Writing strong research protocols

OR

How to get your protocol approved by the Cancer Protocol Review Committee on the first submission

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What is the Cancer Protocol Review Committee (CPRC)?
http://www.cancer.umn.edu/research/clinicaltrials/cprc.html

- The committee that evaluates, approves or rejects, monitors, and re-reviews all clinical cancer research protocols involving human subjects at the University of Minnesota

- Provides the scientific review that the IRB requires before all IRB submissions.

- Two separate committees:
  - Therapeutic Intervention (CPRC-TI)
  - Non-therapeutic Interventions (CPRC-NTI)
Why do I need to get CPRC approval?

- IRB is only evaluating human subject protection issues – does not necessarily have the scientific expertise to evaluate the quality of the proposed science.
- CPRC is responsible for the scientific review of the proposed study.
- Bottom line: it is unethical to ask people to participate in research that is unlikely to yield useful data.
- CPRC review is also the mechanism by which the Cancer Center keeps track of research being conducted by Center members, and whether studies are making appropriate progress.
Therapeutic or Non-Therapeutic?

**CPRC-TI**
- Primary treatment of cancer
  - Chemotherapy
  - Radiotherapy
  - Surgical interventions
  - Transplantation
  - Immunotherapy
  - Gene therapy
  - Combined modality therapy

**CPRC-NTI**
- Supportive interventions for cancer patients, such as:
  - Pain prevention/control
  - Infection prevention/control
  - Nutrition support
- Primary cancer prevention
- Chemoprevention
- Early detection
- Diagnostic interventions
- Observational/descriptive studies
- Health services, outcomes research
Studies that do not require CPRC review

- Animal studies
- Cell culture
- Single-case, compassionate use interventions
- Focus groups
Projects that may be eligible for expedited/ administrative review

- Studies that have been reviewed and funded by federal funding agencies (e.g. NIH, NSF)
- Even if you are eligible for administrative review, as a Cancer Center member, you MUST submit an application and study protocol to the CPRC.
CPRC Application
http://www.cancer.umn.edu/exfiles/research/CPRC_application.doc

Masonic Cancer Center – University of Minnesota
Cancer Protocol Review Committee (CPRC)

Protocol Submission Form Instructions

- Protocols can not be implemented until approved by the CPRC.
- CPRC Submission packets MUST be emailed to cprc@umn.edu, with each page attached as a separate PDF file. Electronic submission is required. The signed CPRC submission form should also be sent to the CPRC, MMC 6, or delivered to B405 Mayo.
- Only complete CPRC submission packets, including all required signatures, will be reviewed by the Committee. Incomplete packets will be returned to the Regulatory Specialist or PI.

<table>
<thead>
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<th>Therapeutic Interventional</th>
<th>Non-Therapeutic</th>
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<td>Abstract (400 words or less)</td>
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- CPRC Protocol Review - Therapeutic Interventional protocols will be reviewed on the 1st and 3rd Tuesday of each month. Non-therapeutic protocols will be reviewed on the 4th Tuesday of each month. Cooperative Groups will be reviewed when they are received. The Cancer Center website has a list of the submission deadlines and meeting dates. [Link](http://www.cancer.umn.edu/exfiles/research/CPRC/Calendar/ProtocolPosting.doc).
- Submission packets are due five Fridays prior to the next CPRC meeting. Deliver to CPRC, Room B405 Mayo, or campus mail to Clinical Trials Office, CPRC, MMC 6 Mayo. Incomplete forms will be returned.
- Required signatures – The Principal Investigator, ISC Team Leader (Interdisciplinary Site Committee) which may also be the PI and Department Chair/Dean are required to sign all submission forms. If there is no ISC Team, indicate “none.” A biostatistician is also required for all investigator-initiated studies.
- Posting trials on ClinicalTrials.gov – Per FDA Public Law 110-85 it is mandatory for the Sponsor/Responsible Party of all “applicable clinical trials” to register study information on a public website within 21 days of first enrollment. Basic results must also be posted within 12 months of primary outcome data collection; secondary outcome data has another 12 month deadline. Click on this link for access to this information: [Link](http://clinicaltrials.gov/).

The International Committee of Medical Journal Editors (ICMJE) requires this registration before first enrollment occurs in the study to consider publication in a reputable journal.

