 Safety Reporting Requirements (Adverse Events & Other Unanticipated Problems), 5.7.2 "The QI/PI is required to report to the REB only those local AEs/ADRs that are deemed to be Unanticipated Problems (unexpected, related/possibly related and involving greater risk'

Consequently, we will only report serious adverse drug reactions (SAR) that are unexpected or for which the development is uncommon (unexpected issue) **and** for which there is a causal relationship (possible, probable or definite) with the experimental drug.

Rationale and Determination of Reportable SAE for the VITdAL-PICU Study

Critically ill patients are at risk of many complications during their ICU course, and attribution of these events to research interventions may be difficult. The standards for reporting serious adverse events must be very high for the vulnerable PICU population, as for any population. However, extra care is required to ensure that SAE reporting is context-specific. Events which are very serious to outpatients are virtually every day occurrences in the PICU, and often of no long-term consequence to a critically ill patient. No internationally agreed upon standards exist for SAE reporting in the ICU setting. Historically, in some multicenter sepsis trials, 80% of ICU patients have an SAE report completed – this is not meaningful reporting, given the nature of critical illness. For example, in our ongoing RCT investigating daily high-dose vitamin D in pediatric congenital heart disease surgical patients, 27 SAE reports were completed (61% of enrolled patients). None of these SAEs were related to the study drug or study enrolment, and all 27 SAEs were determined by the principal investigator and treating physician to be an expected complications of the patient's critical illness, and unrelated to vitamin D as there was no concurrent hypercalcemia/hypercalciuria. Since ICU patients commonly develop complications of critical illness, related or unrelated to the reason for their admission to ICU (e.g., nosocomial infection, organ failure, myocardial dysfunction), these expected events in the course of patients requiring life support will not be reported as SAEs in the VITdAL-PICU trial.

Although the vast majority of the SAE encountered in VITdAL-PICU will be either expected and/or unrelated to study drug, there are some SAE that are an unexpected in critically ill children, but could be anticipated to occur given what is known about vitamin D toxicity:

1. Gastrointestinal bleeding (requiring blood transfusion) and perforation (requiring surgery) are relatively rare occurrences in PICU. If either of these events takes place within 48 hours of drug administration, they will be considered a reportable event.

2. Hypercalcemia - Persistent hypercalcemia (> 24 hours in the absence of parenteral calcium administration) is a rare occurrence in critically ill children. If study patients were to develop renal failure requiring dialysis, nephrocalcinosis, hemodynamically significant arrhythmia, cardiorespiratory arrest or death in the setting of persistent hypercalcemia they will be identified and subject to reporting. Hypercalcemia that occurs in the absence of can SAE will be recorded on the case report form as safety outcome.

3. Hypercalciuria - It remains unclear at this time whether hypercalciuria is common or rare in critically ill children. Until things are better understood we will consider numerous urinary tract SAEs as unexpected in the critically ill pediatric population but potentially related to study drug if they occur in the setting of new or worsening hypercalciuria (nephrolithiasis, renal failure leading to dialysis or death).

In addition to the above, we will also evaluate for and report on SUADR. An example of a SUADR in VITdAL-PICU is difficult to offer, since by definition, a SUADR is unpredictable, in that it has not been identified in nature previously. It will be the responsibility of the Principal Site Investigator, Study Coordinator, Research Assistants, and ICU team to be diligent in the identification and reporting of such events.

Documentation, Monitoring, and Reporting of Adverse Events

The Principal Site Investigator has overall responsibility for the handling of the study at their participating site. The site Coordinator/Research Assistants will liaise with the clinical team and examine the medical records of study participants on an ongoing basis during the period of hospital admission to identify potentially reportable SAEs. Bedside clinicians will treat the study patient at the discretion of the ICU team. The event will be managed medically as applicable, be documented on the SAE form, and then followed until resolution.

Upon recognition of a reportable SAE, the site study staff will contact the Study Coordinator, who will contact the Principal Investigator and the Data Monitoring & Safety Committee (DMSC) Chair to alert them to forthcoming documentation. The site study staff will complete the reporting form and any outstanding case report forms (CRFs) for that patient within 3 days and send them to the Study Coordinator along with all relevant clinical notes (including all physicians' and nurses' notes, relevant diagnostic test results, surgical and other intervention reports). The Study Coordinator will collate these documents into a detailed report for distribution to the Principal Investigator and DMSC Chair within 5 days of becoming aware. These notes will be previewed by the Study Coordinator to ensure that they do not contain sensitive or confidential patient information, in accordance with PHIPA requirements.

After reviewing the clinical notes and CRFs, the DMSC chair will determine whether immediate input from other DMSC members is required and will contact them as needed. The DMSC will send their determinations to the Principal Investigator. Final determinations of the DMSC will be entered onto the relevant case report form, and into the database. The DMSC will also review aggregate SAEs and RUSARs after 30 and after 52 patients have received their initial loading dose. At this time, the DMSC will recommend to the VITdAL-PICU Steering Committee whether to (a) continue patient enrolment, (b) suspend enrolment until careful review by the Steering Committee, or (c) whether more information is required before a recommendation can be made. Furthermore, we will be reporting to regulatory bodies, all life threatening, fatal and all other serious adverse drug reactions potentially related to enrolment in VITdAL-PICU (as previously listed).

Examples of expected morbidities or complications of critical illness:

- Requirement for ventilator support
- Failed extubation
- Nosocomial infections

- Respiratory arrest
- Cardiac arrhythmias
- Unstable blood pressure
- Organ failure
- Myocardial infarction
- Presence of the following abnormal laboratory values:
    - hypoglycemia
    - hyperglycemia
    - hypocalcemia
    - hyponatremia
    - hypernatremia
    - hyperchloremia
    - hypochloremia
    - metabolic alkalosis (elevated bicarbonate)
    - metabolic acidosis (low bicarbonate)
    - lactic acidosis
    - hypokalemia
    - hypomagnesemia
    - Hypermagnesemia
    - Hypophosphatemia
    - Hyperphosphatemia
    - Uremia/elevated creatinine

The complications of critical illness, listed above, are clinically expected events in critically ill children and will generally not be related to vitamin D administration, therefore not subject to expedited reporting to Health Canada and CHEO REB unless the care team or Principal Site Investigator feels that the event is related to vitamin D or study participation (as previously described).

Study Safety Protocol

Since elevated calcium levels have the potential to be related to vitamin D administration, hypercalcemia that occurs >8 hours following administration of enteral calcium will be reviewed by the Principal Site Investigator. Identification of persistent hypercalcemia (> 24 hours, without calcium administration) will be discussed with the clinical team and may trigger an endocrinology consult.

If hypercalciuria (based on urine calcium:creatinine ratios) is identified on two sequential urine samples (excluding the first sample drawn at enrolment) the study nephrologist will be consulted to evaluate specific patient characteristics (how abnormal results are, trends, use of Lasix, renal dysfunction, expected length of stay, etc.) and whether they should have a repeat measurement and/or a renal ultrasound to evaluate for nephrocalcinosis.

Urine and blood calcium results from **research** samples will be signed off by the Principal Site Investigator, and designated as “Below study threshold”, “Above study threshold” if the result is above the study level indicated below but is not associated with any clinical symptoms or concerns, or “Clinically Significant” (C.S.) if the result is above the thresholds below and the patient is experiencing related clinical symptoms. All incidences of hypercalcemia and hypercalciuria will be recorded in the case report form.

