

Memorial Blood Centers

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Memo

To: FDA
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CC: Roberta King-NMDP, Erica Heath IRB-IRC
Date: 5/12/2005
Re: Comments on Guidance for Industry: Using a Centralized IRB Review Process in
Multicenter Clinical Trials-January 2005

This guidance provides the FDA's current thinking on the use of Centralized IRBs when the same clinical protocol will be used at multiple clinical sites. We applaud the intent of this guidance, which is to simplify the process of initiating large clinical trials and to provide consistency of approach across multiple diverse sites. While well intentioned, the guidance will only achieve its end if local IRBs are sufficiently confident that (1) Centralized IRBs will fully carry out their duties in protecting local subjects rights and (2) that the local IRBs and the institutions they represent will not be held accountable for lapses in oversight by the centralized IRB.

Recent actions by the FDA and OHRP following well publicized adverse outcomes of clinical trials through very public warning letters have raised the awareness of research institutions of strict adherence to human subjects research requirements. The net effect of greater scrutiny is to make more difficult any delegation of responsibility for clinical studies at a research institution. There are also conflicting government regulatory pathways that further confuse even the knowledgeable practitioner of human subjects protection requirements. For example, it is our understanding that under the FWA system one institution can rely upon the review of another. The problem is that the relationship demands a change in the institution's FWA – for each instance! OHRP's implementation of 45 CFR 46.114 through that FWA mechanism is difficult for IRB professionals and must be much more arcane for those with only a passing knowledge of FWAs or IRBs. FDA, on the other hand, simply requires AN IRB approval and does not really care who gives it. The two systems it would appear are totally different.

The importance of allowing and encouraging the use of centralized IRBs may be exemplified by two large clinical trial networks that I am personally familiar with, the National Marrow Donor Program (NMDP) and Blood Center screening using tests under IND. The NMDP sponsors clinical trials within its network of donor, transplant, apheresis, marrow collection centers and cord blood banks – almost 300 discrete centers. Depending on the trial's research activities, IRB approval may be required from a significant number of these individual centers. For example, the current trial randomizing donor-recipient pairs to either marrow or peripheral blood progenitor cells (PBPC) has more than 100 participating donor

centers, transplant centers, and apheresis and marrow collection centers with the majority of these centers requiring local IRB review. From the NMDP experience, duplicative reviews at multiple centers has significantly increased the time to full trial participation at all sites and increased the time to implement important amendments to the protocol. In addition, one could also argue that while duplicative review adds significant burden to the already over-burdened IRB system, it does not add significantly to the goal of protecting research participants. On the other hand, a centralized IRB constituted with expertise in the type of research being conducted (e.g., hematopoietic stem cell donation and transplantation) would be able to better address the specific safety and ethics concerns related to the research thus advancing the goal of protecting research participants. While the guidance would seemingly eliminate the requirement for duplicative review, the practical result is that currently virtually all enrolled transplant sites still require local review and modification of myriad documents to meet local standards.

Similarly, recent experience with nucleic acid testing (NAT) for the purpose of blood screening has highlighted the challenges faced by blood centers in obtaining coordinated collaboration between myriad sites. For example, our own moderately sized community blood center performs NAT testing for our own collections and those of up to 16 neighboring community blood center and hospital based collections sites. At the onset of the Hepatitis B NAT clinical trial, the centralized IRB we were using interpreted the OHRP's current thinking at that time to require inter-IRB agreements for the testing. Not only were agreements required between the collection sites and testing site IRB, but if collections were performed at institutions such as hospitals or universities, that inter-IRB agreements were also required between the IRB of where the blood was donated and the testing site IRB. Since we collect at dozens of such institutions, the net effect was a 3 month delay and >\$10,000 of IRB applications fees, not covered by the sponsor.

When West Nile Virus (WNV) was recognized to be a true public epidemic with cases of transfusion transmission in the Fall of 2002, there was a race against time to get testing in place by the following summer's (2003) expected outbreak. The limiting factor for getting testing implemented in many places was, in fact, obtaining IRB approval. Only timely intervention by Dr. Jay Epstein of the FDA saying that inter-IRB agreements from sites of collection were NOT required allowed testing to be implemented in a timely fashion.

Hence, while we appreciate that there clearly need to be inter-IRB agreements for a transplant center IRB to defer to a centralized IRB, such as the NIH-NCI centralized IRB for Cancer clinical trials or other external and central IRBs, there should be some distinction when it comes to public health initiatives as exemplified by WNV screening and that simply collecting blood at a site does NOT require IRB approval from each and every blood drive collection site.

Another proposal for the public health arena only would be requiring everyone to defer to the CDC IRB or to the FDA IRB. While this may meet local resistance, the overwhelming public health benefits, such as prompt implementation of West Nile virus screening, may outweigh any perceived risks to study participants.

Paragraph IV that addresses local requirements is particularly challenging and may not be equally applicable depending upon the nature of specific studies. For example there is a requirement that the IRB review “through diversity of IRB membership, is intended to provide meaningful consideration of various local factors in assessing research activities, including the cultural backgrounds (e.g. ethnicity, educational level, religious affiliations) of the population from which research subjects will be drawn, community attitudes about the nature of the proposed research and the capacity of the institution to conduct or support the proposed research. This make eminent sense where the study might be perceived differently in different areas of the country. However, when a test is virtually mandated as a public health initiative, such as WNV screening where the FDA discouraged release of blood not tested, one wonders whether the myriad modifications of various donor consent materials required by the hundreds of IRBs reviewing these documents provided any measurable increment in human subjects protection. Hence, local review makes sense when local issues pertain. Local review may not be warranted for global public health initiatives.

Furthermore the document does not address the quandary that blood centers nearly universally have authority granted by each state to draw blood from donors younger than 18 without parental consent. Hence, the potential exists to have authority to draw blood from youth (which has a measurable risk) but the donor is not legally authorized to participate in blood screening research (which has infinitesimally small incremental risk), without parental permission, even when the test is mandated as a public health measure, such as WNV screening. Since high school donations represent a significant and vital proportion of most blood center’s Spring and Fall drives, it would create measurable shortages to exclude such collections when research testing is intended for public health benefit.