- Staff definitions:
  - Principal Investigator – The lead scientist on the clinical trial.
  - Co-Investigator – The co-investigators listed on the protocol.
  - Subject/Study Coordinator – The primary nurse and/or coordinator assigned to the study.
  - Regulatory Specialist – The person performing the study’s regulatory functions.
  - Study contact – The person who will receive public inquiries into the study (required by ClinicalTrials.gov).
  - Interdisciplinary Site Committee Team Lead – The person responsible for acknowledging start-up of this trial, especially as it relates to overlapping studies and the ability to accrue patients.

- Program Area – The Masonic Cancer Center Research Program Areas listed and described on the Cancer Center’s website [Link](http://www.cancer.umn.edu/research/index.html). Click on the links inside each program area to find the list of faculty in each program.

- VA Medical Center - Memorandum of Agreement with expected VA accrual and support of VA Section Chief required prior to processing at VA. VA activations require VA Human Subjects and R & D Committee Approvals. Contact Nadine Steele 612-775-2000 ext. 2908.

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CPRC Application
http://www.cancer.umn.edu/exfiles/research/CPRC_application.doc

| Masonic Cancer Center – University of Minnesota | Clinical Trials Office |
| Cancer Protocol Review Committee (CPRC) | MMC 6 / 9405 Mayo |
| CPRC PROTOCOL SUBMISSION FORM | Use instruction page for more information. |

- New submission
- Re-submission: (following denial or disapproval)
- Protocol version date:
- Sponsor protocol #:
- Protocol title:
- Protocol short title: [105 characters]

| MANAGEMENT |
| Principal Investigator (PI): |
| Pi department: |
| Pi room and building: |
| Pi phone: |
| Co-Investigators: |
| Subject/Study Coordinator: |
| Regulatory Specialist: |
| Biostatistician: |
| Study contact [required by clinical trials.gov]: |
| Interdisciplinary Site Committee Team (ISC): |

| Program Area: | |
| Carcinogenesis and Chemoprevention | Genetic Mechanisms of Cancer | Prevention and Etiology |
| Not applicable, explain why: | | Transplant Biology and Therapy |

- Engraftment/Stem cell sources/Immune reconstitution
- GVHD/Malignancies
- Late complications
- Metabolic disorders/Immune deficiencies
- Supportive care/Toxicities/Infections
- ALL
- Bone Marrow Failure/Hemoglobinopathies
- CLL/Lymphoma
- AIDS/AML/MPD
- Plasma cell disorders
- Brain
- Breast
- GI
- Gynecology
- Head and Neck
- Melanoma
- Peds
- Plasma Cell Disorders
- Sarcoma
- Solid Tumor/Phase I
- Thoracic
- Thyroid
- Urology/Prostate/Bladder/Testicular/Renal

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## CPRC Application

http://www.cancer.umn.edu/exfiles/research/CPRC_application.doc

The Clinical Trials Office is offering assistance. Indicate below if you would like the CTO to assist.

1. This study does not meet requirements, do not post. [ ] Check here
   (e.g. industry sponsored, collaborative group study, university consortium study, non-interventional study).

2. My study does meet requirements and I request CTO services to assist me in posting my study on clinicaltrials.gov. [ ] Yes [ ] No, I will do it.

3. I also request assistance in posting my basic clinical trial results per the ClinicalTrials.gov requirements: [ ] Yes [ ] No, I will do it.

### Protocol Details

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<th>II</th>
<th>III</th>
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Does this study involve therapy to treat side effects (e.g. vomiting) related to cancer treatment? [ ] No [ ] Yes

Does this study involve therapy to prevent cancer metastasis or cancer development? [ ] No [ ] Yes

#### Study Type

[ ] Ancillary or Companion [ ] Chart Review
[ ] Compassionate Use [ ] Correlative

#### Disease Site(s): (select all that apply)

- [ ] Any Site
- [ ] Bladder
- [ ] Bone/Joint
- [ ] Brain/Nervous System
- [ ] Breast-Female
- [ ] Breast-Male
- [ ] Cervix Uteri
- [ ] Colon
- [ ] Corpus Uteri
- [ ] Esophagus
- [ ] Eye/Orbit
- [ ] Hodgkin’s Lymphoma
- [ ] In-Kind Diagnostics
- [ ] Kaposi’s Sarcoma
- [ ] Kidney
- [ ] Larynx
- [ ] Leukemia, not otherwise specified
- [ ] Leukemia, other
- [ ] Lip/Oral Cavity/Pharynx
- [ ] Liver
- [ ] Lung
- [ ] Lymphoid Leukemia
- [ ] Melanoma, Skin
- [ ] Multiple Myeloma
- [ ] Mycosis Fungoides
- [ ] Myelodysplastic/Myeloproliferative
- [ ] Non-Hodgkin’s Lymphoma
- [ ] Other Digestive Organ
- [ ] Other Endocrine System
- [ ] Other Female Genital
- [ ] Other Hematopoietic
- [ ] Other Male Genital
- [ ] Other Respiratory/Intrathoracic Organs
- [ ] Other Skin
- [ ] Other Urinary
- [ ] Ovary
- [ ] Pancreas
- [ ] Prostate
- [ ] Rectum
- [ ] Small intestine
- [ ] Soft Tissue
- [ ] Stomach
- [ ] Thyroid
- [ ] Unknown Sites

