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

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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Neurology Specialty Nurse, General Line 501-364-1850, Fax: 501-364-6077, Meg Cash Phone: 501-364-4818
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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

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!

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.

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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

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
researchservices.uams.edu

P + 1 501 686 7976 | C +1 501 416 8054 | F + 1 501 526 6276
4301 W. Markham St. #813, Little Rock, AR 72205
kjberry@uams.edu

Frye, Richard E

From: Brackeen, Margie I
Sent: Wednesday, May 20, 2015 8:29 AM
To: Wells, Thomas G
Cc: Frye, Richard E; Brady, Barry
Subject: Proposed Monitoring Management Plan
Attachments: Proposed Study Monitoring Management Plan Frye.docx

Good Morning Dr. Wells,

I spoke to Dr. Frye this week and received your email with regard to the monitoring of Dr. Richard Frye's study "A Folinic acid intervention for ASD links to folate receptor autoimmunity redox metabolism (IRB#136002/IND#115309)". In order to help facilitate this process, we would like to propose a change in the monitoring practices of this study for at least a three month period.

I have attached a draft proposal and Barry will be chatting with you about it more this morning. Since this is just a proposal it is definitely open for discussion, please let us know if you have anything you would like to change/add or if you would like to discuss further.

Thanks!

~Margie

Margie Brackeen, CHRC
Regulatory Compliance Specialist

Arkansas Children's Hospital Research Institute
13 Children's Way | Slot 842| Little Rock, AR 72202
501.364.3586 direct | 501.364.7373 office | 501.364.2705 fax
brackeenmargiei@uams.edu

http://achri.archildrens.org/

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archildrens.org

FOLLOW ACH:

Study Monitoring Management Plan

Study title: A Folinic acid intervention for ASD links to folate receptor autoimmunity redox metabolism (IRB#136002/IND#115309)

Principal Investigator: Richard Frye, MD

Participants in Management Plan:

Name: Dr. Frye (& staff)
Role: Principal Investigator (PI)/Study Origin/Management
Responsible Party: Richard Frye, MD

Name: UAMS Office of Research Regulatory Affairs (ORRA) – Monitoring Unit
Role: Study monitoring of FDA regulated study
Responsible Party: Tom Wells, MD

Issues to be resolved:

ORRA
Continued non-compliance as reported in monitoring reports
Difficulty in scheduling monitoring visits
Study Group
Perceived errors in monitoring reports by the PI
Communication issues with the monitoring unit

3-Month Management Plan:

1. Improve study group compliance including (but not limited to) 2-hours of mandated study staff continuing education in research recordkeeping and informed consent procedures to be conducted by the ACHRI Regulatory Compliance Specialist.
   a. To be scheduled with study staff within 30-days of plan execution

2. Pre-schedule once-per-month monitoring visits during management period with a monitoring schedule to be reevaluated after that time.
   a. To be scheduled with study staff within 10 days of plan execution

3. ACHRI Regulatory Compliance Specialist attends all monitoring visits during management period.
4. All monitoring reports during management period will be reviewed with study staff in person with ACHRI Regulatory Compliance Specialist present.
   a. All errors in monitoring reports will be corrected or notated by ORRA.

5. All monitoring reports from January 2014 through present will be reviewed at a combined meeting of the Frye study staff and monitoring group
   a. All report errors will be corrected or notated for each report
   b. To be scheduled and completed within 60 days of plan execution

6. All 136002 study related communication between the monitoring unit and the study group will include the ACHRI Regulatory Compliance Specialist during the 3-month management period by carbon copy on email, notification of pertinent phone conversations, presence at meetings, etc.

7. Set a meeting for 1st week of September 2015 to evaluate management plan, set new goals, or continue without any further intervention.
   a. To be scheduled within 30 days of plan execution

Signatures:

_____ _____

Richard Frye, MD –Principal Investigator Date

_____ _____

Tom Wells, MD Date
Director Office of Research Regulatory Affairs

Office of Research Regulatory Affairs

4301 W. Markham St., #813
Little Rock, AR 72205-7199

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UAMS
UNIVERSITY OF ARKANSAS FOR MEDICAL SCIENCES

June 11, 2015

Richard E. Frye, M.D., Ph.D
Director of Autism Research
Director of The Autism Multispecialty Clinic
Associate Professor of Pediatrics
Arkansas Children's Hospital Research Institute / University of Arkansas for Medical Sciences
13 Children's Way, Slot 512-41B, Room R4041
Little Rock, AR 72202

Dear Dr. Frye and Arkansas Children's Hospital Research Institute:

