Harrison, M.C. (Myron)

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Sent: Wednesday, February 07, 2001 11:14 AM
To: Baruch Brody (E-mail); Lorraine Twerdok (E-mail); Lynn Russo (E-mail); Myron C. Harrison (E-mail); Norm Zeiser (E-mail); Otto Wong (E-mail); Patrick Beatty (E-mail); Rich Herold (E-mail); Richard Irons (E-mail); Robert Schnatter Ph. D. (E-mail)
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NHL-AML Protocol

At our meeting in Salt Lake City on October 26, 2000, we reviewed a draft of Dr. Wong's protocol and raised a number of issues of concern. He has addressed them in a series of revisions, culminating in a protocol dated January 11, 2001. It was the unanimous conclusion of the group that we were satisfied that the issues had been appropriately addressed, although there were two on which further work needed to be done by Dr. Wong and there was one on which there was still some disagreement. Let me review what was done, issue at a time:

1. Benefits and burdens to subjects and to community- this form of case control epidemiological study, which primarily involves a questionnaire interview of cases and controls and the gathering of exposure information, offers primarily the prospect of benefit to the public health in Shanghai by providing the basis for a scientifically sound formulation of better benzene exposure regulations, by identifying workplaces with unacceptable levels of exposure, and by identifying other risk factors. Dr. Wong has strengthened the potential for achieving these benefits through his contact with Dr. Liang. Except for concerns about confidentiality, there are no real risks to the subjects of the study. So the benefit-risk ratio is quite favorable, so long as issues of confidentiality are addressed.

power capable of detecting an effect

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2. Confidentiality- the entire effort in Shanghai will involve three components: the diagnostic laboratory to be developed by Dr. Irons, Dr. Wong's study, and Dr. Irons's study. The databases for these three studies will be kept separate. Informed consent of subjects will be required to transfer information from one data base to another. Even when consent is obtained for such a transfer, only relevant information will be transferred. All this is spelled out very carefully in Section 2.10 of the protocol.

3. Informed Consent- At the request of the ethics review process, there will be two separate consent forms, one for the cases and one for the controls. Each will clearly explain whether they are being asked to participate because they are cases with the disease in question or whether they are being asked to be controls The consent forms are complete; what remains to be developed is a summary information sheet which explains the study in a culturally sensitive fashion

4. Excessive Inducements- There was considerable discussion of the amount to pay the subjects. On the one hand, one did not want to exploit the Chinese subjects by paying them less than one would pay American subjects for participaing in a similar study. On the other hand, one did not want to make the inducement so good as to make the offer impossible to refuse. The group decided to emphasize the former value and to avoid concerns about exploitation by paying $30, an amount similar to what Dr. Wong pays subjects for such studies in the U.S.

5. Questionnaire Development- In addition to asking about employment history, Dr. Wong proposes to administer a questionnaire to identify other possible risk factors. A concern was expressed about whether the questions which might be asked are inappropriate in the Chinese cultural setting. The questionnaire remains to be developed.

to be developed with help of Chinese ethicist

6. Control of Results- Although this is an industry sponsored study, it is important that the investigators retain final control over what is said in all publications to protect the integrity of the study and the acceptability of the results. This, and other aspects of a communication plan, are carefully outlined in Section 2.13 of the protocol.

Summary of What Remains to be Done- The information sheet for the consent process and the questionnaire about other factors need to be developed by Dr. Wong, in close collaboration with his Chinese colleagues and a Chinese bioethicist, and the final results need to be reviewed in the ethics advisory process. One other issue remains to be resolved in that process: is there any place in this study for interim review of results (to insure that any convincing results of great public health interest are released

if firmly established), or is that unnecessary in a case control study (in which no participants are put at risk by their continued participation).

Although there is work to be done, this study is ready to move forward from the perspective of an ethics review.

Disease Progression Study

At our meeting in Salt Lake City, Dr. Irons presented his original ideas about this study. They have been modified and developed extensively since that time, and what we now have available is part (not all) of the "front-end" of the protocol. Still, the group felt that we had enough information to make a tentative evaluation of the protocol from an ethics perspective. Once more, this will be done on an issue by issue basis:

1. Benefits and burdens to subjects and community- This study requires the development of an up to date diagnostic laboratory and the training of local personnel to do the diagnostic work. This alone represents a major contribution to Shanghai since the laboratory and the trained personnel will remain after the study is complete. In addition, this will improve the diagnostic reports for individual patients, and this may be of clinical value to them, especially for cases which will be followed in six month intervals (the cases of BP, AA, and MDS). All of this is spelled out in Section IV of the protocol. As the major risks to the subjects involve questions of confidentiality, the benefit-risk ratio of this protocol is quite favorable, so long as these issues of confidentiality are addressed.

will they be sustainable

2. Confidentiality- Although this remains to be spelled out more fully, it is our belief that there will be no problems here because of the basic principles of separation of databases and consent for transfer of information outlined above.

3. Informed Consent- We have not yet received the consent documents for review, although we have been assured that there will be separate consent forms for the different populations in this complex study.

4. Excessive Inducements- The question of the amount to pay the subjects was different in this study, because it was felt that we needed to take into account standard Chinese practice in connection with donations of blood, since such a donation has a different cultural meaning in the Chinese setting. Dr. Irons has proposed a payment schedule which ranges from $30 for control subjects for completing an interview (see analysis above) to $200 for those who donate blood and undergo a bone marrow biopsy and aspiration (this being comparable to what the Chinese receive for donating blood for transfusions).

5. Questionnaire Development- An analysis of confounders will be done (Section 2D) by use of a questionnaire. A concern was expressed about whether the questions which might be asked are inappropriate in the Chinese cultural setting. The questionnaire remains to be developed.

6. Control of Results- - Although this is an industry sponsored study, it is important that the investigators retain final control over what is said in all publications to protect the integrity of the study and the acceptability of the results. A communication plan, built around this principle, remains to be developed.

7. Other Issues- Two issues remain to be addressed in appropriate sections of the protocol not yet developed: (a) how clinicians/subjects will be informed of clinically significant information discovered in the disease progression follow up visits and how public health officials will be informed about the results of workplace visits indicating unsafe conditions; (b) how material will be used for later studies, including genetic studies. What we have heard from Dr Irons makes us feel confident that these issues will be dealt with appropriately.

genetic studies

Summary of What Remains to be Done- The ethics review process needs to

review the completed
"front-end" of the protocol once it is available (probably, in later February). In addition, a series of consent forms, and the questionnaire about other factors, need to be developed by Dr. Irons in close collaboration with his Chinese colleagues and a Chinese bioethicist, and the final results need to be reviewed in the ethics advisory process. One other issue remains to be resolved in that process: is there any place in this study for interim review of results (to insure that any convincing results of great public health interest are released if firmly established), or is that unnecessary in a case control study (in which no participants are put at risk by their continued participation).

Although there is more work to be done from an ethics perspective on this study than on the previous study, we believe that it will certainly meet all of the remaining issues and be ready to move forward from the perspective of an ethics review.

Molecular Epidemiology Study

The ethics review process has not yet seen any part of this protocol. From the discussions with Dr. Irons, there is no reason to believe that there will be any insurmountable problems from an ethics perspective with this planned study, but saying anything more would be inappropriate until we can review the "front-end" of this protocol.