Final IRB Investigation Report: Alleged Non-Compliance by Stephen Olson in Bifeprunox Studies

Preamble:

On February 10, 2014, the IRB Executive Committee, acting as a convened IRB, voted to request a formal investigation of possible non-compliance concerning Principal Investigator Stephen Olson’s research involving the investigational drug Bifeprunox (IRB Protocols #0309M52653, #0610M95446, and #0710M19084). Allegations of non-compliance were raised by Professor [REDACTED] in January and February 2014 and by a former research subject, [REDACTED], who contacted the University of Minnesota President’s Office beginning on February 6, 2014 to report his concerns and complaints related to his participation in the Bifeprunox study 0309M52653 in 2007. The IRB was made aware of [REDACTED] complaints on February 10, 2014.

As charged by the IRB, we, the designated panel of expert IRB members, have conducted a thorough review of [REDACTED] participation in Dr. Olson’s research study 0309M52653, including evaluation of complaints raised by [REDACTED] in August 2012 and February 2014 and interview transcripts from April 30, 2014. As part of this investigation, we have concluded that [REDACTED] is the same complainant who came forward in August of 2012 to report concerns regarding the conduct of Dr. Olson’s research. At that time [REDACTED] reported his concern anonymously through the Research Subject Advocate line, and it was examined by the IRB to the extent possible, given the anonymity of the complainant.

The charge to the investigation panel was to focus on human subject protection and adherence to IRB requirements. The panel notes two issues that impacted this report. [REDACTED]

Second, given the seven year interval between [REDACTED] participation in the study and revelation of his identify, the panel relied most heavily on the written record, both the research record and the non-research medical record, to assess the events during [REDACTED] participation in Protocol #0309M52653. Although both [REDACTED] and Dr. Olson had an opportunity to answer questions during the investigation, the panel did not rely extensively on memories of events seven years in the past.

The panel charge appears in italics, while the panel’s responses are shown in normal text.
1. Conduct an investigation into three studies involving the drug Bifeprunox (IRB Protocols #0309M52653, #0610M95446 and #0710M19084), Principal Investigator Stephen Olson, to determine:
   a) whether serious or continuing non-compliance occurred regarding the rights and welfare of research participant in 2007 under Protocol #0309M52653; and

FINDINGS:
1.1 No serious or continuing non-compliance was found with regard to the rights and welfare of research participant in 2007 under Protocol #0309M52653.

DISCUSSION:
As part of its investigation of whether serious or continuing non-compliance occurred regarding the rights and welfare of research participant in 2007 under Protocol #0309M52653, the investigation panel reviewed the following:
• The IRB file for Protocol #0309M52653 including the original application, changes in protocol, annual renewal applications and all reviews, stipulations and responses to those stipulations related to each.
• The research staff’s documentation supplied by the PI, Steven Olson, MD, for all encounters with the subject beginning , 2007, related to enrollment, participation in, and early withdrawal from Protocol #0309M52653 on , 2007, and a follow-up visit on in 2007.
• The subject’s Fairview medical record beginning with

b) whether serious or continuing non-compliance occurred in any of the three studies related to investigator obligations. Follow the procedures outlined under IRB Policy 408A: Investigation Process in conducting the investigation.

FINDINGS:
1.2 No serious or continuing non-compliance issues with regard to investigator obligations for reporting to the IRB regarding the three studies under Protocol #0309M52653 or Protocol #0610M95446 in accord with the requirements of the sponsor, Solvay, were found. IRB Protocol #0710M19084 was terminated by the sponsor prior to the IRB’s final approval, therefore no research activity occurred.
DISCUSSION:
Number 3 of the Charge to the Investigation Panel requested examination of whether there was serious non-compliance with respect to the rights and welfare of other participants under the three protocols only if serious non-compliance regarding the rights and welfare of was found. Having found no serious or continuing non-compliance with regard to the rights and welfare of under Protocol #0309M52653, the panel did not review individual subject files for other subjects under Protocol #0309M52653 or for subjects under Protocol #0610M95446. Protocol #0710M19084 was terminated by the sponsor before final approval by the IRB, therefore no subject was enrolled.

As part of its investigation of whether serious or continuing non-compliance issues with regard to investigator obligations occurred in any of the three studies, the investigation panel reviewed the following:
- The Clinical Trial Agreements between Quintiles representing the study sponsor, Solvay Pharmaceuticals, and the Regents of the University of Minnesota for Sponsor’s Protocol Number S154302 (IRB Protocol #0309M52653), Sponsor’s Protocol Number S154.3.020 (IRB Protocol #0610M95446) and Sponsor’s Protocol Number S.154.3.021 (IRB Protocol #0710M19084).
- Interim Visit Follow-up Letters from Quintiles staff for periodic on-site audits for Sponsor’s Protocol Number S154302 (IRB Protocol #0309M52653).
- The IRB files for all three protocols including the original application, changes in protocol, annual renewal applications and all reviews, stipulations and responses to those stipulations related to each, and safety and adverse event reports compiled by the sponsor, and forwarded by the PI to the IRB.

