Carroll-Loye Biological Research

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12 September 2006

John M. Carley
Program Analyst
U.S. Environmental Protection Agency
Office of Pesticide Programs

Re: Copy of correspondence between the Study Director and the consulting IRB (IIRB, Inc.), regarding revisions to protocol EMD-003 and EMD-004 'Tests of Personal Insect Repellents' (replacing IIRB-approved version of 18 April 2006)

Dear John,

On the following pages you will find copies of all two-way correspondence between myself and personnel of (IIRB), regarding IRB review of our revised protocols EMD-003 and EMD-004. That correspondence was by email, and took place from 21 July 2006 through 12 September 2006. For your convenience, I have presented my outgoing correspondence herein in black, while the return correspondence from IIRB is in blue. All correspondence is presented in chronological order.

This information is provided in compliance with the EPA Human Studies Rule, § 26.1115(a)(4).

Please contact me should you require any clarification or additional information.

Thank you.

Sincerely,

Scott P. Carroll, Ph.D.
Director and Study Director

21 July 2006 1523 PDT
To: "Robert Roogow" <rroogow@iirb.com>
From: Scott P Carroll <spcarroll@ucdavis.edu>
Subject:

We have continued to work with the protocol and ICF materials in terms of getting US EPA approval for our human subject insect repellent studies. The studies for which you provided protocol review and ICFs are Carroll-Loye Protocols EMD-003 and EMD-004, which are tick and mosquito repellent studies, respectively.

The changes are of two types. First, EPA has revised its science guidelines for the conduct of repellent tests, and new asks that we determine the dosage that people apply in advance of conducting the test, instead of using an arbitrary, industry-standard dose. Second, at the end of June we met with the EPA Human Studies Review Board, whose member made a number of suggestions for revising the ICF and also including a risk-benefit assessment in the protocol.

Accordingly, we have made the following substantive revisions to those documents, and so have new versions in need of your administrative review. Please note that the changes to the tick and mosquito protocols/ICFs basically mirror one-another.

A) PROTOCOLS

1) To both protocols we have added a preliminary dosage determination study, in which we ask subjects to do several trial applications of the test materials so that we can measure how much is actually used. This will serve as a basis for determining the dose to be used in the repellent efficacy studies, and replaces the former, more arbitrary, US/EPA approved dose scheme. It is detailed in sections 10.3.1 - 10.3.5.

2) A revised section 5 includes the treatment of the balance of risks and benefits.

3) An added section 9.1.4, which describes the recruiting methods verbatim to what was originally in the "generic" protocol C-L-001 that accompanied these (and was a relict from former California/EPA requirements but is no longer in play for these studies).

4) In addition, subjects will now practice removing mosquitoes in the lab with a mechanical aspirator (mosquito sucker) before going to the field, where they will use that same instrument to remove any mosquitoes that come. That practice is described in section 10.3.6.

B) ICFs

1)We have added more detail about what subjects will experience to the ICFs. Some of that detail of course treats the new dosage determination precursor to the efficacy testing and the practive mosquito aspiration. In addition, there is also substantially more detail in the ICF in general. The new material is mainly on pages 2-5 (top) and 6.

I think that you will probably find that the ICF changes are very straightforward. I have included pdfs of the revised ICFs, *plus* pdfs showing the changes made in Word tracking mode (in case it is helpful to you to just see the changes highlighted). In addition, the two revised protocols are attached. If you wish, I can send 'changes tracked' versions of the protocols too, but I don't want to confuse things with too many files attached to this one email. Also please let me know if you want Word versions of any of the revised documents.

From the standpoint of human subject safety, the changes mean that subjects will now apply, and immediately remove, repellent several times for dosage determination before the test against the insects. The repellent itself has the best safety profile of all of the major repellents on the market, so I think there is little safety concern from that added procedure, an opinion that US/EPA personnel share. All of the focus seems to be on the possibility of mosquito bites, and we have gone to technical extremes to minimize those risks. Other than that, the revisions are intended to keep the subjects even more thoroughly informed of what they are considering consenting to do.