Definitions of hypercalcemia and hypercalciuria :

Hypercalcemia	
Age <8 weeks	Ionized calcium level of > 1.45 mmol/L
Age >8 weeks	Ionized calcium level of > 1.40 mmol/L
Hypercalciuria	
Age < 1 year	Calcium:creatinine ratio of >2.2 mmol/mmol
Age 1-2 years	Calcium:creatinine ratio of >1.5 mmol/mmol
Age 2-3 years	Calcium:creatinine ratio of >1.4 mmol/mmol
Age 3-5 years	Calcium:creatinine ratio of >1.1 mmol/mmol
Age 5-7 years	Calcium:creatinine ratio of >0.8 mmol/mmol
Age 7-17 years	Calcium:creatinine ratio of >0.7 mmol/mmol

Hypercalcemia and hypercalciuria will only be subject to expedited reporting if it meets the previously described criteria as a serious adverse event that is unexpected for the patient population and could be related to vitamin D administration.

Treatment Discontinuation

The criteria for permanent discontinuation of further study product/interventions for an individual subject are as follows:

- Completion of treatment/intervention as defined by the protocol
- Clinical reasons believed to be life-threatening by the physician
- SAE occurring during and shortly after administration of the study drug that, after review by the Principal Site Investigator, is determined to be potentially related to vitamin D administration

The patient will continue to be followed with the legal guardian's permission if the study drug is discontinued. There will be no changes to the follow-up time point schedule, except no further study drug will be administered.

Premature Study Discontinuation for an Individual Subject

The criteria for permanent discontinuation from the study for an individual subject are as follows:

- Request of the subject to withdraw from the trial
- Any clinical adverse event, laboratory abnormality, intercurrent illness, other medical situation that continued participation in the trial would not be in the best interest of the participant
- The subject is judged by the Principal Site Investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of trial results

Protocol Violations/Deviations

In this pragmatic RCT, there are no protocol deviations that will result in discontinuation of study medication or follow-up. The Principal Investigator, Site Investigators, Study Coordinator, Research Assistants, and institution are responsible for conducting the study according to the most recent protocol version approved by the CHEO REB (or local REB for sub-sites). All protocol deviations or violations will be documented in the CRF.

Protocol Deviation – an incident involving non-adherence to the study protocol that is unlikely to significantly impact a patient's rights or safety, and will not affect the integrity of collected data. At

CHEO, deviations will be reported to the REB with the annual renewal. Other sites will report to their REB according to local procedures.

Examples of a protocol deviation in the VITdAL-PICU study include, but are not limited to:

- Patient is randomized but does not receive the study drug
- Patient dies before receiving study drug
- Study procedures conducted out of sequence, but with no impact on patient safety or welfare

Protocol Violation – an incident involving non-adherence to the study protocol that could significantly impact a patient's rights or safety, or affect the integrity of collected data. A protocol violation is considered more serious, and can result in a patient being excluded from a study analysis, or being withdrawn from a study. At CHEO, violations will be reported to the REB immediately. Other sites will report to their REB according to local procedures.

Examples of a protocol violation in the VITdAL-PICU study include, but are not limited to:

- Enrolment of a patient not meeting inclusion criteria
- Study medication dispensing or dosing error (higher than ordered)
- Study procedure omitted (e.g. failure to discuss abnormal urine calcium results with nephrology)
- Failure to monitor urine calcium levels

DATA HANDLING AND RECORD KEEPING

Data Management and Responsibilities

Data collection is the responsibility of the research staff under the supervision of the Principal Site Investigator. During the study, the Principal Site Investigator (or delegate) must maintain complete and accurate documentation for the study. After informed consent is obtained, the Research Assistants will complete the case report form (CRF) directly into the web-based system. If the Research Assistant prefers to complete the CRF on paper first, the paper copy will be kept and filed with the essential study documents. The Principal Site Investigator will review the data to ensure clarity and accuracy. Paper forms will be stored in a locked office to which only study staff has access. Adverse events will be graded, assessed by severity and causality and reviewed by the Principal Site Investigator or designee.

The case report form will be developed in and managed using an electronic data capture tool, REDCap (Research Electronic Data Capture), which will be hosted at the CHEO Clinical Research Unit (CRU). REDCap is a secure, web-based application designed to support data collection for research studies. Pre-defined ranges for all data values will be set up in this application to allow data entry personnel to validate data as soon as it is entered and send data queries immediately. Missing data will be similarly managed. Protocol violations will be audited and recorded for each patient recruited. The data generated will be exported to SAS® for statistical analysis. Intensive care physicians will communicate with the study team about patient eligibility and study protocols. All members of the health care team and Research Assistants will have access to a 24-hour pager for support from either a member of the VITdAL-PICU Steering Committee or Principal Investigator with respect to any clinical queries or concerns; they will also have access to the Study Coordinator during regular working hours.

Confidentiality

All subject related information including CRFs, laboratory specimens, etc. will be kept strictly confidential. All records will be kept in a secure, locked location and only research staff will have

access to the records. Subjects will be identified only by means of a coded number specific to each subject. The REDCap study database is securely protected and encrypted. All computerized databases will identify subjects by numeric codes only. Upon request, subject records will be made available to the study sponsor, monitoring group's representative of the study sponsor, and Health Canada.

Record Retention

All research records will be retained for a minimum of 25 years after closure.

TRIAL MANAGEMENT

Day-to-Day Trial Management

The CHEO CRU will be the Coordinating Centre for this study with support from the Ottawa Hospital Research Institute (OHRI). The Principal Investigator (JDM) and overall Study Coordinator, along with the CHEO CRU will be responsible for the day-to-day operations of the trial. The OHRI will be responsible for randomization and statistical analysis. Both research institutes have a strong track record in helping to complete multi-centre critical care studies. Clinical Research Assistants at each site will work with Site Investigators on start-up activities (REB applications; study contract; organizing study materials; local in-services) and will attend a start-up investigators' meeting that will be coordinated with a Critical Care Trials Group Meeting (minimizing costs and extra travel). Thereafter, Site Research Assistants will screen, consent and enroll patients, complete electronic case report forms, and respond to data queries from the CHEO CRU. Site Investigators will be available for local support. Research Assistants at each site will maintain a daily screening log which will track every patient who meets inclusion criteria. These screening logs will be sent monthly to the Coordinating Centre. Monthly audit and feedback will maintain frequent communication between the CHEO CRU and participating ICUs and will help to identify potential problems and their solutions for recruitment.