2. Examine any and all aspects of participation in Protocol #0309M52653 as necessary to determine compliance, including but not limited to the following:
   a. Were there adequate mechanisms in place to evaluate whether had the capacity to consent to participation? Is there evidence that lacked capacity to consent?

FINDINGS:
2.1 Mechanisms were adequate to evaluate whether had the capacity to consent to participate.
   - was assessed by the PI and others for clinical reasons before consent; the medical record reports that
   - Consent was limited in the study to subject or his/her legal guardian.
   - The study included an Evaluation to Sign Consent document to assess understanding of the study that was reviewed by the IRB as part of
the initial application process. This Evaluation for [redacted] was completed and signed by two staff members.

- Based on the records and according to the IRB approved recruitment plan, a subject advocate not associated with the study (a social worker first, then, at discharge, [redacted]) was assigned and included in the consent process.

2.2 The evidence shows [redacted] had the capacity to consent.

DISCUSSION:
The Subject Advocate section of the consent form states in part, “A person designated by you, or someone recommended by the researcher, but not otherwise involved in this research, will go through this consent form with you. This person (your "subject advocate") will assist you to make a decision about whether or not to participate in this study...”

For [redacted], the research advocate at the time of his enrollment in the study was a case worker on the psychiatric nursing unit, [redacted]. [redacted] signature on the consent form is dated [redacted], 2007, one day after [redacted] signature. This raised the question of whether she was actually in attendance at the time the consent form was presented to and signed by [redacted].

No documentation to verify whether [redacted] was in attendance on the day of consent was found in [redacted] medical record or in research records provided by Dr. Olson. The panel sent a question to [redacted] regarding his memory of the consent process and who was present. [redacted] chose to respond verbally via telephone, which was transcribed, rather than in writing. As part of his response [redacted] stated, [redacted], was present.” The panel was unable to determine whether [redacted] dated her signature in error or did not actually sign the consent until the following day. However [redacted] statement would seem to suggest [redacted] was present in accord with the study protocol at the time the consent was presented to and signed by [redacted]. In addition, Dr. Olson was asked to respond in writing to the discrepancy between subject [redacted] signature date and the subject advocate signature date. He responded: “I have no recollection of why her signature was dated one day later than [redacted] consent. She certainly would not have signed if allegations that he participated under the threat of being committed were true, nor would any member of the multidisciplinary team have stood by and allowed such an obviously unethical coercion.”

On the last day of [redacted] 2007) [redacted]
agreed to serve as his research advocate and signed the consent. She served in this position for the remainder of involvement in the study.

RECOMMENDATION:
The evidence suggests that the research advocate was present during consent process, and therefore the research advocate’s signature dated one day later than the consent does not constitute a serious non-compliance. However, this panel recommends that Dr. Olson establish procedures to ensure that the research advocate’s signature and date correspond with the consent date. Moreover, this panel recommends that, in the future, the research advocate document her/his involvement in writing with a line or two in the subject’s research records and/or the medical record. Since documentation of the research advocate’s involvement in the consent process (beyond a signature) was not required by the IRB at the time of this study, the absence of such documentation in consent process does not constitute serious non-compliance.

b. Were proper recruitment strategies followed? Is there evidence that was pressured to participate in the study?

FINDINGS:

2.3 Recruitment appears to have been conducted in accord with the process detailed in the application for Protocol #0309M52653. Dr. Olson and his study team had IRB approval to approach hospital patients about the study.

2.4 While the fact that Protocol #0309M52653 provided coverage by the sponsor for all study medication and for hospitalization during the study drug titration period may have been strong incentive to participate, there is no evidence that was pressured to participate. Moreover, the consent process included information with regard to alternative treatment options should choose not to participate in the study.

DISCUSSION:

The panel posed the question to Dr. Olson of whether different medications would have been used over the weekend if there had been no plan for using the study drug. Dr. Olson responded with the following statements:
As far as being NPO, it is our practice to offer a potential subject the option to stay NPO prior to the initial screening visit, informing them that would allow screening labs to be done once the consent is signed. That is not obligatory, but many subjects choose that option rather than returning for a second outpatient visit (or extending their hospital stay another day, [redacted]) to get labs done.

Although [redacted] provided verbal consent to the study over the weekend preceding the formal consent process, the consent process was not completed until [redacted], 2007.

RECOMMENDATION:
In the case of [redacted] the subject had been informed of the trial and expressed verbally the desire to participate. He experienced no harm from the overnight NPO and there is no evidence he was harmed [redacted] prior to starting Bifeprunox. [redacted] enrolled in the study the following day. Thus, this panel believes that actions of Dr. Olson constitute non-compliance, but not serious non-compliance. In the future, the panel recommends that the consent forms must be signed before any study activity has begun, including initiating a medication “washout” period or keeping the subject NPO.

c. Were proper procedures followed regarding the handling and reporting of adverse events? Is there evidence that the PI failed to address serious adverse events experienced by [redacted] or failed to report [redacted] complaints or adverse events to the IRB?

FINDINGS:
2.5 Proper procedures were followed with regard to the handling and reporting of adverse events.
2.6 There is no evidence that the PI failed to address [redacted] complaints expressed at the time of admission or during participation in the study.