Please let me know what you think of these changes and if we can administer them in them in a simple way. I will be glad to answer any question you have about this request and the attached documents.

Thank you very much.
Sincerely,
Scott

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24 Jul 2006 09:51:05
From: "Robert Roogow" <rroogow@iirb.com>
To: "Scott P Carroll" <spcarroll@ucdavis.edu>
Subject: Re: [Revised ICFs, studies EMD -003 & -004, for review]

Hello Scott,

The changes do look straight forward and we will be able to review and approve the changes. I did notice that the changes you made were not to the approved Consent Forms. I have attached the approved Consent Forms for you to make the changes in order to avoid any confusion and limit opportunities for mistakes. Please let me know if you have any questions or concerns.

Regards,
Robert

Robert Roogow, MS, RAC
Regulatory Compliance
Independent Investigational Review Board, Inc.

24 July 2006 2000 PDT
To: "Robert Roogow" <rroogow@iirb.com>
From: Scott P Carroll <spcarroll@ucdavis.edu>
Subject: Revised ICFs for EMD-003 and EMD-004

Hi Robert,

I have attached the new versions of the ICFs for the repellent studies with ticks (EMD-003) and mosquitoes (EMD-004). Based on your prudent suggestion (below), I have made changes with reference to the approved versions. Tracked changes are again shown, with reference to those approved versions.

Please let me know if you have any additional questions.

Thanks very much.

Scott

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1 Sep 2006, 1030 PDT
To: Iirb105@aol.com
From: Scott P Carroll <spcarroll@ucdavis.edu>
Subject: Complying with EPA Human Studies Rule

Dear Kim,

As you will recall, you provided services for my company in the development of insect repellent efficacy testing protocols and IC documentation earlier in the year (mainly March and April). We principally worked with Debbie Siano, formerly of your company, and then Robert Roogow. I am writing with regard to how we might best proceed with additional reviews of our protocols.

The principal issue we faced then, and now, is compliance with the the new EPA rule regarding human subject research in pesticide exposure studies. Insect repellents are regarded as pesticides. In mid-May you engaged Mr. William Jordan, Senior Policy Advisor in EPA's Office of Pesticide Programs, in a discussion regarding IIRB compliance with the new Rule and its implementation with respect to the EPA Human Studies Review Board (HSRB).

I have spent much of the summer continuing to work through the process of HSRB review of our protocols with EPA staff. Formal HSRB reviews were made available to me this week, and I have until approximately September 12 to respond. We have substantially revised our protocols,and added to the ICFs that IIRB drafted. The final revisions will be made over the next few days. At that point my plan is to submit the revised documents to IIRB for review.

Last evening, EPA staff communicated that they will only process our submissions if the requirements of section 26.1125/1115 are met in full. Specifically, John Carley, a Program Analyst who works with Mr. Jordan, e-mailed:

> 'I don't know whether you intend to continue to work with the IIRB. If they are now willing to provide the documentation we require, I see no barrier to your continuing with them. But if your resubmission is not accompanied by all the required IRB records, we won't be able to take your protocols to the October meeting. I think the draft report makes it abundantly clear that the Board will not accept a protocol for review unless this information is present.'

Given the evident intransigence of that position, it is my strong desire to find a way to work with IIRB to secure the needed information to be included in our submission. If you do not wish to have me transmit that information, perhaps I can design a simple system by which it could go directly to the cognizant EPA officer to be included with our submission. However, as you are aware, that information will ultimately become public.