The University of Arkansas for Medical Sciences (UAMS), as Sponsor of IND 115309, is responsible for ensuring study compliance, ensuring that the investigation is conducted in accordance with the investigational plan, as well as maintaining control of the investigational drug. Outlined below are the requirements that must be met prior to the consideration of enrolling new subjects:

- An outside, independent monitor (to be approved by the Sponsor) will be hired to review all study records and data collected to date. ACHRI and the study PI have indicated that the Sponsor's monitors may be biased doe to previous harassment claims against the PI. This external study monitor(s) will be financially supported by Arkansas Children's Hospital Research Institute and/or the PI. The external study monitors are to provide a complete and final monitoring report to the Sponsor and ACHRI for all subjects consented to the study to date.
- Monitoring visits conducted by the Sponsor will resume on a monthly basis, unless no study activity has occurred since the last visit. The Sponsor's study monitors will make this determination.
- Subjects currently on reduced drug dosages must have a new, official prescription written by the PI and issued to the ACH Research Pharmacy for the appropriate drug dosages to be issued.
- The study status in ClinicalTrials.gov needs to be changed to 'suspended' immediately.
- The Principal Investigator, Research Pharmacist, and study staff are required to participate in intensive clinical research training provided by the Sponsor, Arkansas Children's Hospital Research Institute, and/or any other party deemed appropriate by the Sponsor.
- No new study sites will be initiated under IND 115309 while the study is suspended.
- The study is required to have a Data Safety and Monitoring Board (DSMB) that is to include an external statistician and external expert in the area of autism. These external members are not to be affiliated with the study or ACH/ACHRI.
- Re-education of the medical monitor is to be provided by the Sponsor.
- Once the study is allowed to proceed with new enrollment, all inclusion/exclusion criteria for each subject must be reviewed and approved by the medical monitor prior to signing the informed consent form.
- Timely reporting/review of all AEs/SAEs by the PI must begin immediately.

Office of Research Regulatory Affairs

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www.uams.edu/rsc

UAMS
UNIVERSITY OF ARKANSAS
FOR MEDICAL SCIENCES

Sincerely,

Lawrence E. Cornett, PhD
Vice Chancellor for Research

Cc:
ORRA file

Frye, Richard E

From: Frye, Richard E
Sent: Saturday, June 13, 2015 6:24 PM
To: Cornett, Lawrence E
Cc: Brady, Barry; Brackeen, Margie I; Jacobs, Richard F; Gregory Kearns (gregorykearns@me.com)
Subject: Folinic Acid Clinical Trial

Tracking:

Recipient	Delivery	Read
Cornett, Lawrence E	Delivered: 6/13/2015 6:24 PM	Read: 6/13/2015 7:04 PM
Brady, Barry	Delivered: 6/13/2015 6:24 PM	
Brackeen, Margie I	Delivered: 6/13/2015 6:24 PM	Read: 6/13/2015 10:46 PM
Jacobs, Richard F	Delivered: 6/13/2015 6:24 PM	
Gregory Kearns (gregorykearns@me.com)		
Slattery, John C	Delivered: 6/13/2015 6:24 PM	Read: 6/13/2015 6:29 PM

Dear Dr Cornett

Thank you for your meeting last Thursday.

I wanted to let you know that we take any concerns by the monitoring and regulatory group very seriously.

From my understanding there was some questions regarding whether all of our subjects met the inclusion-exclusion criteria and whether we handled adverse effects in a manner consistent with the protocol and FDA regulations.

We are confident that all of our procedures were within the approved protocol and FDA guidelines. In order to support this notion I will send you two documents.

The first document is a pdf of the inclusion / exclusion checklist for all participants that entered the study. You will see from this document that we consistently and systematically assure that each participant meets inclusion criteria using a checklist of each and every inclusion-exclusion criteria based on the protocol version that the participant is consented. Although I have not received the monitoring report, I believe the confusion regarding the inclusion / exclusion criteria by the monitor is due to the application of the incorrect version of the protocol to the particular participant, although I will have to review the finding in order to understand the concern.

The second document is a summary of the adverse effect for Phase 2 of the study (the double blind placebo controlled phase) for each and every participant. We have reviewed every file and provided documentation of evaluation and action taken for each participant based on any adverse effect noted. This document will now be placed in each file to document the adverse effect course throughout Phase 2 of the trial so that any monitor can transparently understand the evaluations and decisions made on each and every patient. The documentation demonstrates that all participants were treated within the protocol and FDA guidelines.

