Vitamin D to Improve Outcomes by Leveraging Early Treatment: Long-term Brain Outcomes in Vitamin D Deficient Patients (VIOLET-BUD)

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1.0 Background

Forty percent of patients who develop acute respiratory distress syndrome (ARDS) will die during hospitalization.[1] Among those who survive, 75% will develop long-term cognitive impairment (LTCI).[2] LTCI is a growing public health problem and is defined as a new deficit or a worsening pre-existing deficit in cognition that remains persistent after an acute illness. Its reach extends beyond ARDS. Our research group observed that 34% of intensive care unit (ICU) survivors, regardless of ARDS status, develop cognitive impairment similar in severity to moderate traumatic brain injury and 24% develop even more severe impairments similar to mild Alzheimer's disease.[3] A substantial proportion of ICU survivors will also develop impairments in executive function,[3] which leads to increased disability, worsening quality of life, and reduced employment.[4,5] Interventions that preserve long-term cognition and executive function after critical illness are lacking.

Early, high-dose oral Vitamin D repletion could potentially preserve long-term cognition in critically ill patients. Vitamin D is a pleiotropic secosteroid hormone that modulates systemic and central nervous system (CNS) inflammatory responses.[6-9] Inflammation in response to an acute illness plays a prominent role in dementia pathogenesis.[10-15] In addition to down-regulating systemic inflammation,[7-9] Vitamin D also exerts its anti-inflammatory effects directly in the brain. Vitamin D receptors are located on microglial cells (CNS macrophages) which play a key role in neuroinflammation.[15-19]

An abundance of recent observational data suggest Vitamin D deficiency is associated with poorer long-term cognition[20,21] and increased risk of Alzheimer's dementia in community-dwelling adults.[21] Based upon our preliminary studies, Vitamin D deficiency is also associated with accelerated cognitive decline in hospitalized, acutely ill patients. To our knowledge, no studies have evaluated if Vitamin D repletion improves these cognitive outcomes in the setting of an acute or critical illness.

2.0 Rationale and Specific Aims

A significant proportion of ICU survivors will acquire LTCI and executive dysfunction, especially in those who develop ARDS during hospitalization. These patients suffer from significant disability, a reduction in employment, and poorer quality of life.[4,5,22-29] Because inflammation is likely to be an underpinning of LTCI pathophysiology, Vitamin D treatment can potentially improve long-term cognition by attenuating systemic and CNS inflammatory responses. Numerous observational cohort studies and our preliminary data have reported that Vitamin D deficiency is associated with LTCI and executive dysfunction. Randomized control trials designed to determine if Vitamin D repletion improves long-term cognitive outcomes are needed.

We propose this ancillary study to a parent double-blinded, placebo-controlled randomized control trial (RCT) evaluating how a single, high-dose (540,000 IU) oral Vitamin D3 treatment affects 90-day mortality in patients who are at high risk for ARDS and have Vitamin D deficiency (plasma 25-hydroxyvitamin D < 20 ng/ml). The parent RCT (Vitamin D to Improve Outcomes by Leveraging Early Treatment [VIOLET], NCT03096314) is part of the Clinical Trials Network for the Prevention and Early Treatment of Acute Lung Injury (PETAL) sponsored by the NHLBI. The VIOLET trial completed enrollment in July 2018 with 1,360 randomized patients. Our proposed ancillary study will provide additional funding to perform comprehensive neuropsychological (cognitive) evaluations, which were not part of the parent trial. These neuropsychological evaluations will be conducted 8 to 26 months after

randomization among a subset of 140 survivors enrolled in VIOLET. This ancillary study will conducted in 7 (out of 42) sites. Our study, entitled VIOLET**:** Long-term **B**rain O**u**tcomes in Vitamin **D** deficient patients (VIOLET-BUD), has the following hypothesis and specific aim:

> **Aim**: Determine if early administration of a single high-dose (540,000 IU) oral vitamin D3 (cholecalciferol) treatment improves long-term global cognition and executive function as determined by comprehensive neuropsychological testing in 140 critically ill patients with Vitamin D deficiency at enrollment.
> *Hypothesis: Critically ill patients with Vitamin D deficiency who are treated with a single high-dose of Vitamin D3 will have significantly better long-term global cognition and executive function than those treated with placebo.*

If Vitamin D is found to improve long-term (8 to 26 months after randomization) global cognition and executive function, then we will have discovered a novel therapy that would allow ICU survivors to keep their cognitive abilities and help them resume their lives as they did prior to the critical illness. Because oral Vitamin D is simple, inexpensive, and safe, this intervention could be feasibly implemented in ICUs worldwide.