Estimated accrual: Total national goal: 

Total local goal: 

Date accrual is expected to begin: 

Date accrual is expected to end: 

Duration of accrual (months): 

Estimated Date of Closure with the IRB: 

Summary accrual only: [ ] No [ ] Yes

Age range of subjects: [ ] Adults [ ] Children [ ] Adults and Children

Is there a reference to the inclusion of women and children? [ ] No [ ] Yes, page # .

Are there competing protocols? [ ] No [ ] Yes [ ] If yes, provide title and PI here or attach an additional document with the information.

If there are competing protocols, indicate the method of prioritization:
## Ongoing Monitoring of Subject Data and Regulatory Documents

Ongoing monitoring of subject data and regulatory documents is required for all Phase I and II investigator-initiated trials, and trials being conducted under a locally held IND. Please indicate who will perform the monitoring function:

- [ ] Not applicable
- [ ] CTO
- [ ] OCR
- [ ] Other, please specify

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<th>Risk Level (check one)</th>
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<th>Minimum Frequency of DSMC Review</th>
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In addition, data and safety monitoring will be conducted by the Masonic Cancer Center's Data Safety Monitoring Committee on a quarterly, twice yearly or annual basis depending on the level of risk assigned by the CPRC. The investigator will be required to complete a summary and submit to the DSMC.

**Scientific relevance and subject enrollment** will be monitored by the Cancer Protocol Review Committee at least annually.

### SIGNATURES

- **Principal Investigator** (printed name and signature)  
  Date
- **Biostatistician** (printed name and signature; investigator-initiated studies only)  
  Date
- **ISC Designer** (printed name and signature)  
  [ ] see attached ISC Protocol Concept Review Form  
  Date
- **Department/Division Head** (printed name and signature)  
  Date

*See instruction page for more information, including required signatures.*

- Protocols can not be implemented until they have received final full approval by the CPRC.
- CPRC Submission packets MUST be emailed to [cprc@umn.edu](mailto:cprc@umn.edu) with each piece attached as a separate PDF file. Electronic submission is also required. The signed CPRC submission form should also be sent to the CPRC, MMC 6 or delivered to 5455 Mayo.
- Only complete CPRC submission packets submitted by the deadline, including all required signatures, will be reviewed by the Committee at the next meeting. Incomplete packets will be returned to the Regulatory Specialist or PI.
Study Protocol

If you have written a grant application for your project, the grant application can serve as your protocol if the methods are sufficiently detailed.

Clinical Trials Office can help in preparing the study protocol.

- However, they are regulatory experts, and not necessarily content experts.

Protocol should include all details needed to successfully implement your study.
Study protocol

1. **Title**: Adequately describes the study.

2. **Background**: Sufficient material to justify the proposed protocol.

3. **Research objectives/Specific Aims**: Primary and secondary objectives that are clearly stated and reasonably achievable by the study.

4. **Eligibility and study requirements**: An appropriate study population must be clearly defined.

5. **Research Design and Methods**: Clearly describe what will be done during the study. Describe any modifications that will be made based on toxicity or adverse events, and the criteria for removing a patient from the study.
Study protocol

6. **Adverse event reporting**: The protocol should adhere to FDA and CTEP guidelines for toxicity reporting.

7. **Drug information**: The drug description for all drugs including known toxicities and formulae when available; means of supply; methods of storage; methods of procurement are to be included. Package inserts are unacceptable.

8. **Definition of outcomes**: All outcomes described adequately.

9. **Statistical analysis**: Should fully describe endpoints, method of data analysis, justification of proposed study accrual, and time frame.
Study protocol

10. **Schema:** Diagram, algorithm, or visual representation describing the proposed research plan.

11. **List of data items:** Identifies required forms to be completed, intervals at which forms must be submitted, location to which forms are submitted.