We will note that the study has had no serious adverse events. The majority of the potential adverse effects were rated as mild and the majority resolved spontaneously. We have data on safety based on the single-site portion of the study since we have unblinded those participants for analysis. The analysis of the adverse effects in the single-site portion of the trial has demonstrated no difference in adverse effects between folinic acid and placebo. In addition, the three individuals that underwent dose reduction in the single-site portion of the trial were all on placebo not folinic acid.

We will also note that folates are considered extremely safe and well tolerated and that folinic acid is used routinely at high-doses in select patient populations with very few known adverse effects. In addition, folinic acid is water soluble, so there is no toxic buildup of the treatment in the body.

Over the next week we will be reviewing the files to summarize the adverse effects in phase 3 (the open label extension) in order to provide more transparent documentation of the adverse effect monitoring.

I hope this information is reassuring.

Thank you for your time and attention to this matter.

Richard E. Frye, M.D., Ph.D.
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Director of The Autism Multispecialty Clinic
Co-Director of The Neurometabolic Clinic
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AAA Website: www.arkansasautismalliance.org
CFD Website: www.cfdresearch.org

Frye, Richard E

From: Frye, Richard E
Sent: Saturday, June 13, 2015 6:25 PM
To: Cornett, Lawrence E
Cc: Brady, Barry; Brackeen, Margie I; Jacobs, Richard F; Gregory Kearns (gregorykearns@me.com)
Subject: Folinic Acid Clinical Trial
Attachments: FAS_I-E_061215.pdf

Tracking:

Recipient	Read
Cornett, Lawrence E	Read: 6/13/2015 7:46 PM
Brady, Barry	
Brackeen, Margie I	Read: 6/15/2015 8:53 AM
Jacobs, Richard F	Read: 6/13/2015 6:26 PM
Gregory Kearns (gregorykearns@me.com)	

Dear Dr Cornett

Attached are the Inclusion and Exclusion criteria for each and every patient.

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
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To: Cornett, Lawrence E
Cc: Brady, Barry; Brackeen, Margie I; Jacobs, Richard F; Gregory Kearns (gregorykearns@me.com)
Subject: Folinic Acid Clinical Trial

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We will also note that folates are considered extremely safe and well tolerated and that folinic acid is used routinely at high-doses in select patient populations with very few known adverse effects. In addition, folinic acid is water soluble, so there is no toxic buildup of the treatment in the body.

Over the next week we will be reviewing the files to summarize the adverse effects in phase 3 (the open label extension) in order to provide more transparent documentation of the adverse effect monitoring.

I hope this information is reassuring.

Thank you for your time and attention to this matter.

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Frye, Richard E

From: Frye, Richard E
Sent: Saturday, June 13, 2015 6:27 PM
To: Cornett, Lawrence E
Cc: Brady, Barry; Brackeen, Margie I; Jacobs, Richard F; Gregory Kearns (gregorykearns@me.com)
Subject: Folinic Acid Clinical Trial
Attachments: FAS_AE_61315.pdf

Tracking:

Recipient	Delivery	Read
Cornett, Lawrence E	Delivered: 6/13/2015 6:27 PM	Read: 6/15/2015 7:20 AM
Brady, Barry	Delivered: 6/13/2015 6:27 PM	
Brackeen, Margie I	Delivered: 6/13/2015 6:27 PM	Read: 6/13/2015 10:46 PM
Jacobs, Richard F	Delivered: 6/13/2015 6:27 PM	Read: 6/13/2015 6:29 PM
Gregory Kearns (gregorykearns@me.com)		

Dear Dr Cornett:

Attached are summarizes of the adverse effects monitoring for each and every participant that received treatment in the double-blind placebo-controlled portion of the trial.

Richard E. Frye, M.D., Ph.D.
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Director of The Autism Multispecialty Clinic
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Frye, Richard E

From: Jacobs, Richard F
Sent: Monday, June 15, 2015 5:43 PM
To: Cornett, Lawrence E
Subject: RE: Deadline
Attachments: ACHRI Response to IND 115309.pdf; UAMS Sponsor of IND 115309.pdf

Importance: High

Larry

Attached is the letter from you to ACHRI and our response

There are some additional items for our discussion tomorrow; let me know a good time to call (or at least the times to avoid)

Thank you

Dick

From: Cornett, Lawrence E
Sent: Monday, June 15, 2015 3:27 PM
To: Jacobs, Richard F
Subject: RE: Deadline

Dick,
The second option would work best for me. Written response today and we talk tomorrow. Thanks.
-Larry

From: Jacobs, Richard F
Sent: Monday, June 15, 2015 3:23 PM
To: Cornett, Lawrence E
Subject: Deadline
Importance: High

