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Dear Dr. Borrer,

Thank you for reviewing my letter to Senator Murray dated August 22, 2006. I'd like to provide additional information for you to consider when evaluating my request that an investigation be opened into how many of the federal rights of the recruited women were violated when they were recruited and accepted to participate in the Women's Health Initiative.

In the course of my research on hypogonadism (menopause) I discovered that unethical and misleading practices were used to recruit women into the Women's Health Initiative (WHI). Once recruited the welfare of these women was not made more important than the stated goals of the WHI, which put them in unnecessary peril and caused unnecessary pain, discomfort, and emotional distress and at no point were they informed of this. Furthermore, because of these misleading and unethical actions taken by the NIH:

- 1) Millions of women are being forced to live with untreated hypogonadism, which puts their health and personal and professional lives in unnecessary peril. Untreated hypogonadism destroys marriages, careers and only results in long term poorer general medical and cognitive health.
- 2) The public, lay and medical, believes that Hormone Replacement Therapy (HRT) is unhealthy for the treatment of hypogonadism in women because Premarin™ was called HRT in the WHI instead of more accurately supraphysiologic or higher than normal estrogen replacement. If Premarin™ .625 mg was called what it is then supraphysiologic estrogen replacement would be associated with poor health and not HRT. Because Premarin™ .625 mg creates a hyper-estrogenic state it is **neither hormone replacement nor hormone therapy**.
- 3) No meaningful research is being done to develop physiologic HRT for treatment of hypogonadism in women. This forces women with hypogonadism to develop their own protocols instead of having the assurance that a protocol has been developed by experts in a safe,

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methodical way. In no other area of endocrine medicine is a patient expected to understand organ failure and to create a hormonal protocol on their own to treat the resulting illnesses.

- 4) Clinical trials on Ovarian Replacement Therapy (ORT) are completely stalled. Studies of physiologic replacement of ovarian hormones, estradiol, testosterone and progesterone, show that breast cancer can be prevented and sexual function restored through the use of ORT, which you would expect of a regimen labeled HRT for hypogonadism. Treatment with Premarin™ does neither of these important functions. Because Premarin™ is incorrectly called HRT, HT (Hormone Therapy), MHT (Menopausal Hormone Therapy) and ET (Estrogen Therapy), studies of physiologic replacement are not being undertaken.
- 5) There has been no modernization of the treatment of hypogonadism in women since 1942 when Premarin™ first was introduced. Every other area of endocrine medicine has evolved with better and healthier regimens because they are based on physiologic, bio-identical replacement. The treatment of hypogonadism for women has been the same for the last 65 years. Because of the perpetuation of the myth that Premarin™ is HRT and the failure of the WHI, the evolution of better, physiologic, bio-identical based hormonal regimens is not being pursued by the NIH. Modernization, however, continues in every other area of endocrine medicine, including insulin replacement for diabetes, thyroid hormone replacement for hypothyroidism, growth hormone replacement for congenital deficiency and testosterone replacement for hypogonadism in men.
- 6) Doctors have no proven protocols based on clinical trials to guide them. Evidence based medicine helps doctors use proven protocols supplied by the NIH. By choosing not to modernize the replacement regimen for ovarian failure in their clinical trials, the NIH has effectively tied doctor's hands by blocking their ability to effectively and safely treat hypogonadism in women. Premarin™, which has been described as HRT for 65 years, does not restore sexual function or reduce the increased risk of breast cancer induced by hypogonadism. Simply put, the NIH has completely abandoned doctors and the women they want to treat and keep healthy.
- 7) New drugs and delivery mechanisms are not being developed. Pharmaceutical companies produce products from successful clinical trials which ensure sales. The NIH has not sponsored a clinical trial on physiologic replacement of ovarian hormones, so there are no products from any trial to produce. Furthermore, the pharmaceutical companies have no direction from the NIH regarding treatment of hypogonadism in women so there is no point in producing products that do not have a protocol to tell doctors how to use them.

