## Frye, Richard E

**From:** Wells, Thomas G
**Sent:** Monday, May 18, 2015 9:56 AM
**To:** Frye, Richard E
**Cc:** Brady, Barry; Brackeen, Margie I; Cornett, Lawrence E
**Subject:** RE: IRB #136002 Monitoring Visit Follow-up Letter

Richard,

As I said, I will check with Kim. Once I find out what is going on, I will either correct the report or meet with you to discuss how we can proceed. Part of the problem is that, with a large number of versions for the protocol and consent, it is very difficult to know which versions to monitor at which time for which subjects.

It would be more productive for John and Leanna to meet with Kim and go through the report together. I would be happy to be there and you are certainly welcome as well.

I am sorry if I misinterpreted the following statement "Until we respond, I do not see how another monitoring visit can be scheduled as such a visit would be aimed at following up on erroneous items." It took us about 5 months to get back to monitor your study after we were delayed by the compliance audit and your response to the IRB. There is a lot of ground to cover and my understanding was that Kim and Leanna were working together to fix things.

This study is very difficult to monitor because of the numerous changes to the protocol and consent. It would be better to work together rather than have your staff spend time preparing a large response. Let me know how you would like to proceed.

Tom

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**From:** Frye, Richard E
**Sent:** Monday, May 18, 2015 9:40 AM
**To:** Wells, Thomas G
**Cc:** Brady, Barry; Brackeen, Margie I
**Subject:** RE: IRB #136002 Monitoring Visit Follow-up Letter

Dear Dr Wells

I am very concerned that you have suggested that I am refusing a monitoring visit.

That indeed is not what I have said at all and I am not sure why you have interpreted it that way.

We have been very happy to work with you and have always complied with your requests.

I have pointed out that there are errors in the current monitoring reports (many errors from first glace) and I have suggested that it should be reviewed and corrected before another monitoring visit occurs.

As I have previously pointed out, if the reports are not correct than your group cannot properly follow-up on action items. This is something you should be concerned with and it is difficult to understand why this is not more of a concern of yours.

As we have brought up to you repeatedly, there continues to be many errors in Kim's monitoring reports. This is something you said would be resolved but appears that it has not. We have brought this up for over a year without resolution.

Richard E. Frye, M.D., Ph.D.
Director of Autism Research
Director of The Autism Multispecialty Clinic
Co-Director of The Neurometabolic Clinic
Associate Professor of Pediatrics
Child and Behavioral Neurologist
Fellowship Trained in Behavioral Neurology, Learning Disabilities and Psychology
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Slot 512-41B, Room R4041, 13 Children's Way, Little Rock, AR 72202
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Autism Multispecialty Clinic Coordinator, Marie Tippett, Phone 501-364-5465, Fax: 501-978-6483
Scheduling Line: 501-364-4000 Option 6 for Pod 6, email: apptctrpod6@archildrens.org
AAA Website: www.arkansasautismalliance.org
CFD Website: www.cfdresearch.org

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**From:** Wells, Thomas G
**Sent:** Monday, May 18, 2015 9:28 AM
**To:** Frye, Richard E
**Subject:** RE: IRB #136002 Monitoring Visit Follow-up Letter

Let me meet with Kim and see what the issues are. I will get back to you. Refusing to have monitoring visits is not an option… according to the regulations, failure to agree to monitoring would constitute non-compliance with FDA regulations. As sponsor, UAMS would have to contact the FDA and report ongoing non-compliance; at the very least the FDA would suspend enrollment in your study and may conduct an audit. No one wants that!

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**From:** Frye, Richard E
**Sent:** Friday, May 15, 2015 4:05 PM
**To:** Wells, Thomas G
**Cc:** Slattery, John C; Delhey, Leanna M.
**Subject:** FW: IRB #136002 Monitoring Visit Follow-up Letter

Hi Dr Wells

From looking over this at first glance it is clear that many of the items that are being called deviations are not.

For example, we specifically sat down with you and the regulatory group to word the protocol to reduce deviation. For example, the protocol is worded so that when questionnaire from teachers are not obtained it would not be a deviation, yet Kim has clearly labeled these deviations.