Larry

I met with Dr. Frye and Marie Bracken this afternoon

We are working up our response and requests/recommendations to present to you

I have also gone over the entire response with Greg Kearns

I have a meeting from 4-5pm that is scheduled quarterly and needs my attention

So, I am asking what is your "end of work" on Monday? I can discuss with you by phone before 4pm (now is good) and then get you our written response after 5pm
Or
I can get you our written response as soon as possible (could be later than 5pm today) and be available to talk tomorrow

Whichever way you want to proceed is fine with me

Just let me know

Dick

Richard F. Jacobs MD, FAAP, FIDSA
Robert H. Fiser, Jr., M.D. Endowed Chair in Pediatrics
Professor and Chairman, Department of Pediatrics
University of Arkansas for Medical Sciences
Pediatrician-in-Chief, Arkansas Children's Hospital
Office: 501-364-5262

Arkansas Children's Hospital Research Institute
13 Children's Way • Little Rock, Arkansas 72202 • 501-364-7373 • TDD 501-364-1184 • FAX 501-364-2705

June 15, 2015

Dr. Lawrence Cornett, Ph.D.
Vice Chancellor for Research
University of Arkansas for Medical Sciences
4301 W. Markham Street
Little Rock, AR 72205

Dear Dr. Cornett,

I recently consulted with Dr. Richard Frye, Dr. Greg Kearns, Barry Brady, and Margie Brackeen of ACHRI concerning the remediation plan presented by your group to Dr. Frye on June 11, 2015 regarding IND115309 (IRB 136002) for which UAMS serves as sponsor. With varying input from all of these sources, I have formulated a response on behalf of ACHRI.

First, we would like to formally call into question the findings of the various monitors who have been assigned to this study during its three year lifespan. From the apparent lack of complete monitoring by the first monitor during its first months to the continued lack of communication between the current monitor and the principal investigator of this study and monitor's apparent conflict of interest, we speculate that the issues of this study are not completely the result of the investigator and his staff. These issues were not appropriately addressed in the meeting since the monitor in question was present, making it difficult for the group to discuss Dr. Frye's impressions of her activities at length. Therefore, we feel that the responsibilities of the UAMS monitoring group and Office for Research Regulatory Affairs as a whole should be examined in this discussion as well as those of the investigator.

Secondly, Dr. Frye and his staff realize that, as with most studies, his study had some recordkeeping shortcomings and lack of documentation. As a response to the current inquiries, they have been working to clarify study documentation, re-evaluating adverse events, and organizing their files over the past several days. Dr. Frye contacted you this weekend to show you the progress they have made in this regard. He will continue with the timely reporting/review of all AEs/SAEs going forward. Dr. Frye also agrees to pause all enrollment of new subjects for this study until these issues have been resolved. He will, however, continue to keep the current subjects on study until they have completed study procedures.

Finally, we would like to request some alterations to the plan that you presented on Thursday.

1. We are willing to engage an outside independent monitor (approved by the sponsor) at our own expense to review the records of this study.
    a. We would like to stipulate, however, that this outside monitor only review the documents insomuch as to respond to the findings of the UAMS monitors in their official monitoring reports.
    b. Since UAMS originally agreed to be the sponsor of this study, had the study been monitored appropriately, there would be no need to re-monitor those files already reviewed.
    c. We do not feel that ACHRI or the PI of this study should be required to shoulder the burden of a function that UAMS already agreed to provide.
    d. If the UAMS monitoring group would like to contribute funds to have the entire study reviewed, we would entertain that request.
    e. We will ensure that this monitoring is conducted and completed before the annual report for this study is due on July 25, 2015.
2. **We would request that the study suspension with the FDA**; the clinicaltrials.gov status change; the DSMB, procedures for the medical monitor; and study staff training; **be reevaluated after the report from the independent monitor can be reviewed.**
3. We agree to monthly monitoring visits by the sponsor monitors going forward, although we request that Ms. Berry is not one of those monitors.
4. We would like to request that, since everyone agrees the study is progressing better now than it ever has, the remote sites (Texas and California) be allowed to open as study sites and proceed with enrollment.

Due to the low risk of serious adverse events with this study compound, we believe that this study does not present an immediate safety risk and may actually present a prospect of benefit to this very difficult to treat autistic population. With this in mind, we feel that this plan going forward will meet the burden of compliance while maintaining a fair and just review for all involved. Feel free to contact us, we would be happy to discuss further.

Sincerely,

/Richard D Jacobs/

Richard Jacobs, M.D.

