8. Undated correspondence to Dr. Rosenfield outlining the findings from the "2nd pre-review" (Tab M of June 22, 2005 submission).

(Correspondence created October, 2004)
Dear Dr. Rosenfield,

This letter is a summary of additional concerns and suggested changes that were raised during an initial review of your study. If possible, please respond by Monday, November 1st. We will be sending the study to a reviewer on November 2nd who will present it at the IRB meeting on Tuesday, November 9th.

1. **Age of Children:** In response to the IRB's question regarding the cutoff age of the youngest children to be enrolled into this study, the memo signed by Debbie Walsh, dated 10/12/04 states that "the onset of premature puberty can be as young as 6 months of age (now defined). The critical (diagnostic) samples can be obtained from children as small as 10kg".

   Please clarify if by this statement, you mean that you intend to study children (patients and controls) as young as 6 months of age if they weigh 10kg or more. The reviewer and myself had very strong concerns about enrolling such young children into this study. I anticipate that the Committee is going to feel the same way. If you have additional justification for why children this young should be enrolled, I suggest providing it prior to the meeting. The reviewer has also suggested that you provide evidence that safety with this testing has been confidently shown in children as young as 6 months of age.

   In addition, please provide references to confirm that the onset of premature puberty can be as young as 6 months of age.

2. **Supplemental Form C for healthy controls:** I noted that the Supplemental Form C for healthy controls indicates that this study is "no greater than minimal risk to the subject". However, the form C for patients indicates the study is greater than minimal risk with prospect of direct benefit.

   The reviewer felt that the study was greater than minimal risk in all children. I suggest revising Form C for healthy controls by indicating that the study does not meet any of the three criteria outlined on page 2 of the form. You could do this by revising your response to question II.A "Justification" on page 1 of the form. You should elaborate on the risks to the healthy controls in this section as well.

3. **IND Number:** The reviewer did not totally agree that an IND is not needed for use of Leuprolide. Given that your past studies have required an IND for use of Lupron, it's unclear why an IND would not be needed in this case as well. The Committee will have to be convinced that 1) the protocol is not intended to be reported to the FDA in support of a new indication for use or support any other significant change in the drug's labeling; 2) the protocol is not intended to support a significant change in the advertising for the product; and 3) the protocol does not involve a change in route

of administration or dosage level, use in a subject population and other change/factor that significantly increases the risks associated with the drug.
If you have additional information to help support these 3 criteria, I suggest submitting it with your response prior to the meeting.

4. **Sending Blood to off-site locations:** During my pre-review, I noted that the protocol and Supplemental Form G (for genetic testing) states blood samples will be sent to several off-site locations, such as University of Michigan and Massachusetts General Hospital for assays. In your response to my pre-review, you removed any reference to these off-site locations (see page 4 of the detailed narrative) and replaced it with "Serum will be stored for assay of inhibin –B, activin, and FAS."

   I also noted a check-box was added to the consent form regarding the use of subjects' blood at other centers for assays of new markers of puberty.

a. The reviewer and I both agreed that if the assays are being done for this study, you must clarify where this is being done. If they are being done at U of M and Mass General (as you initially indicated), this must be explicitly stated in the protocol and in the consent form. You must also have the doctors conducting those assays obtain IRB approval for their activities in this study.

b. If, on the other hand, the assays are not being done for this study, but are being run for other research purposes, you must make this very clear in the protocol. In addition, you must revise the consent form to provide more detail regarding the use of samples for future research studies. If you are involved in any other studies using these samples, you will also have to submit new protocols for these other research activities as well.

5. As adults are to be enrolled into this study, the reviewer felt that separate consent forms should be provided strictly for the adults. Currently, the consent form is written only for the parents.

6. Assent Form Changes: Please clarify what Leuprolide is in the 3rd paragraph. Please do not refer to it as a "medication" in paragraph 4.

7. Consent Form Revisions: The reviewer felt that the consent forms were not clear enough. The following changes are suggested to improve its readability.

   I. In the section entitled "What is involved in the study",
      A. Please consider utilizing bullets to outline study procedures rather than a paragraph form.

   "When your child is admitted to the crc, they will undergo the following tests when they first arrive:
   - x-ray

- urine pregnancy test

B. Please increase spacing between paragraphs.
C. Please add that ferrous sulfate will be given to subjects at the end of the study
D. In regards to the use of blood samples at other centers for assay of new markers of puberty, more information must be provided regarding the use of blood. For example, its unclear if these assays are for this study, or for other studies. It's unclear what identifiers will be sent with samples or what other types of PHI will be sent. Subjects must be told if they can withdraw permission for use of blood
E. In the "DNA sample" section, please define "cell lines". Please clarify what other "researchers" will be sent these samples.

II. In the "risks" section, please list any side effects from the iron supplement.

III. In the "Options" section, please clarify that Factrel is the normal test used for pubertal disorders and that they could undergo that testing.

IV. In the "Confidentiality" section, please add that information is sent to NIH since they help to fund the study.

V. If samples (i.e., blood and DNA) are being sent outside of U of C you must state who is receiving them, what type of PHI is sent, and why they are being sent.

VI. Please specify what "outside laboratories" samples may be sent to "when technology is more advanced". This is not discussed in the protocol. Please add this to the protocol.