Role of the Principal Applicant and Co-Applicants

Each applicant on this grant has contributed significantly to the development of this proposal and has a specific important future role within this project as outlined below. Drs. McNally, Menon, Fontela and McIntyre are members of the CCCTG (see letter of support). Drs. Lawson, Weiler and Fergusson have an established track record of successful clinical trial research and have worked previously with Dr. McNally. The Principal Investigator, Dr. Dayre McNally, will be responsible for overseeing all aspects of the project including trouble shooting day-to-day operations, protocol adherence, protocol amendments, data interpretation, manuscript preparation and dissemination of results. Dr. Kusum Menon has significant expertise in organizing multicentre clinical trials in PICU and is developing a pediatric critical care cost model; she is part of the steering committee and will continue to provide input into set-up, help address barriers, and assist with analyses and interpretation. Dr. Lauralyn McIntyre is an adult intensivist with expertise in Health Canada regulated ICU trials; she will continue to serve as a member of the steering committee providing input into design, analysis plan and interpretation. Dr. Dean Fergusson is an experienced trial methodologist who has assisted with the systematic review, development of the dosing regimen and has provided guidance on the trial design, sample size calculation and analysis plan. Drs. Karin Amrein (endocrinology) and Hope Weiler (PhD, nutrition) have significant experience leading clinical trials on vitamin D and will provide practical input into issues that may arise with respect to recruitment, vitamin D dosing, biochemical and safety analysis, and interpretation of results; Dr. Amrein will also serve as the Site Investigator in Austria. Dr. Margaret Lawson (endocrinology) and Dr. Pavel Geier (nephrology) have significant clinical experience with vitamin D and related adverse events (hypercalcemia, hypercalciuria); and they have helped design a safety plan and thresholds that will be used in final analysis to define toxicity. Drs. Lawson and Geier will engage with their clinical colleagues at the study sites to evaluate and manage

patients who develop toxicity potentially related to vitamin D (if applicable). Dr. Patricia Fontela (PhD epidemiology) and Dr. Anna Gunz are both pediatric intensivists with independent research programs, and have contributed to the study protocol. If additional study sites are added, they have both agreed to act as Site Investigators, and will work within their local research infrastructure to set-up, trouble shoot, enroll patients and provide valuable input into feasibility issues for the phase III RCT. Dr. Matt Henderson is a clinical chemist with experience in vitamin D assays; he will be responsible for arranging point-of-care and definitive biochemical analyses, specifically on vitamin D metabolites.

Trial Steering Committee

The trial steering committee will consist of Drs. McNally, Menon, McIntyre, and Fergusson. Other physicians, in particular the site investigators from other hospitals if they begin patient recruitment, may join the steering committee. The members of the committee have extensive experience in epidemiology, clinical trials, biostatistics, pediatric critical care, and vitamin D deficiency. Dr. McNally is the Principal Investigator of an ongoing Health Canada regulated RCT. Dr. Menon has been the Principal Investigator of several multi-centre studies in pediatric critical care as well as a co-investigator in several others[21,23,54]. Drs. Fergusson and McIntyre also have significant experience in leading and completing multi-centre clinical trials in neonates, children and adults.

QUALITY CONTROL AND QUALITY ASSURANCE

Monitoring

Monitoring at CHEO will be conducted by qualified peer-to-peer monitors. A Monitoring Plan has been developed for this study and outlines the monitoring process for international and domestic sub-sites. , The following outlines the monitoring plan for CHEO only. The Monitoring review will occur approximately every 3 months (or every 6-8 weeks etc.) or as needed based on enrollment. The Essential Documents in the Investigator Regulatory Files will be monitored using the Monitoring Visit Report template. The monitor will identify any items missing from the Regulatory Binder. The consent document will be reviewed for content to ensure it contains the required (and additional, as applicable) regulatory elements. The consent document will be compared to the protocol and REB procedures for informed consent documentation to ensure agreement between the two documents. Consent forms monitoring will be documented in the' monitoring visit report.

Monitoring for this protocol will be coordinated by the Principal Investigator or Study Coordinator. The Principal Investigator and the Study Coordinator will monitor the study regularly and assess evaluations of patients' eligibility and adverse events in the study database. The study will be monitored according to the Monitoring Plan.

Monitoring will review the study for REB regulatory compliance to ensure that it contains the elements required by federal regulations, and Canadian Regulatory compliance (i.e. CTSI, QIU, REBA or equivalent). Specifically, the peer-to-peer monitor will review components of the Monitoring Plan which includes but is not limited to verification that:

- the Principal Investigational product(s) are stored, supplied, returned/disposed as per protocol and applicable regulatory requirement(s),
- the Principal Site Investigator follows the approved protocol and all protocol amendments,
- the written informed consent was obtained before each subject's participation, and was re-consented when amendments were made in the trial,
- the Principal Site Investigator and the investigator's trial staff are performing the specified trial functions in accordance with the protocol and written agreements,
- the Principal Site Investigator is enrolling only eligible subjects,

- the subject recruitment rate,
- the source documents and the other trial records are accurate, complete, and kept up-to-date and maintained,
- the Principal Site Investigator provides all of the required reports, notification, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated and identify the trial

Other responsibilities include:
- Checking the accuracy and completeness of the CRF entries, source documents and other trial-related material,
- Informing the Principal Site Investigator of any CRF entry error, omission, or illegibility in writing,
- Determining whether all adverse events are appropriately reported within the time periods required by GCP, the protocol, the REB, and applicable regulatory requirements,
- Determining whether the Principal Site Investigator is maintaining the essential documents,
- Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the Principal Site Investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

Quality Control and Quality Assurance Procedures

A meeting will be held monthly for the Study Coordinator, Principal Investigator, and Co-Investigators to discuss the progress of the study and ensure compliance with the protocol. Anyone actively involved in the study and who will be delegated any procedures associated with the study will receive thorough training regarding the study protocol content and application, research ethics, standard operating procedures (SOPs), privacy, Good Clinical Practice (GCP) and Health Canada's Division 5 of the Food and Drug Regulations. A Procedure manual will be developed to ensure the quality of every aspect of the study. Quality control systems such as maintenance records, calibration records and process validations, etc. around both the investigational product and the Qualigen rapid test will be in place throughout the study.

Ethical Considerations

This study will be conducted according to Canadian and international standards of Good Clinical Practice for all studies. Applicable government regulations and CHEO research policies and procedures will also be followed. The European site will also adhere to the EMA regulations. Other international sites will also adhere to their regulatory body.

This protocol and any amendments will be submitted to the CHEO REB for formal approval to conduct the study. The decision of the REB concerning the conduct of the study will be made in writing to the Principal Investigators. Sub-sites will submit the protocol and amendments to their local REB.

The trial will first be thoroughly explained, including risks and benefits, and alternatives to participating in the trial. It will be made clear that participation is voluntary, that the patient may withdraw from the study at any time, and that participation or nonparticipation in the trial will not affect the care that the patient receives All subjects for this study will be provided a consent form and assent form if applicable, describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. A copy of the signed consent /assent form will be provided to the family/parent/child. This consent and assent form will be submitted with the protocol for review and approval by the REB. The formal consent of a subject, using the REB-approved consent form, will be obtained before that subject is submitted to any study procedure. This consent

form must be signed by the subject or legally acceptable surrogate, and the Principal Site Investigator-designated research professional obtaining the consent.

BUDGET AND FINANCE

This study will be funded from the following sources: AHSC AFP Innovation Fund 2014-2015 at the Children's Hospital of Eastern Ontario, bridge funding from the Canadian Health Research Institute (CIHR), and Dr. McNally's start-up funds from the Children's Hospital of Eastern Ontario Research Institute (if needed).

PUBLICATION POLICY

Authorship of Papers, Meeting Abstracts, Etc.