(Enclosure)

Frye, Richard E

From: Brackeen, Margie I
Sent: Tuesday, June 16, 2015 2:48 PM
To: Jacobs, Richard F; Frye, Richard E; Brady, Barry
Subject: RE: Meeting minutes 6.11.15 ORRA and ACH discussion of IND 115309
Attachments: Dr. Frye Meeting Minutes with comments.docx

Hi Dr. Jacobs,

I am attaching the minutes document with Dr. Frye's comments as well as one of my own. Please let me know if you have any questions.

Items that I have in my notes that do not appear in her minutes include:

1. Per Lyndsey Avery: UAMS has not filed the annual report for this study yet and she stated that last year's annual report for this study may not have been entirely accurate.
2. Dr. Kearns discussed the topic of "abandonment of an IND/IDE" for which there is case law around the termination of a regulated study
3. Larry Cornett: Said that UAMS was only having this meeting to keep ACHRI informed—not for ACHRI to participate in the decisions
4. Dr. Kearns pointed out that the FDA would visit both campuses and therefore ACHRI should have a say in the proceedings.
5. Dr. Cornett agreed that ACHRI and UAMS do share in the liability in the outcome of these proceedings.

~Margie

From: Jacobs, Richard F
Sent: Tuesday, June 16, 2015 9:14 AM
To: Frye, Richard E; Brady, Barry; Brackeen, Margie I
Subject: RE: Meeting minutes 6.11.15 ORRA and ACH discussion of IND 115309

Richard

I sent my response to Larry

I will be talking to him at 3pm today

If you want to write up the specific points of disagreement with the minutes and send to me, I will review for my conversation with Larry today

I would not send anything to UAMS until after I see how the phone call goes and UAMS's willingness to take our recommendations

Dick

From: Frye, Richard E
Sent: Tuesday, June 16, 2015 7:58 AM
To: Brady, Barry; Brackeen, Margie I
Cc: Jacobs, Richard F
Subject: Fwd: Meeting minutes 6.11.15 ORRA and ACH discussion of IND 115309

I would have to say some of these are a misrepresentation.

I said I did not think the status should be changed. The way it is worded implies that I am refusing to change it.

As far as I know there was only one major concern in the audit and it was not using a suicidality form that we did not know about and the monitoring group did not inform us about despite many reviews of our records.

I did not say that video consents were obtained after the fact, I just pointed out that all subjects had signed video consents and that the were also verbally consented at the time of video taping.

iPhone (email may have been dictated but not read so please excuse any misspellings, grammatical error, punctuation mistakes or homophones)

Begin forwarded message:

> **From:** "Avery, Lyndsey G" <LGAvery@uams.edu>
> **Date:** June 16, 2015 at 7:43:25 AM CDT
> **To:** "Wells, Thomas G" <WellsThomasG@uams.edu>, "Cornett, Lawrence E" <CornettLawrenceE@uams.edu>, "Ironside, Shawn B" <SBIronside@uams.edu>, "Berry, Kimberly J" <KJBerry@uams.edu>, "Avery, Lyndsey G" <LGAvery@uams.edu>, "Brackeen, Margie I" <BrackeenMargieI@uams.edu>, "Brady, Barry" <BradyBarry@uams.edu>, "Frye, Richard E" <REFrye@uams.edu>, "Holloway, Amanda" <HollowayAmanda@uams.edu>, "Parker, Erin E" <ParkerEE@archildrens.org>
> **Subject: Meeting minutes 6.11.15 ORRA and ACH discussion of IND 115309**
>
> To all:
> Attached are the meeting minutes from our discussion on June 11th. Please let me know by close of business today if I have misinterpreted anything.
>
> Please forward as appropriate to Dr. Kearns. I do not have an email for him.
>
> Kind Regards,
> Lyndsey
>
> Lyndsey Griggs Avery, RAC, CCRP
> Regulatory Affairs Manager
> Office of Research Regulatory Affairsjac
> University of Arkansas for Medical Sciences
> 4301 West Markham St., Slot 813
> Little Rock, AR 72205
> Direct Phone: (501) 686-5190
> Fax: (501) 526-6272
> LGAvery@uams.edu

Office of Research Regulatory Affairs (ORRA)
Discussion of IND 115309 Suspension for Continued Investigator Non-Compliance
Arkansas Children's Hospital Research Institute and Dr. Richard Frye (PI)
June 11, 2015 / 11:00 - 12:30 pm
ACHRI 3rd floor conference room