The following adverse events were documented as reported by [redacted] during the time [redacted] participated in Protocol #0309M52653: [redacted]

[redacted] These were perceived by Dr. Olson as not serious, mild in severity and none met IRB reporting requirements as a serious adverse
event or an unanticipated problem involving risk to subjects or others (UPIRTSO). The panel concurs with Dr. Olson’s assessment.

Medical record documentation indicates that The panel believes Dr. Olson was attentive to and made adequate attempts to address complaints.

DISCUSSION:

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FINDING:

2.7 There is evidence that was allowed to withdraw freely and without pressure.

d. Were participants freely allowed to withdraw from participation? Is there evidence that right to withdraw from the study was not respected?
DISCUSSION:

there is no evidence of coercion to continue.

3. If you find serious non-compliance regarding the rights and welfare of examine whether there was serious non-compliance with respect to the rights and welfare of other participants under the three protocols.

As indicated in finding 1.1 above no serious non-compliance regarding the rights and welfare of were found. Therefore, the panel did not conduct reviews of any other subjects under Protocol #0309M52653 or any subjects in Protocol #0610M95446. Protocol #0710M19084 was terminated by the sponsor prior to final IRB approval, therefore no subjects were enrolled.

4. Examine whether there was serious or continuing non-compliance by Stephen Olson with respect to investigator obligations under the three protocols, including but not limited to the following:
   a. Were the risks of taking Bifeprunox adequately disclosed to the research participants? Should the research consent forms have disclosed that a subject died in 2004 or disclosed a risk of hepatorenal failure? Should the investigator have informed participants of the subject’s death once the sponsor suspended the studies in Dec 2007?

FINDINGS:

4.1 The consent form included the risks contained in the Investigator’s brochure.

4.2 The adverse event report of 2004 of the single subject death in Bulgaria did not provide enough evidence for the PI (or the IRB) to conclude this was a significant study risk. The study included a DSMB, charged with assessing the study risk associated with reported adverse events for the whole study. Their reports are not part of the IRB’s file.

4.3 The single hepatorenal death was added to the consent form in March 2006. Subjects consented after that time (including all signed consents with the death revealed in the consent form.

4.4 Given the low frequency of the risk (single subject world-wide), there was no need to inform subjects who had discontinued the drug.

b. Was the FDA decision not to approve Bifeprunox in Aug 2007 a significant new finding that should have been reported to the research participants?
FINDING:
4.5 The FDA decision not to approve Bifeprunox did not need to be reported to research participants.

DISCUSSION:
The letter issued by the FDA in August 2007 did not approve Bifeprunox, but did not direct Solvay to cease testing of the drug nor did it preclude submission of another application with additional research data at some time in the future. In the experience of the IRB investigation panel, it is not unusual for the FDA to require additional testing and data before approving a new drug application.

c. Did the PI fail to report participant injuries or complaints to the IRB?

FINDING:
4.6 The PI did not fail to report participant injuries or complaints to the IRB.

DISCUSSION:
• The IRB files for protocols #0309M52653 and #0610M95446 include regular submission by the PI of safety and serious adverse event reports produced by Solvay.
• The 2006 continuing review form for protocol #0309M52653 reflects reporting of two on-site serious adverse events unrelated to

None of the subject complaints documented in his research and medical records indicated evidence of unexpected complications and were not at a level requiring reporting to the IRB as serious adverse events.

IRB EXECUTIVE COMMITTEE RESPONSE AND RECOMMENDATIONS

At its meeting on 08/11/14, the IRB Executive Committee reviewed the draft investigation panel report and made a decision to accept the report pending modifications.

This report includes suggested edits received by 09/04/2014 that were discussed and accepted by a majority of the IRB Executive Committee at its meeting on 09/08/2014. Dr. Olson was provided a copy of the preliminary report on 9/11/2014 for review and comments but he did not submit any comments or dispute the conclusions or recommendations in the report. The IRB Executive Committee voted at its meeting on October 13, 2014, to accept this report as the final IRB investigation report on alleged non-compliance by Stephen Olson in the Bifeprunox studies.
LIMITATIONS:

This report finds relatively minor incidents of regulatory non-compliance, but does not find any evidence of serious non-compliance. Nor is there any evidence of mistreatment of or disrespect of his condition and his complaints. However, the documents reviewed in this case are necessarily incomplete representations of history. They record facts that are generally considered to be important, but they do not provide a complete account of the more subtle, unexpected, and unique interactions between doctor and patient, or between investigator and research subject. These undocumented interactions may have an important influence on the outcome of an individual's experience as a patient or research subject.

The acknowledged limitations of this investigation, coupled with IRB Executive Committee discussion of the investigation panel conclusions, suggests a need for the IRB Executive Committee to consider the following issues at a future date:

1) Recruitment of prospective research subjects hospitalized under 72-hour holds (voluntary or involuntary)
2) The role and qualifications of the research subject advocate need to be better defined.

The IRB Executive Committee gratefully acknowledges the cooperation of and the investigator in providing information, and the commitment of the investigation panel members in this process.