Below is a table of the general requirements as summarized by EPA personnel. As you are aware, those most critical to the present discussion, which only you can provide, are in the upper sections (26.1115(a)) of the table, especially subsections 2, 5 and 6. Clearly, the issues of confidentiality and professionalism stem mainly from considering who should or should not see documentation to meet the requirements of subsection 2. While making that judgment is entirely your province, my personal intuition is that in the present case, and with regard to the types of studies you will likely handle in the future that fall under this rule, the contents of your response to subsection 2 would normally be very brief and maybe not even very interesting reading (forgive me), relative to that obtaining from the complex issues you must often face for e.g, drug trials for the seriously ill. My point it not to suggest that the insect repellent studies will receive any less scrutiny that other classes of protocols, but merely to point out that the work is sufficiently non-controversial that revealing IIRB discussions, in cogent sketch form, is not likely to compromise your authority over the actions of study directors. Certainly if things were to develop such that you believed your authority to be compromised, you would withdraw from overseeing our work. At present, however, such oversight, plus a modicum of transparency on your part, appears to be the only avenue available to us for the pursuit of this valuable research in the United States.

Thanks very much for considering this matter for us. In the interest of time, given that EPA's schedule requires us to act next week, I request that you reply at your earliest convenience regarding how we might proceed. I will also telephone at 2:45 PM your time today to make certain that we are in contact.

Thank you very much.

Sincerely,
Scott Carroll
Director

1 Sep 2006, 1210 PDT
To: Iirb105@aol.com
From: Scott P Carroll <spcarroll@ucdavis.edu>
Subject: Human Rule summary table

Hi Kim,

Attached is the Human Rule summary table I received from EPA that pertains to IRB documentation.

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2 Sep 2006, 1247 PDT
To: Iirb105@aol.com
From: Scott P Carroll <spcarroll@ucdavis.edu>
Subject: Revised mosquito repellent ICFs

Hey Kim,

To start off simply, I have attached the ICF for study EMD-004. That the study for which there is more interest at EPA because people are more concerned about mosquito than tick exposure.

The two attachments are:

The revised EMD-004 consent form

The revised EMD-004 consent form with changes tracked.

Things to note:

1) The changes to EMD-003, ticks, are nearly identical to those of -004; I can send it on at any time.
2) Over the next couple of days I may determine that each ICF needs to be partitioned into a boy and a girl version. The boy version would lack statements about pregnancy.
3) Additional minor changes may arise in the next day or so. For example, we may just eliminate the positive control to reduce issues with the Board. I'll let you know if so.
4) Please let me know if you need pdf versions.

I hope that we can both find a good path through this changed landscape.

Thanks!!
Scott

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3 Sep 2006, 1310 PDT

To: lirb105@aol.com
From: Scott P Carroll <spcarroll@ucdavis.edu>
Subject: John Carley's EPA contact info

Hi Kim,

As promised:

John M. Carley

Program Analyst
U.S. Environmental Protection Agency
Office of Pesticide Programs
tel: 703 305-7019
fax: 703 308-4776

Carley.John@epamail.epa.gov

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5 Sep 2006, 0851 PDT
To: lirb105@aol.com
From: Scott P Carroll <spcarroll@ucdavis.edu>
Subject:

Good Morning, Kim,

If I may request your professional opinion on further matters I am addressing regarding EPA-based revisions to my current insect repellent protocols–

1) The HSRB noted that the protocols lack a Medical Management Plan. They have not stated that such a plan is critical to conducting the work ethically, and I initially suggested that such a plan was "overzealous" given that the study is not medical, that risk is very very low, and that we monitor subject condition, emphasize it's importance, and have pre-arranged access to medical services should they be required. Based on your experience, is that position to lax? I have drafted a plan for possible inclusion (below); it would required extensive services from trained medical personnel to be on-site.

9.5 Stop Rule and Medical Management

A medically-trained Safety Monitor will be present during testing. Subjects will be introduced to the Safety Monitor and instructed to report any adverse effects or immediate health or safety concerns at once to the Safety Monitor, giving those concerns priority over data collection.