Attendees: L. Avery (ORRA), K. Berry (ORRA), S. Ironside (ORRA), T. Wells (ORRA), L. Cornett (VCR), M. Brackeen (ACHRI), B. Brady (ACHRI), G. Kearns (ACHRI), E. Parker (ACH Compliance Officer), A. Holloway (Institutional Compliance –ACH)

Purpose of meeting:
Inform ACHRI and Dr. Richard Frye (study PI) that UAMS has been unable to secure compliance over the study site as the IND Sponsor; thus, not meeting the Sponsor obligations under 21CFR312. The study is to be suspended by Dr. Cornett, the Sponsor's representative, on Tuesday morning, 6/16/15. ACHRI and the PI have until close of business Monday, 6/15/15, to decide if they would rather terminate the study. A letter from the Sponsor outlining all of the items required to be address by ACHRI and PI was given at this meeting. On Tuesday, 6/16/15, the FDA will be notified of the Sponsor's action.

Meeting minutes:

- Dr. Cornett stated there were only two options for proceeding: termination or suspension to new enrollment.
- Dr. Cornett explained that for investigator-initiated studies conducted under an IND, the University of Arkansas for Medical Sciences (UAMS) acts as the Sponsor. UAMS does not allow Sponsor-Investigators, where the Sponsor and the Investigator serve as the same person.
- Dr. Cornett said he was concerned the study protocol is not being followed, potentially jeopardizing all of research being conducted on UAMS' campus.
- Dr. Wells mentioned that UAMS had a previous study suspended to new enrollment. UAMS had a teleconference with FDA, and the study was put on partial clinical hold. The principal investigator ended up leaving UAMS. The study was closed for this reason.
- It was clarified that the Sponsor would tell FDA the study was being suspended to new enrollment. Subjects currently receiving investigational product would be allowed to continue. FDA can always disagree and issue a different requirement.
- L. Avery discussed the process of notifying FDA, and FDA being required by law to put the IND on clinical hold.
- IND Sponsor vs. funding source sponsor was clarified. UAMS is the IND Sponsor.
- Dr. Cornett mentioned the University of Minnesota incident where a participant in a research drug study committed suicide. FDA is currently investigating.
- Dr. Kearns expressed several times that ACHRI and UAMS need to be mindful in their approach as both institutions have an interest in maintaining existing relationships.
- Dr. Frye has a publication in 2nd draft with JAMA. Dr. Cornett said that UAMS is silent on this matter. It is Dr. Frye's responsibility to handle.

- A list prepared by the Sponsor was presented to ACHRI and Dr. Frye. All of these items must be addressed. The items are non-negotiable. This is an effort on behalf of the Sponsor to develop a plan for moving forward.

Margie: I checked with Dr. Frye and Amanda Holloway who were both in the meeting and we all agree that the highlighted item above was not directly stated in the meeting. They may have insinuated that the items were non-negotiable but it was not stated outright.

- Dr. Frye said that he was not changing the status in clinicaltrials.gov

Dr. Frye: I said I did not think the status should be changed. The way it is worded implies that I am refusing to change it.

- Dr. Frye did not agree that the study should be suspended. He stated that there were no serious adverse events that have occurred, the protocol has always been followed, and all subjects have met the inclusion/exclusion criteria.
- Dr. Frye did not agree that the study needed a Data Safety and Monitoring Board. NIH/FDA did not require one.
- Dr. Frye stated he has already been trained and does not need any re-training. To imply this meant that the Sponsor was questioning his qualifications.
- Dr. Frye explained that per his own calculations, 85% of one of the Sponsor's monitoring reports was inaccurate, and around 56% of another monitoring report was also inaccurate.
- ACH Institutional Compliance conducted a for-cause audit of the study. The audit was performed on 10 subjects and reflected approximately 12% of the total study population. Major findings were discovered during the audit. However, the UAMS IRB deemed it as minor non-compliance.

Dr. Frye: As far as I know there was only one major concern in the audit and it was not using a suicidality form that we did not know about and the monitoring group did not inform us about despite many reviews of our records.

- It was discussed by Dr. Wells and Dr. Cornett that because Dr. Frye did not agree with the Sponsor's monitors, an external, independent monitor will be brought in to monitor all of the study activity to date. This is to allow for an unbiased inspection. If the PI choses termination, no external monitoring group will inspected/review the records.
- Videotaping without consent was discussed by Dr. Wells as one of the many issues of non-compliance. Dr. Frye said that all subjects were verbally consented and informed consents were obtained after the fact.

Dr. Frye: I did not say that video consents were obtained after the fact, I just pointed out that all subjects had signed video consents and that they were also verbally consented at the time of videotaping.