The results of this study will be published and prior to manuscript submission the Principal Investigator will decide the order of authorship:

- The first author will be the Principal Investigator, unless designated otherwise by the Principal Investigator
- Members of the VITdAL-PICU Study Steering Committee may be credited as authors depending upon their level of involvement in the study.
- Additional authors will be those who have made a significant contribution to the overall success of the study and meet ICMJE criteria. This contribution will be assessed, in part but not entirely, in terms of patients enrolled and will be reviewed at the end of the trial by the Principal Investigator.
- Acknowledgement of the Canadian Critical Care Trials Group will be included where appropriate.

Responsibility for Publication

It will be the responsibility of the Principal Investigator to write up the results of the study within a reasonable time of its completion.

Submission of Material for Presentation or Publication

Material may not be submitted for presentation or publication without prior review and approval of the Principal Investigator. Individual participating centers may not present outcome results from their own centers separately before the primary results of the study are published. Draft publications should be submitted to the Principal Investigator to review and provide comments. The Principal Investigator will have 60 days to review. Supporting groups and agencies will be acknowledged.

Authorship and Data Analysis for Sub-Studies

All data analysis will occur at CHEO RI/OHRI. Participant level trial data will not be sent to other sites or researchers. Co-authors may suggest sub-studies and will be given the opportunity to take the lead on manuscript preparation. Data analysis will take place at CHEO RI/OHRI and aggregate data corresponding to what is standard for a manuscript will be provided to the co-author. If participant level data is required, then a contract/DSA will be obtained between institutions.

Acknowledgement

Support from CHAMO and CHEO Research Institute will be acknowledged with the following statement: "This research project was conducted with support from the CHAMO Innovation Fund at the Children's Hospital of Eastern Ontario."

KNOWLEDGE TRANSLATION AND CONSUMER ENGAGEMENT

Our approach to Knowledge translation and consumer engagement is outlined in Appendix H. The eventual phase III trial will include both an economic analysis and consider quality of life measures.

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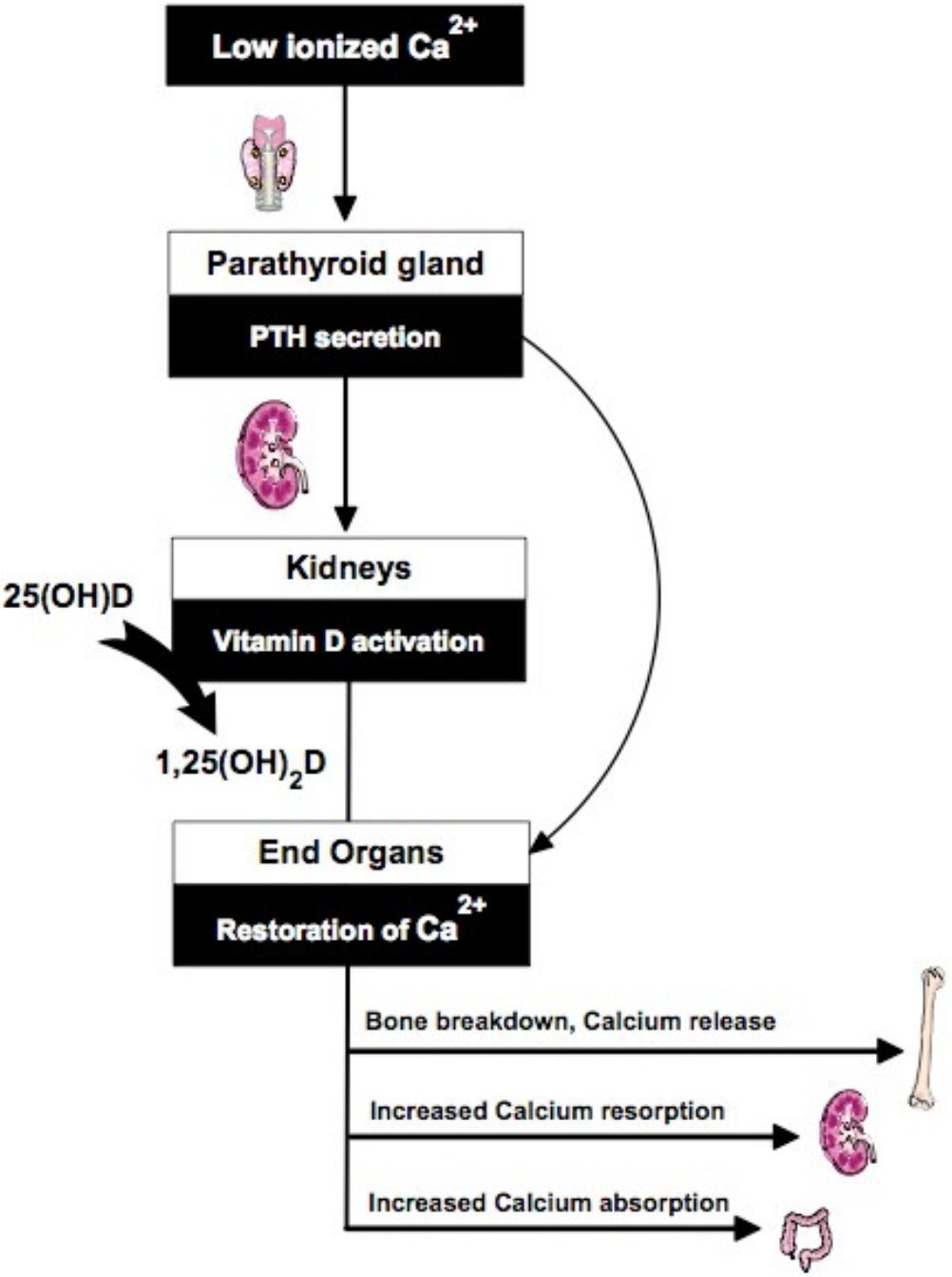
Appendix A – Basic Endocrine Pathway

Vitamin D parathyroid axis and maintenance of blood calcium levels: Functioning of the axis is best understood in the context of its role in maintenance of calcium homeostasis. In response to low calcium, the parathyroid glands increase parathyroid hormone (PTH) secretion. Increased PTH leads to activation of vitamin---D through an inducible renal enzyme, converting 25 hydroxyvitamin D (25(OH)D) to the active hormone or dihydroxyvitamin D (1,25OH_2D).