Specific adverse reactions in subjects to the test materials are not anticipated based on low acute and chronic toxicity profiles of the materials, as well as the research design to

minimize exposures, and the training of subjects to aspirate landing mosquitoes before they probe or bite. Because the products are topical, subjects will self-monitor for allergic and irritant skin reactions, particularly redness, edema, itching or pain, and report any such reactions to the Safety Monitor. The Safety Monitor will also inspect the treated skin for those signs of inflammation in each subject at least once per hour. Any subject showing adverse skin reactions will immediately stop further participation. The treated skin will be gently washed with clean water and mild soap to remove the test product, and the area will be gently dried with a clean towel, or otherwise treated as recommended by the Safety Monitor. The subject will be removed from further exposure to mosquitoes, and the Safety Monitor will determine if the subject will be taken to receive additional medical care at a nearby clinic or hospital, or if self-resolution is likely. Under either scenario, the Safety Monitor will maintain contact with the subject after the end of the test day. In addition, the subject will be asked to contact the Safety Monitor and Study Director at any time should the condition worsen. All subjects are asked to contact the Safety Monitor and Study Director at any time should they develop a rash (a delayed hypersensitivity reaction) within 48 hours of the conclusion of the test day. Subjects are also asked to contact the Study Director and a physician of their own choice should they have difficulty contacting the Safety Monitor or if they are dissatisfied with the Safety Monitor.

The risk of mosquito-associated health risks is likewise regarded as very low due to the complementary precautions outlined herein. However, the Safety Monitor will assess skin condition of affected subjects should any bites inadvertently occur during efficacy testing. In addition, subjects will agree to make contact with the Safety Monitor and Study Director at any time should they have health concerns relating to their participation in the efficacy testing.

As part of Medical Management, the Safety Monitor will record all benign and adverse health observations.

The Safety Monitor will be a certified Physician Assistant, Nurse Practitioner, or Medical Doctor.

2) The IC documents state rather broadly, but perhaps nonspecifically (below), that I will be responsible for anyone who is injured as a result of being in this study. I asked advice this past weekend of a friend who is an IRB-experienced physician regarding a Medical Management Plan, and got unexpected feedback from her that she had never once seen IC documents in a "non-medical" study in which the PI did not disavow liability for research-related injury (e.g., collapse on a treadmill). I am not looking to avoid appropriate responsibility, nor I am asking for legal advice, but again, based on your experience, am I failing to occupy some middle ground that has been regarded as appropriate for PI in studies like mine in the past?

RESEARCH RELATED INJURIES

If you are injured as a result of being in this study, medical treatment will be available from a health care facility that is aware of the study. Carroll-Loye Biological Research will cover the costs of such medical treatment. If necessary, Carroll-Loye Biological

Research will transport you to receive medical attention and pay costs associated with the reasonable and appropriate treatment for any injuries incurred as a result of participation in the study. For further information about this, the research test subject should call the office of Carroll-Loye Biological Research (530) 297-6080.

I need to submit this material to California DPR today, so forgive me if I give you a call a little later to discuss this matter.

Thanks very much,
Scott

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6 Sep 1235 PDT
To: Iirb105-aol.com
From: Scott P Carroll <spcarroll@ucdavis.edu>
Subject: IRB documentation for the HSRB

Hi Kim,

Thanks again for sharing this burden with me. I spoke with the point man John Carley today about protocol matters, and he asked about how things were going with IIRB. 'Great!' I replied, but when I mentioned your reluctance, for proprietary reasons, to share certain SOPs, he thought that position unreasonable because IRB practices are so closely governed by OHRP regulations as to be uniform and basically, I guess, nonproprietary. Granted, I don't even know what OHRP stands for, and I am retaining that ignorant stance rather than even Googling it, but you might either a) concede John's point, or b) consider making the effort to educate him more plainly on the matter than I was in a position to do.

I don't think you will find him unpleasant, but he seems to prefer a clear argument or justification.

Best regards,
Scott

PS. Our revised protocols are now at Cal DPR for review and should go our to you on Thursday.