Summary:

ACHRI is to let Dr. Cornett know by close of business 6/15/15 whether the study is to be terminated or suspended to new enrollment. Dr. Frye disagrees with the Sponsor and does not feel there are any

reasons to suspend/terminate this study. ACHRI and UAMS agree that bringing an external, independent monitor to review the records will help resolve any issues between the Sponsor's study monitors and Dr. Frye.

Frye, Richard E

From: Jacobs, Richard F
Sent: Tuesday, June 16, 2015 3:26 PM
To: Frye, Richard E; Brackeen, Margie I; Brady, Barry; Gregory Kearns (gregorykearns@me.com) (gregorykearns@me.com)
Subject: UAMS

I discussed the case with Dr. Cornett

We did not have agreement on the monitor's findings but he was willing, by the end of the conversation, to agree to think about our proposal/requests

He made it clear that the independent monitor would have to be approved by him and would work for him (as the Sponsor)

I just talked to Margie, who will call Barry, and make contact for a potential monitor
The clock is ticking for this report of the UAMS monitor's alleged findings before the 60 day time line from May 26

I also have a call into Greg to see if we can get his help with potential names

Larry will call me back tomorrow with his response to our letter and his decision

More tomorrow

Dick

Richard F. Jacobs MD, FAAP, FIDSA
Robert H. Fiser, Jr., M.D. Endowed Chair in Pediatrics
Professor and Chairman, Department of Pediatrics
University of Arkansas for Medical Sciences
Pediatrician-in-Chief, Arkansas Children's Hospital
Office: 501-364-5262

Frye, Richard E

From: Jacobs, Richard F
Sent: Wednesday, June 17, 2015 10:52 AM
To: Frye, Richard E; Brady, Barry; Brackeen, Margie I; Gregory Kearns (gregorykearns@me.com) (gregorykearns@me.com)
Subject: UAMS decision

Richard

UAMS has decided to suspend the study and notify the FDA

I had 2 conversations with Dr. Cornett and their final decision has been made

He assures me that they want to continue to work with you and your study team and ACHRI to remedy deficiencies and findings in their review and work to get the study back open

With this decision, I would advise the following actions

It will do no good to make calls, send emails or show anger, disappointment or disagreement. The decision is final from the sponsor of the study

We should continue to work on the study, the areas that you have been working on to address the areas of improvement that have been identified

Await the notification and be prepared for any communication or requests from the sponsor or the FDA

ACHRI will need to be ready for inquiries or communications from the FDA

UAMS expects a conference call with the FDA soon after submitting their report

This is not what we wanted, but anything that is counter to professional behavior and an effort to work through this will just detract from the study and our position

I expect everyone to remain respectful, professional and continue to work on what is important. That is making improvements and getting the study back open

Dick

Richard F. Jacobs MD, FAAP, FIDSA
Robert H. Fiser, Jr., M.D. Endowed Chair in Pediatrics
Professor and Chairman, Department of Pediatrics
University of Arkansas for Medical Sciences
Pediatrician-in-Chief, Arkansas Children's Hospital
Office: 501-364-5262

Frye, Richard E

From: Avery, Lyndsey G
Sent: Wednesday, June 17, 2015 3:06 PM
To: Frye, Richard E
Cc: Furgerson, Billy; Brackeen, Margie I; Brady, Barry; Jacobs, Richard F; Cornett, Lawrence E; Wells, Thomas G; Parker, Erin E; Holloway, Amanda; Clark, Melisa G; Berry, Kimberly J; Ironside, Shawn B
Subject: IND 115309 - Notification of suspension to new enrollment
Attachments: Notice of Suspension to new enrollment for IND 115309.pdf

Dear Dr. Frye,
Please find the attached letter regarding IND 115309 to serve as notification of suspension to new enrollment, effective June 17, 2015. No new subjects may be enrolled at this time; however, subjects currently enrolled on protocol will be allowed to proceed.

The United States Food and Drug Administration has been notified as of June 17, 2015 of this suspension.

A copy of the official submission to FDA will be sent to you in a separate email for your files.