3.0 Inclusion/Exclusion Criteria

All patients enrolled in the VIOLET parent study will be considered for enrollment in VIOLET-BUD. VIOLET-BUD has the following exclusions:

1) Deaf or blind
2) Non-English speaking

Patients who are deaf or blind will be excluded, because the neuropsychological testing have auditory and visual components. Non-English speaking patients will be excluded because the neuropsychological raters can only perform the assessments in English only.

4.0 Enrollment/Randomization

Because VIOLET-BUD is an ancillary study to the VIOLET parent study, randomization to the Vitamin D3 versus placebo group has been completed. The PETAL Clinical Coordinating Center performed computerized randomization using 1:1 allocation stratified by enrolling hospital. For VIOLET-BUD, the site research and clinical staff, patient and authorized surrogate will be blinded to treatment assignment.

VIOLET-BUD will enroll patients from 7 (out of 42) PETAL sites that participated in VIOLET. The local site will contact all patients who were enrolled in VIOLET to recruit patients for VIOLET-BUD. As part of the VIOLET parent study's informed consent document, participants agreed to be contacted for future studies. Although the patient contact will typically occur by phone, the initial method of contact may occur by e-mail, letter, or text depending on patient preferences or availability. To maximize the feasibility of the study, the long-term follow-up assessments conducted between 8 and 26 months) after randomization will be allowable. Patients enrolled in VIOLET will be contacted consecutively.

Once a VIOLET patient has been contacted, the local site study coordinator will use a phone or e-mail script (**Appendix A**). He/she will describe VIOLET-BUD's study protocol in lay terminology over the phone. It will be emphasized that the data collected will be for research purposes. The research staff will inform the patient that there is no obligation to

participate in the study. If the patient refuses to participate in VIOLET-BUD or died prior to the long-term follow-up, then this will be recorded. If the patient cannot follow-up because they reside in a skilled nursing facility or has significant mobility issues, lives too far from the local site, cannot obtain transportation to the local site, is incarcerated, or is too cognitive impaired to participate, then this will be recorded.

If the patient agrees to participate, then the local staff will review the informed consent document with the patient. Because patients may have LTCI significant enough to affect capacity, there is a possibility that the patient may not be capable of provide informed consent. In these cases, consent will be obtained from an authorized surrogate. The determination of whether or not a patient can provide informed consent will be determined by the study coordinator or investigators. They will be trained to determine who is not consentable through clinical judgment and direct patient interaction (**Appendix A**). Patients will be deemed capable of consenting if: 1) they are able to carry a normal adult conversation and 2) they are able to recall aspects of the consent (e.g. Can you tell me what the purpose and risks of the study are?"). The patient will be asked questions about the study to ensure they comprehend study procedures. If they unable to adequately answer these questions, then consent will be obtained from an authorized surrogate to also be contacted by phone.

If the patient or their authorized surrogate provides consent to participate in VIOLET-BUD, then the local site coordinator will setup an appointment for the patient to receive their outcome assessment at the local site. Patients will be contacted from 8 to 26 months after randomization in the parent study. Because the VIOLET parent study has completed enrollment, the wide enrollment window will facilitate recruitment and help achieve our sample size. After the appointment is setup, the local site study coordinator will send the patient or their authorized surrogate a copy of the informed consent document via their preferred method of contact. A letter (**Appendix B**) with the local site study coordinator's name and contact information, the appointment date, time, location, and a map with directions to the videophone neuropsychological testing area will also be enclosed or attached. On the day of the appointment, the patient or authorized surrogate will be provided an opportunity to ask additional questions. If they agree to participate in VIOLET-BUD, then they will sign the informed consent document. A copy of the informed consent document will be provided to the patient or their authorized surrogate. Afterwards, VIOLET-BUD's data collection, including the long-term outcomes, will be performed. Patients will be provided financial compensation once the long term follow-up visit has been completed.

5.0 Study Procedures

5.1 Data to be obtained from the VIOLET parent study

The VIOLET parent study has collected patient demographics, home medications, including vitamin D and calcium supplementations, Sequential Organ Failure Assessment (SOFA) Score to day 7, Lung Injury Prediction Score (LIPS), calcium levels, Charlson Comorbidity Index, duration of mechanical ventilation, and ARDS status. These data were obtained through patient/caregiver interview and medical record review. The SOFA score is a marker of illness severity and estimates risk of mortality.[30] It quantifies CNS, respiratory, cardiovascular, hepatic, renal, and coagulation dysfunction/ failure and ranges from 0 to 24 (>90% risk of ICU mortality).[31] ARDS was determined by local review of daily ventilator status/settings, PaO2 and SpO2 values,

and chest x-ray. These data will be obtained from the PETAL Clinical Coordinating Center at Massachusetts General Hospital.