12. **Data and Safety Monitoring Plan:** indicates compliance with Cancer Center Data and Safety Monitoring guidelines.
Vitamin D Status Among Hematopoietic Cell Transplantation Survivors

Principal Investigator: Kim Robien, PhD, RD
Epidemiology and Community Health
University of Minnesota

Co-Investigators:
Hematology/Oncology and Transplantation:
Linda J. Burns, MD
Navneet Majhail, MD
K Scott Baker, MD
Daniel Mulrooney, MD

Epidemiology & Community Health:
DeAnn Lazovich, PhD

Protocol Number: MT 2008-03R

Version Date: September 29, 2008
## Protocol Revision History

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<th>Version Date</th>
<th>Summary of Changes</th>
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<td>Sep. 4, 2008</td>
<td>Clinic personnel will enter orders, not Study Coordinator and comparison of Fairview Diagnostic Lab to Heartland Assay dropped – to be done as a separate study.</td>
<td>9/4/2008</td>
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<td>Sep. 29</td>
<td>Remove last ref. to Heartland Assay from consents per IRB stipulation</td>
<td>9/29/08</td>
</tr>
</tbody>
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**PI Contact Information:**

Kim Robien, PhD, RD  
University of Minnesota  
Epidemiology and Community Health  
1300 S. 2nd St. #500  
Minneapolis, MN 55454  
Campus Mail Code 7525  
Phone: 612-625-8279  
Fax: 612-624-0315  
Email: robie004@umn.edu

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Vitamin D status among hematopoietic cell transplantation survivors

STUDY PROCEDURES

Patient Population:
- At least 1 year from the date of hematopoietic cell transplantation (HCT) for any diagnosis except multiple myeloma.
- Scheduled to be seen in the Blood and Marrow Transplant (BMT) Clinic, the Adult BMT Long-Term Follow-Up (BMT LTFU) Clinic or the Pediatric Long-Term Follow-Up Clinic (LTFU) at the University of Minnesota.

Accrual Goals:
- 47 pediatric and 50 adult HCT survivors

Approximately 6 weeks prior to scheduled clinic visit:
- Potential participant will be identified by the Study Coordinator.
- If eligible, the Study Coordinator sends a letter to the patient explaining the study goals and procedures, why they are eligible and how they were identified for this study. This letter will be from either K. Scott Baker, M.D. (pediatric patients), or Linda Burns, M.D. (adult patients). The letter will also contain a consent form, questionnaire regarding usual dietary intake and supplement use, recent sun exposure, and sun screen use and a self-addressed stamped envelope (SASE).

Telephone Consent
- Approximately two weeks after the letter is sent, the Study Coordinator will contact the potential participant, review the purpose of the study and the consent form, answer patient’s questions and if the patient agrees to participate, ask them to mail the signed consent form and completed questionnaire.

Laboratory Orders
- If a signed consent has been received, or the potential participant has expressed agreement to participate over the phone, the Study coordinator will submit orders to the clinic personnel the day before their scheduled lab appointment for 25OHd to be performed by the Fairview Diagnostic Laboratories. The clinic personnel will then enter the orders into the system for the day of the participant’s upcoming clinic appointment.

Upon check in at one of the Clinics
- If the signed consent form and completed questionnaire has not been received prior to the potential participants scheduled clinic visit, the Study coordinator will meet with the patient prior to any lab work, review the consent, answers patient’s questions, and if patient is still interested, obtain written consent and complete the questionnaire.
- The patient is then given a goldenrod colored Lab Request Form to take with them to the lab with the detailed draw instructions and research charge account number. If the patient is no longer interested in participating, the clinic personnel will cancel the 25OHD laboratory orders.
- Treatment related variables (such as original cancer diagnosis, pre-treatment height and weight, HCT treatment regimen, donor matching status, GVHD prophylaxis, history of acute and chronic GVHD, medications, and co-morbidities) will be abstracted from the medical record by the study coordinator.
Vitamin D status among hematopoietic cell transplantation survivors

Within 2 weeks:
- Each study participant will receive a letter with the results of the 25OHD testing signed by Kim Robien, PhD, RD. A copy also will be sent to referring primary care physician, if applicable. For individuals found to be vitamin D deficient, the letter will encourage the individual to consult their primary care physician to develop a plan for vitamin D repletion along with monitoring of serum calcium levels.