Regards,
Lyndsey

Lyndsey Griggs Avery, RAC, CCRP
Regulatory Affairs Manager
Office of Research Regulatory Affairs
University of Arkansas for Medical Sciences
4301 West Markham St., Slot 813
Little Rock, AR 72205
Direct Phone: (501) 686-5190
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Little Rock, AR 72205-7199

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www.uams.edu/rsc

UAMS
UNIVERSITY OF ARKANSAS FOR MEDICAL SCIENCES

June 17, 2015

Richard E. Frye, M.D., Ph.D
Director of Autism Research
Director of The Autism Multispecialty Clinic
Associate Professor of Pediatrics
Arkansas Children's Hospital Research Institute / University of Arkansas for Medical Sciences
13 Children's Way, Slot 512-41B, Room R4041
Little Rock, AR 72202

Dear Dr. Frye:

The University of Arkansas for Medical Sciences (UAMS), as Sponsor of IND 115309, hereby informs you that the study entitled, "A Folinic Acid intervention for ASD: links to folate receptor-α autoimmunity & redox metabolism" has been suspended to new enrollment effective June 17, 2015, due to continuing investigator non-compliance.

No new subjects may be enrolled into the study. Subjects currently receiving investigational product will be allowed to continue on protocol.

The Sponsor has notified the US Food and Drug Administration of this suspension.

Please submit this letter to the UAMS Institutional Review Board within three business days.

Sincerely,

Lawrence E. Cornett, PhD
Vice Chancellor for Research

Cc: ORRA file
B. Ferguson / B. Brady / M. Brackeen / E. Parker

Frye, Richard E

From: Avery, Lyndsey G
Sent: Thursday, June 18, 2015 2:01 PM
To: Frye, Richard E
Cc: Furgerson, Billy; Brackeen, Margie I; Brady, Barry; Jacobs, Richard F; Cornett, Lawrence E; Wells, Thomas G; Parker, Erin E; Holloway, Amanda; Clark, Melisa G; Berry, Kimberly J; Ironside, Shawn B; Doderer, Marcy
Subject: Notification of Full Clinical Hold for IND 115309
Attachments: Notification of Full Clinical Hold for IND 115309.pdf

Importance: High

Dear Dr. Frye:
The Sponsor of IND 115309 has been notified by the US Food and Drug Administration that IND 115309 has been placed on full clinical hold. All subjects must be removed from the study, and investigational drug returned to the ACH Research Pharmacy, effective today, June 18, 2015.

Please find the attached letter to serve as the official notice to suspend all clinical study activity immediately.

A full clinical hold letter from FDA will be sent to the Sponsor over the next week. A copy will be provided to you for your files once received.

Regards,
Lyndsey

Lyndsey Griggs Avery, RAC, CCRP
Regulatory Affairs Manager
Office of Research Regulatory Affairs
University of Arkansas for Medical Sciences
4301 West Markham St., Slot 813
Little Rock, AR 72205
Direct Phone: (501) 686-5190
Fax: (501) 526-6272
LGAvery@uams.edu

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UAMS
UNIVERSITY OF ARKANSAS FOR MEDICAL SCIENCES

June 18, 2015

Richard E. Frye, M.D., Ph.D
Director of Autism Research
Director of The Autism Multispecialty Clinic
Associate Professor of Pediatrics
Arkansas Children's Hospital Research Institute / University of Arkansas for Medical Sciences
13 Children's Way, Slot 512-41B, Room R4041
Little Rock, AR 72202

Dear Dr. Frye:

The University of Arkansas for Medical Sciences (UAMS), as Sponsor of IND 115309, has been notified by the United States Food and Drug Administration that IND 115309 has been placed on full clinical hold.

Effective June 18, 2015, all subjects must be removed from study.

Please notify all subjects currently on study to discontinue use of the investigational drug product/placebo and return all unused product to the Arkansas Children's Hospital Research Pharmacy immediately.

The Research Pharmacy is to quarantine all investigational product pending further direction from the Sponsor.

Sincerely,

Lawrence E. Cornett, PhD
Vice Chancellor for Research

Cc: ORRA file
B. Ferguson / ACHRI / M. Doderer / E. Parker

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MITCHELL V Mathis
06/19/2015

Frye, Richard E

From: Clark, Melisa G
Sent: Friday, June 19, 2015 3:05 PM
To: Frye, Richard E
Cc: Wells, Thomas G; Cornett, Lawrence E; Jacobs, Richard F; Brady, Barry; Brackeen, Margie I; Furgerson, Billy; Slattery, John C
Subject: FDA Clinical Hold Letter - IND 115309
Attachments: IND 115309 - Clinical Hold letter - 19JUN2015.pdf

Dr. Frye,

Please find attached the FDA Full Clinical Hold letter for IND 115309.

Regards,
Melisa

Melisa G. Clark, MS, CCRP
Regulatory Specialist
Office of Research Regulatory Affairs (ORRA)
University of Arkansas for Medical Sciences
4301 W. Markham Street, slot #813
Little Rock, AR 72205
Tel: 501-686-8098
Fax: 501-526-6272
MGClark@uams.edu