5.2. Data to be collected specifically for VIOLET-BUD (Table 1)
The primary outcomes for VIOLET-BUD are long-term global cognition and executive function. Only patients who have LC-MS confirmed Vitamin D deficiency (plasma 25-OHD < 20 mg/dL) at enrollment will have their outcomes determined. All outcome assessments will be blinded to treatment group. We will use comprehensive neuropsychological assessment which allows for detailed evaluation of specific cognitive domains. Prior work suggests Vitamin D deficiency predominantly affects short-term and working memory,[44,45] attention,[45,46] and executive function.[47]

Long-term global cognition will be assessed for using the ***Repeatable Battery for the Assessment of Neuropsychological Status (RBANS, 30 min, Appendix C)***, which we have extensively used in our prior work.[3] The RBANS is a comprehensive neuropsychological battery for the evaluation of global cognition and has been validated in subjects with mild cognitive impairment, moderate to severe traumatic brain injuries, vascular dementias, and Alzheimer's disease.[34-38] In addition to providing a score for global cognition, it also provides individual scores for immediate and delayed memory, attention, visuospatial construction, and language.

To quantify executive function, we will use tests from the ***Delis–Kaplan Executive Function System (D-KEFS)*** which is the most definitive executive functioning battery in existence.[39] Executive functioning refers to a wide array of "higher order" abilities that exist across a spectrum of cognitive sub-domains. Recent factor analyses have suggested that the majority of executive sub-domains fall broadly under conceptual flexibility, inhibition, and monitoring.[39] As such, we have selected tests of executive functioning from the D-KEFS to assess these three broad abilities ***– the DKEFS Proverbs subscale (conceptual flexibility, 5 min, Appendix D), the DKEFS Trail Making-Number/Letter Switching subscale (inhibition, 2 min, Appendix E),*** and ***DKEFS Verbal Fluency Category Switching subscale (monitoring, 3 min, Appendix F).*** An executive function composite score will be calculated from these three DKEFS subscales.

The RBANS and executive function tests will be conducted by experienced neuropsychologists from the Vanderbilt ICU Delirium and Cognitive Impairment Study Group via videophone-assisted neuropsychological testing. Eight to 26 months post-randomization, study participants will return to their local study site where they were originally enrolled. At the local study site, there will be a trained proctor (research nurse or research assistant) with the patient to provide on-site support and assist the neuropsychologist rater (e.g., hand the appropriate instrument to the patient). To minimize the risk of poor connectivity, computers will connect to the internet using a local area network (LAN) connection rather than a wireless device. In the rare event of a poor internet connection, we have developed specific contingency plans and protocols (e.g., training the proctors to administer portions of the neuropsychological tests) to overcome any connectivity issues.

Study Assessment	Description	Source	Length
Past history of dementia or is on an acetylcholinesterase inhibitor medication (galantamine [Reminyl], Donepezil [Aricept] and rivastigmine [Exelon]) prior to randomization	This will be used to characterize the presence of pre-existing cognitive impairment.	Medical record	5 mins
Age, race, ethnicity sex, level of education, region of residence, and highest occupation[32,33]	These data will be used to estimate premorbid intelligence using an actuarial formula.	Informant or patient	5 mins
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS, Appendix C).[34-38]	This neuropsychological battery will quantify long-term global cognition which is our primary outcome. It assesses immediate and delayed memory, attention, visuospatial construction, and language.	Patient	30 mins
Delis–Kaplan Executive Function System (D-KEFS) Proverbs subscale (conceptual flexibility, Appendix D), the DKEFS Trail Making-Number/Letter Switching subscale (inhibition, Appendix E), and DKEFS Verbal Fluency Category Switching subscale (monitoring, Appendix F).[39]	This neuropsychological battery will be used to quantify long-term executive function which is our primary outcome. It assesses conceptual flexibility, inhibition, and monitoring which are the cornerstones of executive function.[39] An executive function composite score will be calculated from these three DKEFS subscales.	Patient	10 mins
Katz Activities of Daily Living (ADL, Appendix G)[40]	Quantifies basic ADLs -- bathing, dressing, toileting, transferring, continence, and feeding.	Informant or patient	5 mins
Lawton Instrumental Activities of Daily Living Scale (IADL, Appendix H)[41]	Quantifies the patient's IADLs such as his/her ability to use the telephone, shopping, food preparation, housekeeping, laundry, transportation, medication management, and finances.	Informant or patient	10 mins
Outcomes After Critical Illness and Surgery (OACIS) Employment Status Questionnaire (Appendix I) [42,43]	9-item survey that characterizes the patient's baseline (prior to the critical illness) and current level of employment (full, partial, or not employed).	Informant or patient	10 mins
Death	While attempting patient contact, we will determine death status. If the patient died before the long-term follow-up, we will record date of death.	Medical record, informant, obituary web searches, or National Death Index	5 mins
Nursing Home Placement	During patient contact, we will determine if the patient placed in n nursing home. The date of placement will be recorded.	Medical record, patient, informant	5 mins

Table 1. VIOLET-BUD data to be collected by the local study team. The gray cells indicate data collected during the long term (8 to 26 month) follow-up visit and should take approximately 70 minutes.