The recruited women had their right to be fully informed denied and failed to have their health ensured while in the study in the following ways:

- 1) Supraphysiologic dosages of estrogen were given to them instead of the expected physiologic replacement advertised as HRT. The recruited women had the expectation that when they would be receiving HRT, it would be physiologic replacement. Because every other area of endocrine medicine is based on physiologic replacement there is no reason the recruited women would have expected anything different.
 - a. Per §46.116 (a)(2) once enrolled in the study the women traded hypogonadism for hyperestrogenism and were never told. The women should have been told that there was

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- no intention of giving HRT for hypogonadism, but rather to create hyperestrogenism to stimulate HDL production.
- b. Per §46.116 (a)(1) there was no provision to measure the level of any replaced hormone before, during or after ingesting Premarin™ because the emphasis of the WHI trial was on manipulating the HDL with the hyperestrogenism and not preventing the hyperestrogenism. Assays for testing Premarin™ estrogens were available and the level of Premarin™ estrogens could have easily been determined if desired. The rights of the women to be told that they were trading hypogonadism for hyperestrogenism were violated when they were not told. The resulting levels of estrogen were at least 15 fold higher than the average level of 100 pg/ml of estradiol (the strongest human estrogen) during a normal menstrual cycle. It is estimated that equilin, just one estrogen of the many estrogens that Premarin™, contains has an estradiol equivalent of about ½. Levels of equilin are at least 2500 pg/ml or an estradiol equivalent of 1250 pg/ml which is 12 times higher than an average menstrual cycle. Levels of estrone, another Premarin™ estrogen, are at least 3,000 pg/ml. Estrone is estimated to be about 1/10 the strength of estradiol or an estradiol equivalent of 300 pg/ml which is 3 times higher than an average menstrual cycle. The total from just these two estrogens results in an estradiol equivalent of at least 1500 pg/ml which is at least 15 times higher than a normal menstrual cycle. The total amount of estrogen is even higher because Premarin™ contains many more estrogens than I mentioned. Intentionally giving a woman a preparation that knowingly results in hyperestrogenism and telling her it is HRT and not hyperestrogenism violates her right to be properly informed.
 - c. Per §46.116 (a)(2) there was no procedure in place to correct under or overdosing because the levels of Premarin™ and human estrogens were not monitored at any time before, during or after treatment. The women should have been told that hyperestrogenism was the goal, which was why there were no tests for hormone levels or any mechanism in place to reduce the level of estrogen to replacement values instead of supraphysiologic.
 - d. Per §46.116 (a)(2) Hormone Replacement Therapy (HRT) was advertised to recruit women. HRT implies replacement of hormones to appropriate levels. The recruited women were not told they were receiving higher than normal replacement of estrogen and no replacement for the other ovarian hormones, testosterone and progesterone.
 - e. Per §46.116(a)(2) HRT for ovarian failure was expected because every woman had to be suffering from untreated hypogonadism to be considered eligible for the WHI. Taking only Premarin™ .625 mg supplies supraphysiologic levels of estrogen and causes available levels of testosterone and progesterone to be below levels found with hypogonadism, which results in a distorted ratio of ovarian hormones. Functional human ovaries create a ratio of estradiol, testosterone, and progesterone of approximately 1:10:100. There is no dispute in the medical community that the hormones supplied by Premarin™ do not represent the ratio of hormones from functional ovaries and that this dose creates supraphysiologic levels of estrogens. After taking Premarin™, the ratio of ovarian hormones is closer to 20:1:5. If a woman went to her doctor and had a ratio of ovarian hormones of 20:1:5 it would be considered abnormal. She would be evaluated and have her ovarian hormone ratio corrected as this is a distorted and completely

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abnormal ratio. If a woman presented to her doctor with an estradiol level over 1500 pg/ml, or 15 times higher than expected and levels of available testosterone and progesterone below the levels found with ovarian failure her doctor would foresee poorer health without medical intervention. Taking Premarin™ .625 mg dosage creates the hormonal milieu outlined above which is not physiologic ovarian hormone replacement. Calling this ratio replacement is not only irresponsible to the women taking it but to the doctors following their health and well-being. The NIH felt strongly that they had to advertise Premarin™ as HRT to get women to sign up for the WHI. It was misleading to not inform these women that the WHI was not planning to give physiologic replacement but rather an excess of estrogen combined with no testosterone and no progesterone components, creating a whole new hormonal milieu that, in other circumstances, a doctor would be very concerned about and attempt to correct. This information has never been disclosed to the recruited women.