End of direct patient participation
1. OVERVIEW AND SPECIFIC AIMS

Vitamin D, a sterol hormone precursor, is well known for its role in maintaining calcium homeostasis and normal bone structure. Recent evidence suggests that in addition to calcium homeostasis, the vitamin may also play a role in cancer incidence and recurrence (1), risk of infectious diseases (2), and modulation of inflammatory pathways (3, 4). Thus, for cancer survivors treated with hematopoietic cell transplantation (HCT), maintaining adequate vitamin D status throughout the course of HCT may decrease risk of graft-vs-host disease (GVHD), graft rejection, infectious complications and disease relapse, which in turn, could result in improved survival rates compared to individuals who are vitamin D deficient. In fact, several recent studies have reported an association between higher serum 25-hydroxyvitamin D levels and improved survival among individuals with colon (5), breast (5), prostate (5), and non-small cell lung cancers (6), as well as Hodgkin’s lymphoma (5). Vitamin D deficiency has been associated with muscle weakness (7, 8), musculoskeletal pain (9), and impaired cognition (10); all issues common among cancer survivors which may contribute to diminished quality of life.

Little is known about serum vitamin D levels during and after HCT, although there is reason to believe that vitamin D deficiency is common. Following HCT, patients are instructed to avoid sun exposure and to use sunscreen due to increased risk of melanoma and chronic skin GVHD. Use of certain medications, such as glucocorticoids commonly used to treat GVHD, have been found to reduce serum vitamin D levels (11-13). Also many individuals have alterations in gastrointestinal (GI) absorptive capacity following HCT as a result of GI GVHD, intestinal bile salt deficiency, pancreatic enzyme insufficiency, or bacterial overgrowth; consequently, these individuals may have difficulty absorbing dietary fat and fat soluble vitamins such as vitamin D (14). Osteoporosis is a common among long-term HCT survivors, especially following glucocorticoid therapy. Individuals found to have osteoporosis are typically treated with vitamin D supplementation (typically as calcifediol or nasal spray calcitonin) to enhance calcium absorption and bone matrix formation, however this is the only current routine use of vitamin D supplementation in the HCT population.

The specific aim of this pilot study will be to determine the prevalence of 25-hydroxyvitamin D (25OHD) deficiency among long-term (>1 year) cancer survivors who received HCT. At this time point post-HCT, individuals should be more stable in terms of treatment regimens, yet may have been vitamin D deficient for a prolonged period of time compared to earlier points in the transplant process. We hypothesize that the majority of these individuals will have suboptimal serum vitamin D levels due to avoidance of sun exposure, regular use of sunscreen, suboptimal dietary/supplemental intake, and treatment-related factors.

The information to be gained from this research is an important first step towards a future study which will evaluate the association between serum 25OHD levels and risk of chronic GVHD, infectious complications, and cancer recurrence.
Vitamin D status among hematopoietic cell transplantation survivors

2. BACKGROUND

Vitamin D₃ (cholecalciferol), produced endogenously in the skin upon exposure to UV radiation, and vitamin D₂ (ergocalciferol), available exogenously through fortified foods and dietary supplements, enter the circulation through the skin or absorption from the intestinal tract, and are converted to 25-hydroxycholecalciferol (25(OH)D) via 25-hydroxylase (mitochondria: CYP27A1; microsome: CYP2R1) in the liver. Serum levels of 25(OH)D reflect current vitamin D status. Further hydroxylation of 25(OH)D via 1α-hydroxylase (CYP27B1) to form 1,25-dihydroxycholecalciferol (1,25(OH)₂D) occurs in the kidney. 1,25(OH)₂D is involved in enhancing absorption of calcium in the intestine, and re-absorption of calcium into the kidney. 1,25(OH)₂D has strong intracellular anti-proliferative and pro-differentiation activity, and thus plays an important role in growth regulation (1). As cancer is a disease of disordered growth regulation, 1,25(OH)₂D is likely to play a role in prevention of carcinogenesis and cancer progression. Steroid hormones are hydrophobic, and thus require specific transport proteins in circulation (15). Vitamin D binding protein is the transport protein for both 25OHD (higher affinity) and 1,25(OH)₂D (lower affinity) (16). Catabolism of 1,25(OH)₂D occurs via 24-hydroxylase (CYP24A1), and results in production of 24,25(OH)₂D or 1,24,25(OH)₃D. Ultimately, the net availability of the active 1,25(OH)₂D metabolite is dependent on a balance between availability of ergo- and cholecalciferol substrates and activating enzymes (CYP2R1, CYP27A1, CYP27B1) with the inactivating enzyme, CYP24A1 (16).