Several studies have found results for neurocognitive testing to be very similar when assessments are completed by videoconferencing and by face-to-face evaluations.[48-50] Galusha-Glasscock et al. observed that the videoconference-assisted RBANS, our primary cognitive measure, was highly correlated with the in-person RBANS with a correlation coefficient of 0.88 (p-value < 0.0001) in patients with and without dementia.[48]

The local study team will also collect other long-term secondary outcome measures: functional status as measured by the Katz activities of daily living (ADL) scale and Lawton instrumental activities of daily living (IADL) scale, employment as measured by the Outcomes After Critical Illness and Surgery (OACIS) Employment Status Questionnaire, nursing home placement, and death.

For subjects who are unable to come to the local site for the long-term follow-up visit (e.g., due to mobility issues), the local site local study team will have the option to conduct the visit at their place of residence. To perform the videophone-assisted neuropsychological testing at the subject's resident, the study team will connect their laptop to the subject's local area network via wireless or ethernet connection. The local site study team may also use a mobile hotspot with a 4G LTE signal to perform the videophone-assisted neuropsychological testing.

VIOLET-BUD will also collect whether or not a patient has a past history of dementia or is on an acetylcholinesterase inhibitor medication (galantamine [Reminyl], Donepezil [Aricept] and rivastigmine [Exelon]) from the medical record. This will help determine if the patient has a history of pre-existing cognitive impairment prior to randomization. The determination of pre-existing cognitive impairment via medical record review will also be conducted in VIOLET subjects who were enrolled at the local site but died prior to the long-term outcome assessment or refused follow-up visit. These data will allow us to conduct survivor average causal effect (SACE), which will help determine the extent in which the competing of risk of death biased our findings

To facilitate merging of data sets, VIOLET-BUD participants will be assigned the same unique identification number as assigned in VIOLET. All VIOLET-BUD data will be entered into a secure REDCap database. Because the written and drawing portions of RBANS and executive function assessments need to be scored by the Vanderbilt ICU Delirium and Cognitive Impairment neuropsychologists, the local study team will upload these forms to the REDCap database.

6.0 Risks

This is a minimum risk study since there is no intervention. The Vitamin D intervention and safety monitoring has already been conducted as part of the VIOLET parent study. The VIOLET-BUD ancillary study will obtain long-term data using neuropsychological testing and survey instruments. For VIOLET-BUD specifically, subjects will undergo a neuropsychological examination at 8 to 26-months that can take approximately 40 minutes to perform. There is a small risk that a patient enrolled in VIOLET-BUD may become fatigued or distressed during the study neuropsychological assessments. In these cases, we will immediately stop the assessment and give the patient an opportunity to rest. Afterwards, we will ask the patient if we can continue with the neurocognitive assessments or if we should reschedule the long-term (8 to 26) follow-up appointment. Occasionally, patients and their families may get visibly frustrated and

distressed if the patient is unable to perform the cognitive tasks. We will reassure them that these tasks can be difficult to perform, and that such difficulties are common. If the patient or his or her family continue to be distressed after this reassurance, we will skip that particular task or stop the assessment altogether.

After the neuropsychological assessments, we administer surveys to the patient or authorized surrogate to collect additional data about the patient's functional status, baseline and current employment, education, region of residence, and highest occupation. These surveys will take an approximately 30 minutes to collect. If the patient is completing the surveys and becomes fatigued, then we will give the patient an opportunity to rest. If the patient can't continue with the survey, then we will attempt to get the survey data by phone at a later date.

Because patient identifiers are accessed throughout all phases of the study, there is a small risk of loss of patient confidentiality. Federal regulations at 45 CFR 46 111 (a) (7) requires that when appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. To maintain confidentiality, all evaluation forms and reports will be identified only by a coded number. The same coded number will be used for subjects enrolled in both VIOLET and VIOLET-BUD. All related participant study records will be kept in a locked, password protected computer. The coded number will be generated by a computer at the PETAL CCC, and only the study team will have access to the codes. All records will be kept in a locked, password protected computer. All computer entry and networking programs will be done with coded numbers only. All paper case report forms will be maintained inside a locked office. Study information will not be released without the written permission of the patient, except as necessary for monitoring by the Vanderbilt Clinical Coordinating Center.