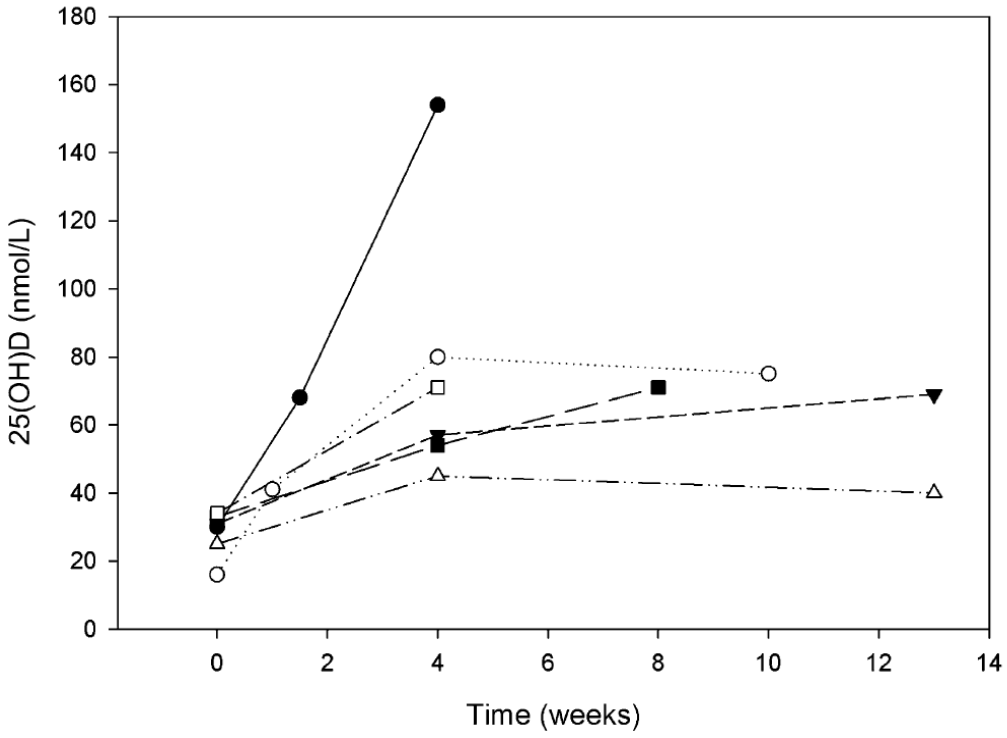


Appendix B – Summary Table of Published Vitamin D in PICU Studies

Table demonstrating the findings reported within published PICU observational studies. An empty cell indicates that this information was not provided. ‡PRISM and PIM represent illness severity scores. Abbreviations: 25(OH)D, 25-hydroxyvitamin D; CHD, Congenital heart disease; LOS, Length of stay; PICU, Pediatric intensive care unit; PIM, Pediatric index of mortality; PRISM, Pediatric risk of mortality

	McNally, 2012	Madden, 2012	Rippel, 2012	Graham, 2013	McNally, 2013	Rey, 2014	Ayulo, 2014	Hebbar, 2014
Study size								
Total (n)	326	511	316	70	58	156	216	61
CHD subgroup (n)	122	0	210	70	58			
Vitamin D status								
Threshold used (nmol/l)	50	50	50	50	50	50	37.5	50
PICU Deficiency rate (%)	69%	40%	35%			30%	28%	60%
CHD Deficiency rate (%)	73%		41%	84%	86%			
Population								
Location	Canada	USA	Australia	USA	Canada	Spain	USA	USA
Age (eligibility criteria)	0-17 yr	< 21 yr	NR	Neonates	0-17	< 16 yr	1-21 yr	0-18 yr
Illness severity and outcomes markers								
Vasoactive infusions	+	+	+	+	+	+		
Calcium	+	+	+		+		+	
Calcium supplementation			+		+			
Fluid requirements	+				+			
Mechanical ventilation	+	+	+		+	+		
PRISM/PIM/PELOD/SOFA‡	+	+	+			+	+	+
LOS - PICU	+		+	+	+	+		
LOS - Hospital			+	+	+			
Mortality	+		+		+		+	

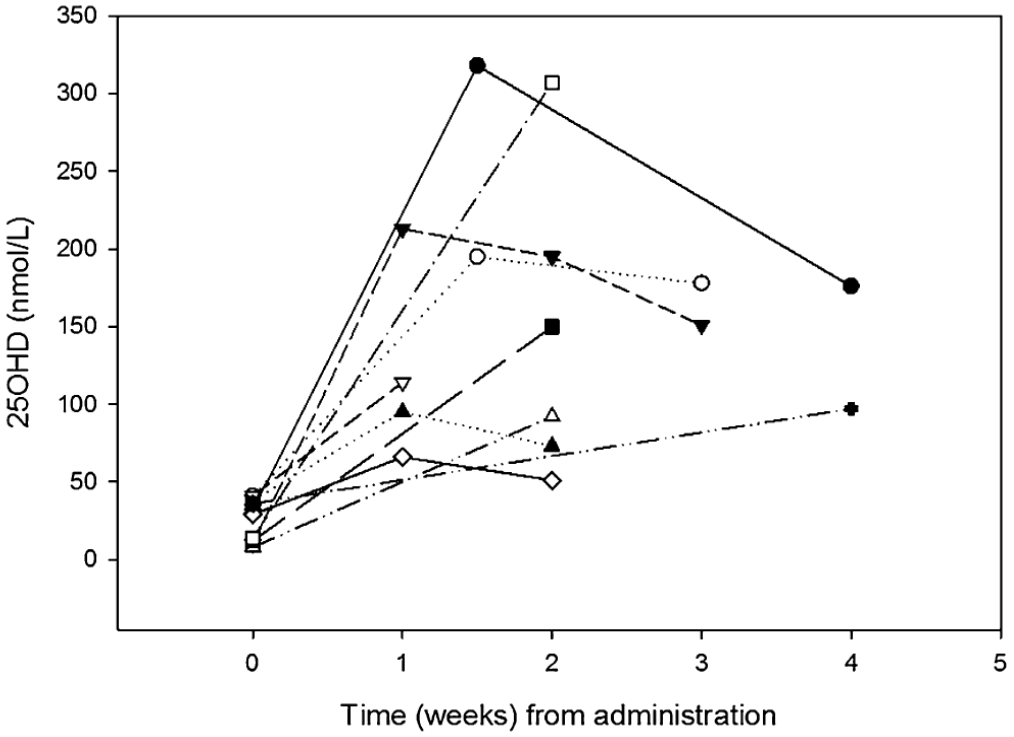
Appendix C – Short-Term 25(OH)D Response to Daily High Dose Vitamin D



Appendix C: Short term 25(OH)D response to high dose daily vitamin D intake. Six study arms evaluated 25(OH)D response in vitamin D deficient children within 1 month of initiating dosing approximating the IOM daily upper tolerable intake level (1000-4000 IU).
(●) Holst-Gemeiner 1987
(o) Markestad 1985
(Δ) Leger 1989
(▼) Vervel. 1997
(■) Dong. 2010
(□) Park 2010

Adapted from McNally, J.D.*, et al.* Rapid Normalization of Vitamin D Levels: A Meta-Analysis. *Pediatrics* **135**, e152-e166 (2015).

Appendix D – Short-Term 25(OH)D Response to Loading Dose Vitamin D



Appendix D: Short term 25(OH)D response to vitamin D loading therapy. Ten study arms were identified that evaluated 25(OH)D response in vitamin D deficient children within 1 month of administering a loading dose of vitamin D.
(●) Holst-Gemeiner, 1987
(□) Zeghoud, 1994
(▼) Stogmann, 1985
(o) Raghuramulu, 1982
(■) Zeghoud, 1994
(v) Manaseki-Holland, 2012
(▲) Thacher, 2010
(Δ) Zeghoud, 1994
(◊) Thacher, 2006
(Cross) Kari, 2013

Adapted from McNally, J.D.*, et al.* Rapid Normalization of Vitamin D Levels: A Meta-Analysis. *Pediatrics* **135**, e152-e166 (2015).