- 2) An unnecessary exposure to uterine cancer was created. Rather than prevent the cancer in the first place, the women were subjected to a painful procedure (uterine aspiration) to find cancer after the fact. If cancer were found then the women's only option for an effective treatment would be surgery. This was a particularly vulnerable population as they could be quite elderly and suffered from hypogonadism.
 - a. Per §46.116 (a)(2), §46.116 (a)(3) avoiding the addition of a progestin, which would have reversed the positive effect the Premarin™ estrogens had on the HDL, further demonstrates that replacement was not the goal. Instead, a supraphysiological dose of estrogen was used to stimulate the liver to produce more HDL, which was the goal. The women should have been told that they were being given an estrogen based cholesterol drug which would cause supraphysiological levels of estrogens. Intentionally withholding the progestin at the onset of the WHI clearly demonstrates that the goal of this trial was not to provide replacement ovarian hormones as a treatment to prevent disease but to manipulate cholesterol via a very high dose of oral estrogen and catch uterine cancer early when it is the most treatable. Advertising that the women would receive HRT was misleading. If HRT was provided as advertised then uterine cancer would have been prevented, thus sparing the women the unnecessary risk and subsequent surgery to treat it.
 - b. Per §46.116 (a)(2) the recruited women were exposed to a risk of breast cancer already present from the untreated hypogonadism. At no time were the women ever told that hyperestrogenism was the goal of the HRT arm of the WHI and not actual HRT. An HRT regimen for hypogonadism should be expected to reduce breast cancer because the primary reason for the dramatic increase is due to ovarian failure and the resultant hypogonadism. The fact that this regimen was called HRT and did not decrease breast cancer left these women vulnerable to a risk of breast cancer they could have avoided if they were given HRT.
 - c. Per §46.116 (a)(2) Available progesterone and testosterone levels fell below the already low levels found with ovarian failure and the resultant hypogonadism. The hyperestrogenism from the Premarin™ estrogens not only stimulated the liver to increase production of HDL but also corticosteroid binding globulin (CBG) and sex hormone

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- binding globulin (SHBG). Increases in these binding proteins lowers the already very low levels of sex steroids available to the bodies' tissues to levels below ovarian failure levels. The women were never informed that they would receive the equivalent of an excess of one ovarian hormone, estrogen, and sub-ovarian failure levels of other ovarian hormones, testosterone and progesterone.
- d. Per §46.116 (a)(1) The result of taking Premarin™ .625 mg is a hormonal milieu that would only happen in a disease state. Telling the recruited women that they were getting HRT violated their right to know what was actually being given to them and was completely misleading.
- 3) There should have been no expectation of success for the WHI once medroxyprogesterone (MPA) was added as it completely cancelled out the cholesterol improvement from the Premarin™ because it lowers HDL levels as much or more than the expected rise from the Premarin™ estrogens.
 - a. Per §46.116 (a)(1) the women were never informed of this development when this progestin was added.
 - 4) Giving a person with untreated hypogonadism a preparation called HRT that, for the 65 years since its introduction, has been known to not restore sexual function, is cruel. Since its introduction in 1942, Premarin™ .625 mg has never been associated with restoring sexual function. Men with hypogonadism would not be given a regimen called HRT that would not restore sexual function without being told. The recruited women deserved to know ahead of time so they could adjust their expectation of the HRT regimen that was advertised by and given to them by the WHI.
 - a. Per §46.116 (a)(2) the women should have been informed of this limitation of Premarin™ and had their expectations adjusted.
 - 5) At no time was testing done to ensure hypothyroidism did not occur as a result of taking an oral estrogen preparation, thus putting their overall health in jeopardy. In an elderly population a thyroid test both before and after taking an oral estrogen is standard practice because of the higher prevalence of undiagnosed hypothyroidism. Untreated hypothyroidism causes negative changes in lipid levels and would have cancelled out the improvement sought with using supraphysiologic amounts of an oral estrogen. Hypothyroidism also causes a host of other ailments and there was no mechanism in place within the WHI to make sure this very important test was done and treatment of hypothyroidism provided both before and after starting Premarin.
 - a. Per §46.116 (a)(2) the health and welfare of the participants was not as important as maintaining the supraphysiologic levels of estrogen.
 - 6) At no time were the women ever informed of the prolonged presence of equine estrogens after they stopped taking Premarin™. Premarin™ estrogens can stay in the body at elevated levels for at least 3 – 6 months. To know this is of paramount importance, particularly if a woman is diagnosed with an estrogen receptor positive cancer. This is important to know because if a woman has a large, non-suppressible source of estrogen, the only effective way to keep this non-

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suppressible source of estrogen from the tumor would be to use an estrogen competitor like tamoxifen rather than an aromatase inhibitor.

- a. Per §46.116 (a)(2) Without this information a woman is placed in unnecessary peril while the Premarin™ estrogens are being metabolized out over a period of many, many months.
- 7) At no time before, during, or after the trial were the recruited women informed of the possibility of physiologic replacement using Ovarian Replacement Therapy.
- a. Per §46.116 (a)(4) participants in a clinical trial must be informed of other treatments that provide a better outcome.

