From: Caposino, Paula
To: Powell, Cynthia M.
Cc: Milko, Laura V.
Subject: RE: G150258/S001
Date: Friday, March 10, 2017 7:11:04 PM
Attachments: image001.png

Hi Cynthia,
I understand your rational so I think its ok to ignore item #9 since WES is not being performed on the parents.
Thanks,
Paula
I would really appreciate updated documents as soon as possible since our decision is due on Thursday. Do you think I could get the documents by Tuesday?

From: Powell, Cynthia M. [mailto:powellcm@med.unc.edu]
Sent: Thursday, March 09, 2017 10:50 PM
To: Caposino, Paula
Cc: Milko, Laura V.
Subject: RE: G150258/S001

Hi Paula,

I want to let you know that I received your latest email. I will put together a response to your questions and requests by next week. I don't foresee any problems complying with your requested changes except for item #9. Since what we will be doing is targeted Sanger or PCR mutation testing of the parents in a CLIA clinical molecular laboratory and not WES and is not considered "screening", this is not applicable nor accurate information. If you can provide me with some clarification for #9 to help me understand this request and what it would refer to, since we are not doing whole exome sequencing or screening in the parents. I am afraid that it will cause confusion if we have to put it into the consent document.

Thank you,
Cynthia

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From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Thursday, March 09, 2017 3:05 PM
To: Powell, Cynthia M.
Cc: g150258-S001@docs.fda.gov; Milko, Laura V.
Subject: RE: G150258/S001

Hi Cynthia,
I am finalizing the review of your IDE supplement. Because of the information you provide in the emails dated March 6, 2017, we request the following changes to the protocol and to the informed consent document for the new cohort (parents). For ease of review, the text that I have copied and pasted from your documents appears in red.

For the protocol:

1. On page 28, regarding the following information: "In cases where the family cannot return for an in person visit, for example, if they have moved from the area, we will return results by telephone or Skype. The reports will be emailed securely before the call so parents can review it prior to our discussion." Please add that that the results will be emailed no more than 24 hours before the call (as agreed during our January 17, 2017 call to discuss G150258/R001).

2. Also on page 28, regarding the following text: "Relatives, primarily parents of children in the diagnosed cohort, may be asked to provide a saliva sample to help us interpret a variant or combination of variants that may provide an explanation for the child's symptoms. In the case of recessive conditions, like many of those tested for in NC NEXUS, there may be two genetic variants identified but the laboratory test cannot tell whether they are each present in different copies of the gene (inherited separately from each parent) or together in one copy of the gene (both inherited from the same parent). This information can be important in determining whether the variants that were detected fit with a recessive inheritance pattern for the condition. In other cases, the laboratory cannot immediately determine whether a variant is harmful or not. These variants are called "variants of uncertain clinical significance" (VUS). A VUS result means that a genetic variant was found, but there is not enough information about it to know for sure whether it cause disease or not.

   An estimated 50 relatives will be consented before a sample is obtained. The sample will be labeled with a NC NEXUS study number. When the testing is completed, the lab will report the results to a certified genetic counselor or medical geneticist on the research team by a secure email and they will report the results to the relative by phone. The child's clinical report will be amended to include the information learned as a result of testing; however, the relative will only be identified by his or her relationship to the participant and not by name. Parents will be counseled that the accuracy of the results depends upon knowing the true biological relationship of the relatives being tested and that if the stated father of a participant is not the true biological father, the interpretation may be incorrect."

   Please change "relative" to "parents" (per your email dated xxx). Also, in the email you indicated that 150 parents in the diagnosed cohort will be consented. Please make sure that your protocol lists the maximum number of parents that will be tested. Again, per your March 6, 2017 email, I understand that you anticipate a maximum of 150 parents. Regarding identifying the parent according to the relationship to the

child, we request that they be identified as "parent 1" and not "mother" or "father". Let me know if this makes sense to you. We want to make sure that the privacy of the parent is protected as much as possible.

3. On page 37, you state "We expect that relatives who are sampled will tolerate this procedure well." Again, please change "relatives" to parents.

4. For the changes proposed on page 40, please change "relatives" to "parents". Please remove the following paragraph "In the rare case that a sample from relative who is not the parent would be useful, the genetic counselor/medical geneticist will ask the parent to contact the relative and have the relative contact the study office to schedule a study visit at the CTRC. Consent will be obtained from the relative by the genetic counselor/medical geneticist and the sample obtained and processed as described above."

Regarding the informed consent for the parents: We have the following requests:

5. Please make sure to change the term "relative" to "parent" or "child" as needed throughout the informed consent document as needed.

6. On page 2, you indicate "Your sample will be tested only for the presence of absence of the specific variants(s) identified in your relative." and "Your sample will be tested only for the presence or absence of the VUS identified in your relative." These statements are a bit confusing. What is the difference between both? How will the parent know what they are consenting to?