The 25OHD metabolite is the primary circulating form of vitamin D, with a half-life in healthy adults has been estimated to be between 10 - 23 days, depending on assay methodology (20). The metabolically active 1,25(OH)₂D form is present only in picomolar quantities, and is tightly regulated in order to maintain calcium homeostasis. Thus, 25OHD is considered the more clinically relevant form for assessing overall vitamin D status. Optimal vitamin D intake and vitamin D serum levels are not known (21, 22); however, it has been hypothesized that serum 25OHD levels of 36-40 ng/mL (90-100 nmol/L) are optimal in healthy populations (23). Several leading vitamin D researchers have recently suggested that the goal should be to achieve and maintain serum 25(OH)D levels of 30-32 ng/mL (75-80 nmol/L) (21, 24). To raise 25(OH)D levels from 20 to 32 ng/mL (50 to 80 nmol/L) via diet in otherwise healthy individuals, it has been estimated that an additional daily intake of 1720 IU of vitamin D would be needed (25). The tolerable upper intake level for vitamin D was set at 2000 IU/day by the Food and Nutrition Board of the Institute of Medicine in 1997 (26), but data linking vitamin D

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Vitamin D status among hematopoietic cell transplantation survivors

25OHD levels in this study population. However, the upper age limit to be eligible for the case-control study was fairly young at 59 years.

In a multivariate analysis, age, BMI, month of blood draw, usual dietary vitamin D intake, supplemental vitamin D intake, and self-reported daily sun exposure in the month prior to blood draw explained 53% of the variance (R²) in serum 25OHD levels. Including the CYP2R1 and VDR variants in the multivariate model improved the model fit to explain approximately 60% of variation in serum 25OHD levels.

4. RESEARCH DESIGN AND METHODS

Study population. Study participants for this pilot study will be recruited from the Blood and Marrow Transplant (BMT) Clinic, the Adult BMT Long-Term Follow-Up (BMT LTFU) Clinic or the Pediatric Long-Term Follow-Up Clinic (LTFU) at the University of Minnesota. Study entry is open to patients regardless of gender or ethnic background. While there will be every effort to seek out and include minority patients, accrual to this study is expected to be no different than that of transplant studies at the University of Minnesota.

Inclusion Criteria:
- At least 1 year from the date of hematopoietic cell transplantation (HCT) for any diagnosis except multiple myeloma
- Scheduled to be seen in the Blood and Marrow Transplant (BMT) Clinic, the Adult BMT Long-Term Follow-Up (BMT LTFU) Clinic or the Pediatric Long-Term Follow-Up Clinic (LTFU) at the University of Minnesota.
- Voluntary written informed consent before performance of any study-related procedure not part of normal medical care.

Approximately 100 – 150 HCT survivors are anticipated in each of the three clinics each year.

Overview of study procedures. Potential participant will be identified by the Study Coordinator. The Study Coordinator will send a letter to the eligible participant explaining the study goals and procedures, why they are eligible and how they were identified for this study. This letter will be from either K. Scott Baker, M.D. (pediatric patients) or Linda Burns, M.D. (adult patients). The letter will also contain a consent form, questionnaire regarding usual dietary intake and supplement use, recent sun exposure, and sun screen use and a self-addressed stamped envelope (SASE).

Approximately two weeks after the letter is sent, the Study Coordinator will contact the potential participant, review the purpose of the study and the consent form, answer patient’s questions and if the patient agrees to participate, ask them to mail the signed consent form and completed questionnaire.

If a signed consent has been received, or the potential participant has expressed agreement to participate over the phone, the Study coordinator will submit orders to the clinic personnel the day before their scheduled lab appointment for 25OHD to be performed by the Fairview Diagnostic Laboratories. The clinic personnel will then enter the orders into the system for the day of the participant’s upcoming clinic appointment.
Vitamin D status among hematopoietic cell transplantation survivors

Clinic visit. If the signed consent form and completed questionnaire has not been received prior to the potential participants scheduled clinic visit, the Study coordinator will meet with the patient prior to any lab work, review the consent, answers patient’s questions, and if patient is still interested, obtain written consent and complete the questionnaire. The patient will be given a goldenrod colored Lab Request Form by the Study Coordinator or the clinic personnel to take with them to the lab with the detailed draw instructions and research charge account number. If the patient is no longer interested in participating, the clinic personnel will cancel the 25OHD laboratory orders.

Treatment related variables (such as original cancer diagnosis, pre-treatment height and weight, HCT treatment regimen, donor matching status, GVHD prophylaxis, history of acute and chronic GVHD, medications, and co-morbidities) will be abstracted from the medical record by the study coordinator.