In conclusion, not only were the rights of the recruited women violated but the public trust, both lay and medical, was violated. The ethics of the NIH should have played a prominent role in how Premarin™ was advertised to recruit women for the WHI. At the NIH, HRT means HRT in every area of medicine except in the treatment of hypogonadism in women. This is unacceptable and a double standard. Hypogonadism, whether it is called menopause or not, whether it is felt or not, is very unhealthy when left untreated. Hormone replacement therapy is beneficial in every other area of medicine because it is physiologically based and replaces what is no longer being produced by the body. Any person suffering from hypogonadism that is offered HRT expects to receive physiologic replacement. Right now only a man with hypogonadism can expect and receive physiologic replacement in the proper ratio of estradiol, testosterone, and progesterone. Right now women can expect to receive a 1:10:100 ratio and instead receive a 20:1:5 ratio and not be told the truth, that Premarin™, whether it is called HRT, HT, ET or MHT, it is still not physiologic replacement and should not have been described as such.

Menopause is not a trivial health issue. It is the end result of organ failure and causes a very unhealthy medical condition called hypogonadism. In both women and men, hypogonadism, failure of the ovaries and failure of the testes, creates the very same symptoms and poor health. When a man is offered HRT by the NIH via a clinical trial he can expect, and receive, physiologic replacement and he is healthier for it. When a woman is offered HRT by the NIH she may expect, but will not receive, physiologic replacement and she is worse off for it. Women are not told that they are not receiving HRT, leading them to associate poorer health with HRT. This is in sharp contrast to HRT being beneficial in every other area of hormone replacement. The science is available to provide physiologic replacement for women and the NIH has chosen not to use it.

According the NIH Medline Plus Encyclopedia, the definition of hypogonadism is:

Alternative names:

Gonadal deficiency

Definition:

Hypogonadism is when the sex glands produce little or no hormones. In men, these glands (gonads) are the testes; in women, they are the ovaries.

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The need for gonadal hormones never goes away and untreated menopause is untreated hypogonadism. As long as the gonads are not producing gonadal hormones the condition exists. Hypogonadism is defined by the lack of sex hormones, estradiol, testosterone and progesterone and both sexes experience deficiency syndromes which adversely affect their health. What isn't the same is that the treatment for hypogonadism, HRT, for men is based on physiologic replacement and improves health status, while the treatment of hypogonadism for women is not based on physiologic replacement and has proven to be unhealthy.

In all other areas of endocrine medicine HRT is based on physiologic replacement and is proven to improve health status. The recruited women expected replacement because of their gonadal deficiency. Instead, they were lured with a promise of HRT for their hypogonadism because that is what made them eligible to participate in the WHI. Instead of receiving that they got another condition called hyperestrogenism combined with levels of testosterone and progesterone that would never occur naturally either with ovarian function or ovarian failure (see Figure 1). The recruited women exchanged one disease state for another and were never informed of it. Premarin™ may have been nicknamed HRT but the NIH had no obligation to call it HRT. The NIH had a responsibility to the lay and medical community to take hypogonadism and the public's trust seriously and it did neither. The NIH was not honest with the recruited women, which violated their federal right to know what was being given to them.

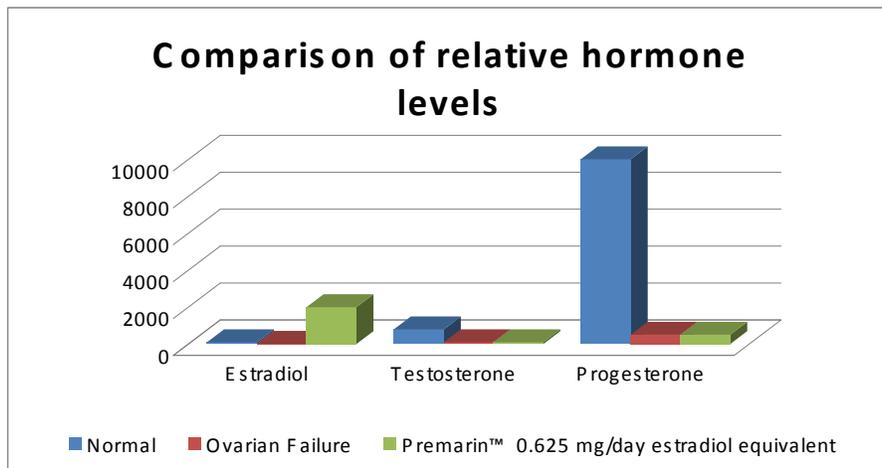


Figure 1: Comparison of relative hormone levels

Based on this information I am asking that an investigation be started into the misleading advertising for the WHI and the subsequent violations of the federal rights of the recruited women.

Thank you.

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