REI Clinical Trials Workshop Information
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At the NICHD Young Investigators Meeting, there is a Clinical Trials Workshop. In this activity, we will be discussing and designing a clinical trial. Prior to the workshop there will be a presentation on the topic to set the stage. In addition, the material below will help you to prepare for the workshop – you will be expected to have reviewed this material and the suggested reading to actively participate in the workshop.

Clinical Question: Can vitamin D prevent uterine fibroids?

Scope of clinical issue:

Uterine leiomyomas or fibroids as they are more commonly known are the most prevalent tumor in reproductive aged women. Approximately 70% of women will have fibroids by the age of 50. While not all women with fibroids have symptoms, the 30-50% who are symptomatic tend to have multiple symptoms which can include abnormal uterine bleeding, pain, infertility, recurrent pregnancy loss, urinary symptoms, and bloating. The prevalence and morbidity of these tumors combined, result in fibroids being the leading cause of hysterectomy in the USA.

Despite the prevalence of these tumors, little progress has been made on shifting the paradigm on their treatment or prevention. Surgery remains the mainstay treatment and while there are medical treatments approved for fibroid related findings/symptoms i.e. anemia and AUB, there are no FDA approved medications to treat/prevent the tumors directly. The ideal treatment would be safe, effective, selective, low cost/generic, easy to administer, and free from interactions with other drugs. One such possible candidate is vitamin D. Recent case-control and basic science studies have found an association between Vitamin D levels and fibroids but no randomized controlled trials (RCTs) have been done to date. Our goal is to pave a roadmap to design an RCT to determine if vitamin D can prevent fibroid development.

Care should be taken when addressing the need and design of any randomized clinical trial. In preparation for our session, review and be prepared to participate in a discussion of the following:

- Background and importance
    - Before doing an RCT, is there a need for additional studies (a) descriptive epidemiology; (b) observational study(ies) to determine if there are associated morbidities and assess the effectiveness and safety of treatment (c) review of current trials? Is this study possible?
        - Quality of Evidence:
            - I - RCT
            - II-1 Controlled Trials / No randomization
            - II-2 cohort (case control studies)
            - II-3 multiple time series / dramatic effect
            - III Opinion of experts / descriptive studies, expert committees

- What is the quality of evidence for an intervention achieving normal Vitamin D levels? What interventions would you avoid?

- General goal – what is the hypothesis?

- Outcomes: Primary – What is the primary outcome? What are the secondary outcomes?

- Population of study – who to target: Anyone with a uterus? high risk population?

- Inclusion and exclusion criteria. Is there an age limit to participation? Should imaging be required? Are there some medical conditions or confounding medications or treatments that should be excluded?

- Study design and overview
    - In development of the study design, what treatment regimens should/can be compared? What is/are the control group(s)???
    - How many treatment/control groups should the study have?
    - Can you single or double blind any of the interventions?
    - Do the interventions have to begin and end concurrently for all treatment groups?

- Interventions
    - How should treatment be administered and followed?
    - For disparate treatments, how should study visits be conducted?
    - What key information: medical, imaging, biochemical, etc. should be collected/conducted at each visit? i.e. what should the study visit table look like?
    - What is the treatment duration?

- Randomization
    - What is the best randomization method?
    - How do we preserve allocation concealment?

- Sample size
    - What sample size is reasonable for NIH (RO1, U10 level resources)
    - What sample size is reasonable for NIH R21 grant?

- Safety analysis – how to define AE's
    - How to collect AEs
    - What is a SAE in non-primary participants, i.e. fetus if a subject becomes pregnant during the study?

- Analysis plan –
    - Should you examine rates per group or Kaplan Meier Curves? What prespecified subgroup analyses do you want to conduct? How do you incorporate lost to follow up into an intention to treat design

- Compliance with protocol and protocol violations:

- What do you do with patients who are blatantly non-compliant with taking supplemental vitamin D?
- How do you handle drop out?

Suggested Reading:

1. Paffoni A, Somigliana E, Vigano' P, Benaglia L, Cardellicchio L, Pagliardini L, Papaleo E, Candiani M, Fedele L. Vitamin D status in women with uterine leiomyomas. J Clin Endocrinol Metab. 2013 Aug;98(8):E1374-8.Epub 2013 Jul 3.
2. Ciebiera M, Włodarczyk M, Słabuszewska-Jóźwiak A, Nowicka G, Jakiel G. Influence of vitamin D and transforming growth factor β3 serum concentrations, obesity, and family history on the risk for uterine fibroids. Fertil Steril. 2016 Dec;106(7):1787-1792.Epub 2016 Oct 12.
3. McCullough ML, Bostick RM, Daniel CR, Flanders WD, Shaukat A, Davison J, Rangaswamy U, Hollis BW. Vitamin D status and impact of vitamin D3 and/or calcium supplementation in a randomized pilot study in the Southeastern United States. J Am Coll Nutr. 2009 Dec;28(6):678-86.
4. Baird DD, Hill MC, Schectman JM, Hollis BW. Vitamin d and the risk of uterine fibroids. Epidemiology. 2013 May;24(3):447-53.
5. Brakta S, Diamond JS, Al-Hendy A, Diamond MP, Halder SK. Role of vitamin D in uterine fibroid biology. Fertil Steril. 2015 Sep;104(3):698-706.
6. Marsh EE, Ekpo GE, Cardozo ER, Brocks M, Dune T, Cohen LS. Racial differences in fibroid prevalence and ultrasound findings in asymptomatic young women (18-30 years old): a pilot study. Fertil Steril. 2013 Jun;99(7):1951-7. Epub 2013 Mar 15.