His info again:
John M. Carley

Program Analyst
U.S. Environmental Protection Agency
Office of Pesticide Programs
tel: 703 305-7019
fax: 703 308-4776

Carley.John@epamail.epa.gov

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8 Sep 0610 PDT
To: lirb105-aol.com
From: Scott P Carroll <spcarroll@ucdavis.edu>
Subject: This is the submission of revised protocol EMD-003

Dear Kim,

I have attached the revised Protocol EMD-003 and its ICF. The ICF is also embedded at the end of the protocol at the request of US/EPA, but the resolution of pdfs within Word documents is poor so I am attaching the ICF separately as well. The EMD-004 documents will follow momentarily.

Please let me know if you need either file in different format, or have any questions.

The ICF is a unisex document. I treat the gender issue that we discussed by telephone on Thursday in a new protocol section as follows:

> **9.1.6 Enrollment of alternate subjects and its relation to individual privacy:**
>
> We will enroll three more subjects than are required to meet our sample size. All subjects will be informed during the Consent process that on the day of testing, a small number of subjects may be designated as alternates and sent away after being compensated for coming to the test site. Alternate subjects may return later to replace subjects that initiate testing but withdraw before useful data are generated. They also serve as insurance against any enrolled subjects who fail to appear.
>
> The possibility that any subject may be designated as an alternate will assist in protecting the privacy of any subject that must withdraw in or near the presence of other subjects at the start of the test day (i.e., before treatment and testing begins), for reasons such as a positive pregnancy test result, or for any other personal circumstance to which possibly inappropriate attention might otherwise more readily be drawn. In the case of privacy concerns related to pregnancy detection, we regard this "indirect" approach as potentially as discrete and less likely to result in errors that would be the case if we were to employ, e.g., separate male and female Informed Consent Forms, with pregnancy only mentioned on the female form. The latter approach does not address loss of privacy among females, nor does it control the possibility of indiscrete revelation of pregnancy testing by females to males during the test or later, and it also creates the risk of a female subject using the wrong form. Separate forms would also assume that we may treat individual subjects unequally on the basis of postulated gender-based differences in the information the merit receiving in to arrive at their informed consent decision. The soundness of making such an assumption enters

ethically complex grounds requiring an intricacy of analysis and breadth of treatment beyond the scope appropriate to the privacy concerns of the present study.

As you have already noted from your review of the draft ICF (for EMD-004, but 003 is similar), the procedures for the test have changed very little in revision except for the inclusion of a front-end dosimetry study to determine what the dosing rate should be when we test repellent efficacy. These is much more substantial justification for the research in general (risks versus benefits) and with reference to specifics (e.g., sample size, dosing). The ICF now includes substantially more detail about what subjects can expect to be doing, and a fuller treatment of the scope of risks.

Please let me know what else I can provide you with.

Thank you very much for your help and guidance. I look forward to hearing the results of your review and will keep you posted regarding timing issues for US EPA.

Sincerely,
Scott

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8 Sep 0613 PDT
To: lirb105-aol.com
From: Scott P Carroll <spcarroll@ucdavis.edu>
Subject: This is the submission of revised protocol EMD-004

Dear Kim,

The comments regarding EMD-003 in the foregoing email apply to -004 as well.
Scott

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8 Sep 1037 AM
To: lirb105-aol.com
From: Scott P Carroll <spcarroll@ucdavis.edu>
Subject: Last minute minor material added from Cal DPR Hi Kim,

As you can imagine everyone involved has been working assiduously to meet the request of US EPA.

Janet Spencer at Cal/EPA Department of Pesticide Registration has done a great job with review in the compressed time frame and just called with two final, very minor requests for additions that I felt I should try to include now out of respect for her efforts. However, if you determine that at this point it is better to handle those changes as administrative amendments, I understand, and that is fine.

1) To each ICF we added (shown here in red), on page 2 just below the table of times,

You will be given a training manual and will have a chance to review it and to read along with the instructions.

2) To the Protocols we added (shown here in red),

9.1.5 Identification method and records retention:
Subjects will initially be identified by first and last name, and assigned a unique number for purposes of this study. Individual data will be entered into the computer for retention and analysis with reference to individual number, not name. Records relating individual names to individual numbers will be retained separately. The Study Director will retain records indefinitely. Subjects may obtain their own records from the Study Director.