Appendix E – Predicted 25(OH)D Levels after Vitamin D Loading Therapy

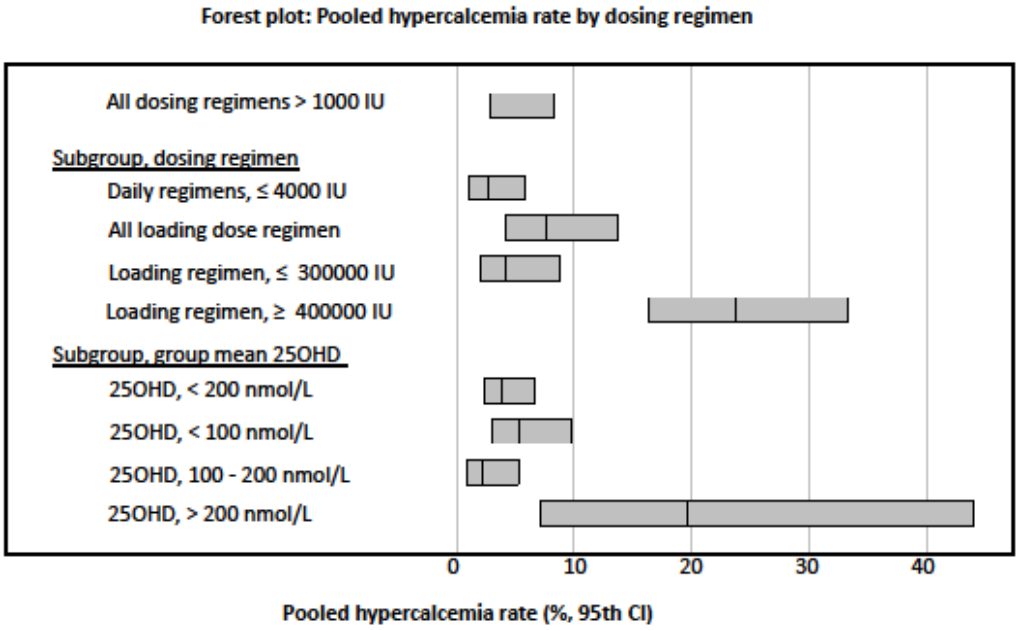
Predicted final group 25(OH)D levels after vitamin D loading therapy

Age Group	50 000 IU	150 000 IU	300 000 IU	600 000 IU
Infant (3 mo), nmol/L	86 (35)	112 (45)	152 (60)	232 (91)
Preschool age (2 y), nmol/L	83 (34)	108 (43)	144 (57)	217 (85)
School age (9 y), nmol/L	76 (29)	93 (34)	118 (43)	168 (61)
Adolescents (15 y), nmol/L	66 (24)	73 (27)	82 (31)	101 (40)

The predicted group 25(OH)D levels 1 week after 4 different loading doses of vitamin D are shown. The population was considered to be unhealthy and to have an average baseline 25(OH)D level of 30 nmol/L. Predicted SDs are shown in parentheses.

Adapted from McNally, J.D.*, et al.* Rapid Normalization of Vitamin D Levels: A Meta-Analysis. *Pediatrics* **135**, e152-e166 (2015).

Appendix F – Forest Plot of Hypercalcemia Rates by Vitamin D Dosing Regimen



Appendix F: Forest plot of hypercalcemia rates by dosing regimen. Random effects meta-analysis was used to calculate pooled hypercalcemia rates and 95% confidence intervals for the all high dose vitamin D regimens (> 1000 IU) and regimen subgroups. Point estimates are shown as the line and 95% confidence intervals are represented by the edge of the box. The Y-axis describes the various subgroup analysis.

Adapted from McNally, J.D.*, et al.* Rapid Normalization of Vitamin D Levels: A Meta-Analysis. *Pediatrics* **135**, e152-e166 (2015).

Appendix G – Summary of Safety Procedures for Abnormal Research Samples

SAMPLE TYPE	TRIGGER FOR SAFETY PROCEDURES	ACTION
Blood Calcium	Persistent hypercalcemia >24 hours without calcium administration	Endocrinology consult, managed clinically as determined by Endocrinology
Blood 25(OH)D	25(OH)D of >200 nmol/L in the last blood sample collected before discharge Note: 25(OH)D level will be analyzed using the Qualigen FastPak® or sent to a certified laboratory for analysis	Endocrinology consult, managed clinically as determined by Endocrinology
Urine Calcium:Creatinine	Hypercalciuria, as determined by an elevated calcium:creatinine ratio, in two sequential urine samples (excluding enrolment sample)	Case reviewed by Nephrology. If Nephrology has any concerns, then patient will be followed by Nephrology as an outpatient and a requisition will be given to have a urine calcium:creatinine level done as part of a future doctor appointment (at the hospital or at a local physician's office)

Appendix H - Knowledge Translation and Exchange Plan

Knowledge Translation and Exchange (KTE) Overview

The proposed project will implement a comprehensive KTE framework[1] that includes both integrated knowledge translation (iKT) and end-of-Project KT. The overall KT goal is to increase interaction among researchers and knowledge users. Key components of this model include stakeholder and knowledge user participation to identify priority problems, agree on approach, and conduct high quality research. Priorities will include feedback of our research program and any results as the project progresses to ensure knowledge users and stakeholders are informed about the work being done[2].

Project Partners, Engagement and Roles: A multilayered inter-disciplinary collaboration along the development-discovery-delivery continuum will engage partners from different stakeholder groups including researchers, clinicians and other health care professionals, patients and families, industry partners and funding bodies (CIHR and others). We have assembled a team of experts and held planning meetings to develop the research question and formulate the methodology described herein. Clinicians (see below) and research partners (D. Fergusson and the Canadian Critical Care Trials Group, CCCTG) have been instrumental in the study design and will be involved as the projects progress. Other stakeholder groups will participate in implementing and evaluating the KTE plan towards the end of the project and beyond.

Clinical specialists: Clinicians involved include, pediatric and adult intensivists (K. Menon, L. McIntyre), endocrinologists (M. Lawson, K. Amrein), nephrologist (P. Geier), methodologist (D. Fergusson), pharmacist (C. Blanchard), nutritionist (H. Weiler) and clinical biochemist (M. Henderson). These partners bring their specific expertise and unique perspective to the project.

Industry partners: Europharm (see letter of support) has agreed to prepare and provide a highly concentrated vitamin D formulation appropriate for the pediatric ICU patient (in kind) for this study.

Patients and families: Consumers are central to this research study and previous studies completed by our team in this area have given us insight into the feasibility of the current proposal. Parents and caregivers see value in and are concerned about vitamin D deficiency. Families are given a voice during the informed consent process and their willingness to participate in vitamin D related studies has been positive, demonstrating buy-in from the majority of families approached.

KTE expertise on the Team: KTE expertise and supports are available to our team on a variety of different levels. Experienced members of my team (D. Fergusson, M. Lawson) and KTE experts nationally (CCCTG) will be engaged for opinion, advice and to help cultivate appropriate relationships in order to ensure an exchange of knowledge between relevant stakeholders. The Director of Media Relations at CHEO (A. Vienneau) has been successful in the past at promoting our research program in the form of press releases and media interviews[3]. In addition, our team intends to seek additional KTE expertise for the development of a decision aid for caregivers (Co-applicant M. Lawson research group) and additional KTE media materials intended to raise awareness.