Within two weeks after the clinic visit, each study participant will receive a letter with the results of the 25OHD testing signed by Kim Robien, PhD, RD. A copy also will be sent to referring primary care physician, if applicable. For individuals found to be vitamin D deficient, the letter will encourage the individual to consult their primary care physician to develop a plan for vitamin D repletion along with monitoring of serum calcium levels.

Serum determinations. The primary serum 25OHD determinations will be performed at the Fairview Diagnostic Laboratories using liquid chromatography/tandem mass spectrometry (LC-MS/MS) methods.

Additional data collection. Treatment related variables (such as original cancer diagnosis, pre-treatment height and weight, HCT treatment regimen, donor matching status, GVHD prophylaxis, history of acute and chronic GVHD, medications, and comorbidities) will be abstracted from the medical record.

5. DATA ANALYSIS
For the purposes of data analysis, serum 25OHD deficiency will be defined as serum levels <32 ng/mL (80 nmol/mL) (24). Serum 25OHD levels will be reported with descriptive statistics including means, standard deviations, frequencies and ranges. Datasets mean serum vitamin D levels and prevalence of vitamin D deficiency in the MMF funded pilot study (“Evaluating vitamin D exposure and metabolism” described above) will be used as a healthy, geographically-similar population comparison for mean serum level and prevalence of vitamin D deficiency.

The prevalence of serum 25OHD deficiency will be reported for the entire cohort, and stratified by age at the time of the blood draw (less than vs. greater than or equal to 18 years of age). If/where sufficient numbers are present, we will also stratify on key covariates such as sex, BMI (categorical: < 18, 18-24.9, ≥25), self-reported race (white vs. other), type of cancer, type of HCT (allologenic, autologous, cord blood, myeloablative, non-myeloablative), donor relationship (related vs. unrelated), HLA matching, history of GVHD and current use of glucocorticoids (yes/no). The number of individuals with serum 25OHD deficiency in each stratum of a given variable will be compared using Chi-Square testing.
Estimated sample size required, power calculations. We anticipate that the prevalence of vitamin D deficiency among HCT survivors will be somewhat higher than that of the general population. The general population estimates of vitamin D deficiency during winter months (would approximate what would be expected for HCT patients instructed to avoid sun exposure) from NHANES III are outlined in Table 1. Bearing in mind that the NHANES III analysis used a lower cut-point to define vitamin D than current definitions (25 ng/mL vs. 32 ng/mL), it seems reasonable to expect that at least 35% of pediatric HCT survivors and 50% of adult HCT survivors will be found to be vitamin D deficient. In order to determine the prevalence (± 10%) and corresponding 95% confidence interval in a population of 100 (approximately number of HCT survivors seen yearly in each of the LTFU clinics), we estimate that we will need to include 47 pediatric and 50 adult HCT survivors (41).

### Table 1. Prevalence of vitamin D deficiency during winter months, NHANES III

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>%</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-19</td>
<td>25</td>
<td>17-32</td>
</tr>
<tr>
<td>20-39</td>
<td>43</td>
<td>37-49</td>
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<tr>
<td>40-59</td>
<td>39</td>
<td>32-46</td>
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<tr>
<td>60-79</td>
<td>38</td>
<td>31-46</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-19</td>
<td>47</td>
<td>39-55</td>
</tr>
<tr>
<td>20-39</td>
<td>55</td>
<td>50-61</td>
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<tr>
<td>40-59</td>
<td>57</td>
<td>50-63</td>
</tr>
<tr>
<td>60-79</td>
<td>52</td>
<td>45-59</td>
</tr>
</tbody>
</table>

*defined as serum 25(OH)D <25 ng/mL (62.5 nmol/L).

6. ADMINISTRATIVE REQUIREMENTS

Retention of Records. The investigator will retain study records, including source data, copies of data collection forms, and all study correspondence indefinitely in a secured facility.

7. REFERENCES

Biostatistics Shared Resource
http://www.cancer.umn.edu/research/cores/biostats/index.html

• Provide biostatistics expertise in study design, including endpoint definition, sample size estimation and power calculation, randomization procedures, data collection from design, plans for report generation, interim reviews, and final analysis.

• Limited services are provided free of charge to researchers planning cancer-related grant applications and research protocols or conducting cancer-related research (pilot and feasibility studies).