7. You state "Your relative's clinical report will be amended to include the information learned as a result of your testing; however, you will only be identified by your relationship to your relative and not by your name." Please include an example of how the parents will be identified. Again, we request that you identify the parents as "parent 1" and "parent 2" or something similar.

8. We also recommend that you include information reminding the parents that they have made a choice (or can still make a choice—whichever is appropriate) about whether this clinically confirmed positive results (including any results from the parents) will become a permanent part of their child's UNC Hospitals electronic medical record (EMR).

9. Please also include the following information regarding a negative result "A negative screening result does not rule out the possibility that you have one or more variants that could lead to a genetic disorder. It is not known how often this may happen during this study and is one of the questions the research is designed to help answer. We cannot rule out the presence of any variant tested by genomic sequencing, also referred to as WES, even if the result is negative, since the rate of false negative results for WES in this research study is not known." or a similar statement.

10. Lastly, you state that the "accuracy of the results depends upon knowing the true

biological relationship of the relatives being tested. If the stated father of a participant is not the true biological father, the interpretation may be incorrect." It seems that you could remove the first part of the statement? Otherwise, you may want to change it to indicate that the accuracy of the interpretation of the result depends on…

11. If there is a chance that this testing could reveal non paternity (or misattributed paternity), we recommend that you add this to your informed consent document.

Please return an amended protocol and informed consent document as soon as possible. I would also appreciate it if you could confirm that you received this email and if you could let me know when I can expect a response.

Thanks,
Paula

From: Powell, Cynthia M. [mailto:powellcm@med.unc.edu]
Sent: Monday, March 06, 2017 2:22 PM
To: Caposino, Paula
Subject: RE: G150258/S001

Yes, that is correct.
C.

From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Monday, March 06, 2017 2:20 PM
To: Powell, Cynthia M. <powellcm@med.unc.edu>
Subject: RE: G150258/S001

Thanks for clarifying. This is very helpful. The supplement describes that relatives may be approached, but I understand from your email that this testing will be confined to parents and not other relatives correct?
Thanks,
Paula

From: Powell, Cynthia M. [mailto:powellcm@med.unc.edu]
Sent: Monday, March 06, 2017 2:17 PM
To: Caposino, Paula
Subject: RE: G150258/S001

Hi Paula,

1. We are estimating that a maximum of 150 parents total across both cohorts may need to be offered targeted gene variant testing in order to interpret the gene variant sequencing findings in their child.

2. The parents will already have watched the decision aid tool and met with a genetic counselor to review the study and receive answers to their questions prior to their infant being enrolled. Only parents of infants participating in the study will be asked for samples to help clarify the child's results (for example whether the variants are in cis or trans and whether inherited or de novo). The need for getting a blood or saliva sample from them will be explained during a direct face-to-face genetic counseling session reviewing the findings in their child. Of course the parents WILL NOT have whole exome sequencing themselves. The consent form has been approved by the UNC IRB and conforms to their requirements. Again, the parents will be meeting face-to-face with a genetic counselor and/or MD at the time they are asked to consent and provide a sample for targeted gene variant analysis.

3. The information from the parental testing will be included in the CLIA lab report generated for the child if a result of clinical significance is found. The targeted mutation testing is being done only to interpret the child's results (this is standard of care for clinical molecular genetic testing) so that results for the parent(s) will not be reported separately or put into their own medical record. Here are some examples:

   The amended report for the child would look something like this for a de novo for example:
   ADDENDUM
   Genotyping of this patient's unaffected parents were both negative for the XXX variant.
   The results of parental testing indicate that this variant is likely a de novo mutation that arose in this individual, although we cannot rule out the possibility of germline mosaicism in one of the parents. These results are supportive, but not definitive, evidence that XXX is pathogenic and provides a genetic explanation for Condition X (such as PKU) in this patient. Clinical correlation is recommended.
   OR if inherited;
   Testing of this patient's mother is positive for the XXX variant. This result makes it unlikely that this variant provides an explanation for any of this patient's clinical features.

   Please let me know if you have any additional questions.

   Thank you,
   Cindy

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From: Caposino, Paula [mailto:Paula.Caposino@fda.hhs.gov]
Sent: Monday, March 06, 2017 8:18 AM
To: Powell, Cynthia M. <powellcm@med.unc.edu>
Subject: G150258/S001

Good morning Cynthia,
I have a few questions regarding your informed consent process for the additional cohort.

1. You are proposing 50 relatives total across all babies (and not up to 50 per baby) correct?
2. Will the relatives watch the educational material explaining the study as part of the informed consent process? We are concerned that someone not well versed in genetics may have problems understanding the consent form.
3. You indicate that the results will be included in the relative's clinical report. Can you explain what the clinical report is? Will this information (the genetic information of the relative) end up in the babies' medical record?

Thanks,
Paula

Paula Caposino, Ph.D.
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