Another obvious example is that the ADI-R evaluation is NOT necessary for eligibility criteria, it is just one test that can be used to establish eligibility. In addition, the protocol specifically says that when the ADI-R is used would be scheduled prior to the first dose, not completed. Yet, Kim continues to make statements about its use as part of the eligibility of participants as a deviation, which it is not.

Another obvious error is that the protocol says that other therapies will be "attempted" to remain constant. The protocol says nothing about withdrawing patient from the study if their therapies change.

We really thought that we were going to have a fresh start but it appears that we are back to the same old mess.

John and Leanna will go through each item in detail and respond to each item individually.

Until we respond, I do not see how another monitoring visit can be scheduled as such a visit would be aimed at following up on erroneous items.

Richard E. Frye, M.D., Ph.D.
Director of Autism Research
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Child and Behavioral Neurologist
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Scheduling Line: 501-364-4000 Option 6 for Pod 6, email: apptctrpod6@archildrens.org
AAA Website: www.arkansasautismalliance.org
CFD Website: www.cfdresearch.org

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**From:** Berry, Kimberly J
**Sent:** Friday, May 15, 2015 3:41 PM
**To:** Frye, Richard E
**Cc:** Slattery, John C; Delhey, Leanna M.
**Subject:** IRB #136002 Monitoring Visit Follow-up Letter

Hi Dr. Frye –

Please see the attached monitoring visit follow-up letter for the above-mentioned protocol. The original is on the way Leanna Delhey via campus mail for inclusion in the regulatory files. The next monitoring visit is scheduled for June 1-2 & 4-5, 2015. I am working on the list of subject files to be reviewed on each day and will include this information in the confirmation letter. If you have any questions, please let me know.

Thank you,
Kim

Kim Berry, CCRP, CRS
Monitoring Manager
UAMS Office of Research Regulatory Affairs – Monitoring Unit
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 115309

**FULL CLINICAL HOLD**

Lawrence E. Cornett, M.D., Ph.D.
Vice Chancellor for Research
University of Arkansas for Medical Sciences
4301 West Markham St., Slot 813
Little Rock, AR 72205

Dear Dr. Cornett:

Please refer to your Investigational New Drug Application (IND) submitted April 20, 2012, received April 24, 2012, under section 505(i) of the Federal Food, Drug, and Cosmetic Act for folinic acid (compounded leucovorin USP).

We also refer to your e-mail communication dated June 18, 2015, providing a courtesy copy of your June 17, 2015 amendment informing the Agency of compliance at the study site.

CAPT Paul David notified you through the June 18, 2015, telephone conversation with Lyndsey Griggs Avery, that the study you proposed is on clinical hold and may not be initiated. The following are the specific deficiencies and the information needed to resolve the deficiencies.

21 CFR 312.42(b)(2)(i): Unreasonable and significant risk of illness or injury to human subjects

Your communication states the following compliance violations:

- Lack of PI oversight
- Not following the protocol
    - Enrolling of ineligible subjects without obtaining a waiver from the medical monitor
    - Not dose reducing appropriately per protocol; nor subsequently withdrawing subjects per protocol
- Potential for adulterated drug product

For this clinical hold to be lifted, you must fully elaborate on the above deficiencies, and inform the Agency how these deficiencies have been resolved.

Until you have submitted the required information and we notify you that you may initiate the clinical study, you may not legally initiate or resume clinical studies under this IND.

Please identify your response to the clinical hold issues as a "**CLINICAL HOLD COMPLETE RESPONSE**". An incomplete response will not start the review clock. Your complete response submission should reference, by date, any information previously submitted necessary to fully respond to these clinical hold issues. To facilitate a response to your submission, submit this

information in triplicate to the IND. In addition, send a copy of the cover letter to CAPT Bill Bender.

Following receipt of your complete response to these issues, we will notify you of our decision within 30 days.

If we have additional comments or information requests not related to this clinical hold, we will notify you. Your responses to any non-hold issues should be addressed in a separate amendment to the IND.

Please cite the IND number listed above at the top of the first page of any communications concerning this application. Each submission to this IND must be provided in triplicate, an original and two copies. Please include three originals of all illustrations which do not reproduce well. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call CAPT Bill Bender, Regulatory Project Manager, at (301) 796-2145.

Sincerely,

*{See appended electronic signature page}*

Mitchell V. Mathis, M.D
CAPT, USPHS
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research