• Contact: Bruce Lindgren, MS, Coordinator and Senior Research Fellow, lindg001@umn.edu
# CPRC Review Schedule


## 2011 Cancer Protocol Review Committee (CPRC) Schedules

Dates are subject to change. Call 6-5174 to verify the next meeting date.

### Therapeutic Interventional CPRC

<table>
<thead>
<tr>
<th>Application Due Date</th>
<th>CPRC-TI Meeting Date 1st/3rd Tues</th>
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<tbody>
<tr>
<td>January 7, 2011</td>
<td>January 18, 2011</td>
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<tr>
<td>January 21, 2011</td>
<td>February 1, 2011</td>
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<tr>
<td>February 4, 2011</td>
<td>February 15, 2011</td>
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<tr>
<td>February 18, 2011</td>
<td>March 1, 2011</td>
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<tr>
<td>March 25, 2011</td>
<td>April 5, 2011-April 12, 2011</td>
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<tr>
<td>April 8, 2011</td>
<td>April 19, 2011</td>
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<tr>
<td>April 22, 2011</td>
<td>May 3, 2011</td>
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<td>May 6, 2011</td>
<td>May 17, 2011</td>
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<td>May 20, 2011</td>
<td>June 7, 2011</td>
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<td>June 3, 2011</td>
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<td>July 5, 2011</td>
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<td>July 8, 2011</td>
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<td>July 22, 2011</td>
<td>August 2, 2011</td>
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<td>August 5, 2011</td>
<td>August 16, 2011</td>
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<td>September 6, 2011</td>
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<td>September 20, 2011</td>
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<td>November 23, 2011</td>
<td>December 6, 2011</td>
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<td>December 20, 2011</td>
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### Non-Therapeutic Interventional CPRC

<table>
<thead>
<tr>
<th>Application Due Date 2 Fridays before meeting date</th>
<th>CPRC-NTI Meeting Date 4th Tuesday</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 14, 2011</td>
<td>January 25, 2011</td>
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<tr>
<td>February 11, 2011</td>
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<td>April 26, 2011</td>
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<td>June 10, 2011</td>
<td>June 21, 2011</td>
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<td>July 15, 2011</td>
<td>July 26, 2011</td>
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<td>September 16, 2011</td>
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<td>October 14, 2011</td>
<td>October 25, 2011</td>
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<td>November 11, 2011</td>
<td>November 22, 2011</td>
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<tr>
<td>December 9, 2011</td>
<td>December 20, 2011</td>
</tr>
</tbody>
</table>
What happens once I submit my application?

- CPRC manager compiles a list of applications to be reviewed at the monthly meeting.
- CPRC manager and CPRC chair assign each application to a primary and secondary reviewer, and one of the biostatisticians for review.
- Committee members read the application, and write out their review.
- CPRC committee meets to review and discuss each protocol.
- CPRC manager prepares a written summary of the committee discussion.
- CPRC chair writes a letter to the researcher describing the committee decision, and listing any stipulations to be addressed.
Who are the CPRC members?

- Volunteer faculty members of the Cancer Center
- Members are selected to represent the diversity of expertise needed to scientifically review the protocols.
- Most CPRC members are experienced researchers.

Chair, CPRC-TI: Robert Kratzke, MD

Chair, CPRC-NTI: Anne Joseph, MD, MPH
What are the reviewers looking for?

Similar to the NIH review process

1. Is the study designed in a way that is likely to be successful?
2. Will the study design allow the researchers to answer the research question?
3. Are the necessary resources available to the researchers?
4. Is the data analysis plan appropriate for answering the research question?
5. Is the study adequately powered to answer the research question?
Potential outcomes of the CPRC review

Approved
• Approved for opening to accrual contingent upon obtaining IRB approval and completion of all other protocol activation steps.

Approved with minor stipulations
• Approval from the CPRC, but the PI needs to address minor issues. The CPRC Chair will provide final approval for implementation.

Deferred
• Sufficient problems exist with the protocol such that substantial revisions and formal reconsideration by the CPRC are required.

Disapproved
• The protocol is not approved for opening to accrual at the UMN.
Responding to stipulations, concerns

- If your study is not approved on the first submission, you will receive a list of concerns/stipulations from the CPRC.
- These comments are intended to strengthen your study, and should be taken seriously.
- When submitting a revised protocol, be sure to include a cover letter outlining the changes that you have made to the proposal.
- You cannot submit your study to the IRB until you obtain approval from the CPRC.
Time invested in planning your project will translate to a more effective project

- Collect the right data the first time.
- Avoid well known hurdles in study implementation.
- Improve your chance of being funded in future projects.
Questions?