Knowledge Users: In our iKTE plan, knowledge users, including researchers, health care providers, patients and consumers, are part of the research process. The clinicians and health practitioners involved in this research study (described above in Project Partners) are part of the targeted audience and ultimate knowledge users. This approach should produce findings that are directly relevant to knowledge users. A major challenge to KTE is increasing diversity of translational research teams in which participants are from distinctively different disciplines[4]. Aware of this potential barrier, we believe effective communication is the key to promote successful transdisciplinary interactions. Each discipline represented on our team will be encouraged to take our Project findings back to their respective

professional groups (locally, national and international meetings) in order to reach a greater audience, encourage interest and promote uptake.

Main Messages
We anticipate learning whether a weight based enteral load of vitamin D can rapidly and safely normalize vitamin D levels in critically ill children

1. Demonstrate that rapid normalization is possible
    a. Learn about vitamin D dosing strategy for rapid normalization
    b. Understand adverse events, if any

   Audience: this main message will be of interest to clinicians and researchers.
2. We anticipate developing and validating a rapid test for rapid bedside determination of vitamin D in the ICU (transferrable to other hospital settings).
   Audience: A rapid test will be of interest to vitamin D researchers and clinicians involved in acute care, family physician offices, isolated clinics, and developing worlds.

KTE Goals
Using the Knowledge-To-Action Process[5,6] we have set the following KT objectives:

1. Increase awareness of the importance of vitamin D in critical illness, the study goals and how to get involved by engaging staff, patients and families.
2. Facilitate the translation of our main messages (described above) to reach all applicable clinical and research disciplines.
3. Promote the use of the rapid test in other applicable research and clinical settings.

Dissemination Strategies, Process, Impact and Evaluation
Overall approach: Our objectives will be achieved through well-defined integrated KTE plans and evaluations, as well as the use of tested evidence-informed KTE frameworks[7] and strategies.

Media tools, pamphlets and posters: We will contract KTE expertise at Media House (CHEO) to help develop infographics for a series of media tools including pamphlets, posters and potentially videos for trial at the participating centers. These will be intended for three different audiences: the general public, ICU patients and families and clinicians.

Decision aid for parents and caregivers: In order to raise awareness about vitamin D deficiency and treatment strategies as well as increase family involvement, we will create a decision aid to help families make informed choices around testing vitamin D levels and the options for clinical management of the results. A member of our team (M. Lawson) has significant experience around the development of decision aids. We will engage additional KT expertise to carry out a small study on decision aid impact in the ICU.

Scoping review of the field and searchable database: We have completed a systematic review of all clinical trials investigating vitamin D in pediatrics[8]. This review was the necessary first step to gain the support of physicians, pharmacists and nutritionists for development of rapid normalization protocols in children. To make this information available to others, we are in the process of creating a searchable online database. This database will make it possible for clinicians and researcher to quickly determine the level of evidence surrounding vitamin D supplementation in specific disease and age groups. We believe that this database will save clinicians and researchers significant time and money. We are committed to publicizing and maintaining this database for KT purposes.

Strategic mailing list of stakeholders: We will establish an email list of all interested stakeholders in order to share updates, results and other information pertaining to the study. Oral presentations and other media from various forums (including journal clubs, lectures, rounds, seminars, workshops and

scientific meetings) will be available in print after the presentation using Dropbox services. The goal is to promote information exchange and develop a common knowledge base among stakeholders.

Publications: We will publish in international scientific journals and anticipate publications with respect to the main study objective on 25(OH)D levels achieved, rapid vitamin D test, and decision support aids. We will use traditional bibliometric techniques to measure publication impact.

Conferences: The team will present interim and final results at national and international scientific meetings, including other team members sharing the results at their professional meetings, outside of the critical care discipline. In addition, the CCCTG will be updated on the Project and progress biannually at their scientific meetings.

Newsletter: Part of our end-of-project KT will include the generation of a news bulletin to distribute to participating ICUs across the country with updates on the trial, its goals, methods (including the rapid vitamin D determination test), results and next steps. Through the CCCTG we will also offer the bulletin to ICUs not participating in the study, but interested in the progress and results.

Integrated KT and Engagement Frequency: End-user engagement is an important component of this research. At the beginning of the study, we will hold a face-to-face meeting with all stakeholders to present the goals and proposed methods (design, interpretation, dissemination). Research investigators and personnel will participate in monthly meetings and/or teleconferences. Sub-committees of involved knowledge users will meet at least three times annually for review and update on the progress of the study.

KTE Impact & Evaluation: It is the intention to maximize the impact of activities by designing KTE strategies for specific audiences, primarily research and clinical practice. We will apply the CIHR evaluation framework to monitor individual KTE processes and the impact (e.g. reach and usefulness indicators). This monitoring plan will be consultative, layered and ongoing and include tracking of multiple indicators of quality, productivity, uptake, reach and impact.

KTE Resources and Budget Items

In order to carry out the KTE goals described, we will apply for additional knowledge translation funding. If we are not successful in securing additional funding, the KTE plan and available funds will be reviewed by the Steering Committee and to prioritize aspects of the plan that will be carried out with the financial support that is available.

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Appendix I – Blood Sample Analysis for Sub-Sites

Blood and Urine Calcium – Blood and urine calcium results will be analyzed in real-time in order to monitor patients for vitamin D related adverse events. Therefore, these analyses will be performed at each site's respective laboratory.

25(OH)D Screening Sample – The 25(OH)D level for screening is required in real-time in order to assess eligibility. This sample will be analyzed at each site's respective laboratory. Extra plasma collected at this time point that is not used for the screening 25(OH)D level will be stored and sent to the Coordinating Centre.

Discharge 25(OH)D Level – in order to determine if patient's require follow-up after hospital discharge (patients with discharge 25(OH)D level >200 nmol/L), this sample will be analyzed in real time at each site's respective laboratory. Extra plasma collected at this time point that is not used for the screening 25(OH)D level will be stored and sent to the Coordinating Centre.

All Other 25(OH)D Levels – Blood samples collected on Day 1, Day 2, Day 3, Day 7, and after interventions will be stored and sent to the Coordinating Centre for analysis.

Storage Requirements - Samples will be processed and then stored at -80°C. Pre-labelled cryovials and a pre-labelled freezer box will be provided to each site for sample storage.

Shipment Frequency - Shipping frequency will depend on recruitment rate and the site's preference, and will be determined through discussions with the Site Investigator and/or laboratory personnel at each site.

Shipping Procedures - Samples must be shipped from each site on dry ice according to the TDG Regulations for Class 6.2 and 9.0, Category B specimen, and packed according to the appropriate International Air Transport Association (IATA) packing instructions (see VITdAL-PICU Laboratory Standard Operating Procedures (SOP) for further details)

Laboratory Standard Operating Procedures - A SOP for laboratory procedures in the VITdAL-PICU study will be provided to each site.

Appendix J – Guidelines for Administration of the PedsQL™

PedsQL™ Administration Guidelines℠

The following guidelines are intended for use by individuals trained in the administration of standardized questionnaires. The PedsQL™ administrator is crucial in developing rapport with the respondents, emphasizing the importance of the questionnaire, addressing concerns, and ensuring that the PedsQL™ is completed accurately and confidentially.