That is everything.

Thanks once more,
Scott

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10 Sep 2006 11:44:14 EDT
To: spcarroll@ucdavis.edu, klerner@iirb.com
From: Iirb105@aol.com
Subject: Re: Last minute minor material added from Cal DPR

please send me the word version of the icf's with the rack changes ASAP

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10 Sep 2006 11:50:11 EDT
From: Iirb105@aol.com
To: spcarroll@ucdavis.edu, klerner@iirb.com
Subject: Re: Last minute minor material added from Cal DPR

Dear Scott,

A revised protocol must be submitted with a summary of changes and rationale, and a listing of the changes that have been made. In addition the coversheet of the protocol must identify the date of the version that it replaces.

Please submit ASAP.

Kim

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10 Sep 1156 PDT
To: Iirb105@aol.com
From: Scott P Carroll <spcarroll@ucdavis.edu>
Subject: Your instructions for the revised protocols

Dear Kim,

Thanks for those instructions, which I am fulfilling now. I will have the documentation to you within 1-2 hours.

Scott

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10 Sep 1451 PDT
To: Iirb105@aol.com
From: Scott P Carroll <spcarroll@ucdavis.edu>
Subject: Cover materials for review of revised protocols EMD-003 and -004

Hi Kim,

Cover letters accounting the revisions to EMD-003 and 004 are attached. In addition, I have attached the revised cover sheets for each protocol that give the approval date for the former versions.
What's more, I have attached Word versions of the ICFs.

I hope that these help to complete what you need to review the revisions.

Regards,
Scott

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11 Sep 1336 PDT
To: Iirb105@aol.com
From: Scott P Carroll <spcarroll@ucdavis.edu>
Subject: Human Rule summary table

Hi Kim,

Attached is the Human Rule summary table I received from EPA that pertains to IRB documentation.

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12 Sep 1148 PDT
To: Iirb105@aol.com
From: Scott P Carroll <spcarroll@ucdavis.edu>
Subject: Today's review of EMD-003 and EMD-004, as revised

Dear Kim,

I am aware that today is your very busy meeting day. However, if you can grant me a preliminary assessment of the outcome of the IRB deliberations concerning our revised protocols, that would be most useful for my communications with the interested parties,

and for my implementation of the next steps for the coming few days of (planned) document finalization for the EPA HSRB.

Thanks very much,
Scott

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12 Sep 2006 15:45:41 EDT
From: lirb105@aol.com
To: spcarroll@ucdavis.edu, klerner@iirb.com
Subject: Re: Today's review of EMD-003 and EMD-004, as revised

approved - youll get the pdf's about 6pm EST

Kim Lerner, Chairman

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12 Sep 2006 1800 EDT
From: lirb105@aol.com
To: spcarroll@ucdavis.edu, klerner@iirb.com
Subject: EMD-003 and EMD-004 - word doc.'s

attached are the most current word doc versions - w/track changes

minor changes were made; i.e. grammatical repetition, blah blah blah..

Kim Lerner, Chairman

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12 Sep 2006 1803 EDT
From: lirb105@aol.com
To: spcarroll@ucdavis.edu, klerner@iirb.com
Subject: EMD-003 and EMD-004 - word doc.'s

attached are the pdf's of the approved documents!

kim

Kim Lerner, Chairman

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12 Sep 2006 2021 EDT
From: lirb105@aol.com

To: spcarroll@ucdavis.edu, klerner@iirb.com
Subject: Round 1 [IRB documentation]

PLEASE REVIEW THE ATTACHED

let me know if you think changes necessary!

k

Kim Lerner, Chairman

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12 Sep 2006 2114 EDT
From: lirb105@aol.com
To: spcarroll@ucdavis.edu, klerner@iirb.com
Subject: emd-004 1 [IRB documentation]

Good night!

if you need any thing else it will have to be in the AM (I will be out of the office on Wed between 9 and 11 AM0

k

Kim Lerner, Chairman