7.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

As this is a non-intervention study, we do not anticipate having any adverse events. However, should any occur, they will be reported to the IRB per institution policies and procedures.

8.0 Study Withdrawal/Discontinuation

If patient or caregiver declines participation at the outset or does not meet inclusion criteria, they will not be included in the study. If patients wish to discontinue taking part in the study, they will be instructed to contact local site principal investigator or the research staff and let them know that they wish to withdraw. At that time, no further data will be collected on the patient. All health data previously collected before they withdraw their consent will still be used for reporting and research quality.

9.0 Statistical Considerations

We will determine if single, high-dose enteral Vitamin D treatment improves long-term global cognition and executive function compared with placebo using multiple linear regression. One model will be constructed for long-term RBANS and another for long-term executive function. We will use multivariable linear regression over unadjusted analyses because it is hypothesized that there will be a 5% absolute risk reduction in death for those who receive enteral Vitamin D. This may imbalance potential confounders between the treatment and placebo groups. Additional imbalances may

occur because of random chance. Multivariable regression will minimize this bias and lead to moderate gains in power.[51]

The models will be adjusted for the covariates listed in **Table 2**. Nonlinear predictor effects for continuous variables will be incorporated into the models. If necessary, non-normally distributed continuous variables will be transformed. To account for correlation within a center, we will use robust standard errors.[52]

Covariates	df
Vitamin D vs placebo	1
Age	2
Severity of illness (SOFA)	2
Comorbidity (Charlson)	2
Pre-existing cognitive impairment	1
Time to long-term cognitive assessment	2
Premorbid intelligence	1
ARDS development	1

Table 2. Covariates for the multivariable linear regression models.

In the event of significant missing covariate data, *multiple imputation* will be considered.[53-55] Multiple imputation will also be performed if portions of the cognitive assessments are missing;[3,56,57] patients with completely missing cognitive data will be excluded from the study. Because several of our covariates (e.g., premorbid cognition and intelligence) may be highly correlated, we will assess for collinearity using variance inflation factors and use only one of those variables if a high degree of collinearity is observed. The final models will be validated using bootstrap internal validation and cross validation approaches.[58] After the initial analysis has been completed, we will also evaluate if there is any effect modification of age, dementia status (medical record), baseline severity of illness (SOFA), mechanical ventilation status, and ARDS status. We will also perform a sensitivity analysis where death within the follow-up window will be considered equivalent to the worst cognitive outcome. This will be performed to further determine the effect of death on our findings.

Secondary analyses will be performed where we will determine how Vitamin D treatment affects the individual RBANS cognitive domains (e.g., immediate and delayed memory, attention, visuospatial construction, and language). We will also determine if treatment significantly improves long term functional status, employment as measured by the ICAP survey, nursing home placement, and death.

To estimate our sample size requirements, we used half a standard deviation (SD) of that particular test to define the minimum clinically important difference (MCID) threshold.[59-62] Based upon the preliminary studies, the SD for the RBANS was 12.[3] As a result, we considered a 6-point difference to be the MCID threshold for the RBANS. Based upon a two-sided alpha of 0.05 and 81% power, we will need outcome data in a total of 140 patients (~70 patients in each group) to detect a 6-point difference in RBANS between treatment groups. This sample size is feasible to obtain over 10 months. From September 2017 to July 2018, the six VIOLET-BUD sites enrolled 339 patients in VIOLET. Based upon the BRAIN-ICU study,[3] we anticipate that 99% will not be deaf or blind, 62% will survive and 75% will follow-up at 8 to 26 months. We have the potential to enroll 155 patients making our required sample size of 140 patients very achievable. For our executive function composite score, the SD was 2.34 (**Section C6**), so the MCID threshold would be a 1.17 point difference. If we complete long-term executive function assessments on 140 patients as planned, we will have 81% power to detect this 1.17-point difference in the executive function composite score assuming a two-sided alpha of 0.05.

10.0 Privacy/Confidentiality Issues

The patient's information, without identifiers, may be shared with other institutions or universities. Dr. Han, his co-investigators, and their staff will comply with any and all laws regarding the privacy of such information. There are no plans to pay the patient for the use or transfer of their de-identified information or specimens.

11.0 Follow-up and Record Retention

The duration of this study is approximately one year. We will try to enroll 140 patients during this time. Data collected will be retained indefinitely.

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