General Protocol

Create a procedure for assigning identification numbers that will allow for parent/child comparisons as well as comparisons of baseline/follow-up data.
If feasible, the PedsQL™ should be completed *before* the respondents complete any other health data forms and *before* they see their physician or healthcare provider.
The parent/child should first complete the PedsQL™ Generic Core Scales and then complete any additional PedsQL™ Module.
Parents, Children (8-12) and Teens (13-18) may self-administer the PedsQL™ after introductory instructions from the administrator. If the administrator determines that the child or teen is unable to self-administer the PedsQL™ (e.g., due to illness, fatigue, reading difficulties), the PedsQL™ should be read aloud to the child or teen. For the Young Child (5-7), the PedsQL™ should be administered by reading the instructions and each item to the young child word for word. At the beginning of each subscale repeat the recall interval instructions (one month or 7 days) to remind the young child to respond only for that specific recall interval. Use the separate page with the three faces response choices to help the young child understand how to answer. When reading items aloud to a child, intonation should be kept neutral to avoid suggesting an answer.
If a child has difficulty understanding the age-appropriate PedsQL™, the preceding age group version may be administered to the child (e.g., administering the Young Child (5-7) Self-Report version with the three faces response choices to an 8 year old). However, if a child presents with severe cognitive impairments (as determined by the administrator), the PedsQL™ may not be appropriate for that child. In such cases, only the Parent-Proxy Report should be administered to the child's parent.
The parent and child must complete the questionnaires *independently* of one another. Discourage the parent, child, or other family members from consulting with one another during the completion of the questionnaire. Let them know that they can feel free to discuss their answers following completion of the questionnaires, but that it is important to get both the parent's and the child's *individual* perspectives. If you are administering the questionnaire to the child, the child should be facing away from the parent.
If the child or parent has a question about what an item means or how they should answer it, do not interpret the question for them. Repeat the item to them verbatim. Ask them to answer the item according to what *they think the question means*. If they have trouble deciding on an answer, ask them to choose the response that comes closest to how they feel. The child and/or the parent has the option of not answering a question if they truly do not understand the question.
If a parent/child asks you to interpret the responses, tell her/him that you are not trained to interpret or provide a score for the answers given. If the PedsQL™ is being used for a clinical study, let the parent/child know that their answers will be combined with other participants' answers and analyzed as a group rather than as individual respondents.

9. Document all reasons for refusals and non-completions of the PedsQL™.

Administering the PedsQL™

The following scripts have been developed as a guide to introduce the PedsQL™ to the child and his/her parent(s). Modify the language to a style that is most appropriate for you and the respondent.

For the child:

The PedsQL™ asks you questions about how you feel and what you think about your health. It is not a test, and there are no right or wrong answers. It takes about 5 minutes to complete. If you have any questions, please let me know.

For the parent:

The PedsQL™ is a questionnaire that assesses health-related quality of life in children and adolescents. It contains questions about your child's physical, emotional, social, and school functioning ***in the past one month (****or for the Acute version****, in the past 7 days)****.*

The PedsQL™ is brief and typically takes less than 5 minutes to complete. It is not a test, and there are no right or wrong answers. Please be sure to read the instructions carefully and choose the response that is the closest to how you truly feel. Please do not compare your answers with your child's responses. We are interested in your and your child's **individual** perspectives. However, feel free to discuss the questionnaire with your child **after** you have both completed it and returned it to me. If you have any questions, please let me know.

Provide the respondent with a pen or pencil and a solid writing surface. If a table is not available, the participant should be provided with an item such as a clipboard. Remain nearby should questions or concerns arise.

When the parent/child returns the PedsQL™, look it over and check to see that all answers have been completed. Verify that no item has more than one response. If any responses are incomplete, illegible, or there are multiple responses for an item, please ask the parent or child to indicate their response.

Ask the participants if they had any difficulties completing the questionnaire or if they have any other comments regarding the questionnaire. Document any important feedback.

Thank the parent and child for taking the time to complete the questionnaire. If the study design involves following up with these respondents, let them know that they may be asked to complete the PedsQL™ again at another time. Indicate when they can expect to be contacted again if known.

Appendix K – Study Timeline (Gnatt Chart)

		01/2015 -12/2015				01/2016-12/2016				01/2017-12/2017				01/2018-12/2018			
		Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
#	Task	Milestones															
1.0	**Project Launch**																
1.1	Presentation to and approval from CCCTG																
1.2	Protocol, CRF and related document development																
1.3	Training and testing of point-of-care device																
1.4	Recruitment of qualified personnel (CHEO)																
1.5	Health Canada approval of dosing regimen																
1.6	CHEO REB approval																
2.0	**Proposed Trial**																
2.1	Receive study drug & placebo from Europharm																
2.2	Initiate recruitment at CHEO																
2.3	Evaluate recruitment rate and troubleshoot barriers																
2.4	Interim analysis by the DSMB																
2.5	Collection of final study participant samples																
2.6	Biochemical assays																
2.7	Statistical analysis																
3.0	**KTE Plan**																
3.1	Scoping review and searchable database																
3.2	Presentation of progress and results: CCCTG																
3.3	Media tools and Infographics																
3.4	Vitamin D decision aid development																
3.5	Manuscript preparation																
3.6	News bulletins for Canadian ICUs																

Appendix L – Research Program Timeline (Gnatt Chart)

RESEARCH PROGRAM OVERVIEW															
Training		Pediatric residency		PICU clinical & research fellowship			MSc Clin Epi			PICU Clinician Investigator at CHEO					
Year 20-		'07	'08	'09	'10	'11	'12	'13	'14	'15	'16	'17	'18	'19	'20
#	*Research Studies*	*Milestones (initiation through to study publication)*													
I	Vitamin D in pediatric arthralgia, epidemiologic considerations (PMID 19040297)														
II	Vitamin D deficiency in young children with acute lower respiratory infection (PMID 19746437)														
III	Capillary blood sampling for the assessment of 25(OH)D levels (PMID 18805487)														
	The association of vitamin D status with pediatric critical illness (PMID 22869837)														
IV	Impact of anesthesia and surgery for CHD on the vitamin D status of infants and children: a prospective, longitudinal study (PMID 23470437)														
V	The relationship between vitamin D status and adrenal insufficiency in critically ill children (PMID 23547046)														
VI	Vitamin D receptor polymorphisms and severe bronchiolitis: a meta analysis (PMID 24019226)														
VII	Efficacy of high-dose vitamin D in pediatric asthma: a meta analysis (PMID In press)														
VIII	Rapid normalization of vitamin D levels: a meta-analysis (PMID In press)														
IX	1,25(OH)D deficiency in critically ill children														
X	1,25(OH)D deficiency in congenital heart disease														
XI	Rapid result 25(OH)D assay development – partnership with industry														
XII	Phase II clinical trial: daily high dose vitamin D supplementation in CHD														
XIII	**Phase II clinical trial: pilot study to determine vitamin D loading dose and feasibility in ICU**														
XIV	Phase III clinical trial: multi-center study to provide practice changing evidence (vitamin D in critical illness)														