#1408

NEEDLE EXCHANGE PROGRAM

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Joan Claybrook, President

December 12, 1996

Harold Varmus, MD
Director
National Institutes of Health
Building 1, Room 126
9000 Rockville Pike
Bethesda, MD 20892

Dear Dr. Varmus:

We are writing to correct some of the many distortions and misleading comments contained in Dr. Dennis Fisher's November 12, 1996 letter to you concerning our request that you withdraw the $2.4 million NIH needle exchange grant awarded to him. One very central issue in assessing the ethics of the proposed study is whether the data on needle exchange program (NEP) efficacy are sufficient to preclude a randomized controlled trial. For the second time, Dr. Fisher acknowledges in writing that he believes that the effectiveness of NEPs has been demonstrated: "The reason for our research on this question is to test whether needle exchange decreases disease transmission and does not increase drug use, which the evidence to date indicates." (Page 7 of November 12 letter which we have just received.) This echoes the even more stark acknowledgment in his grant application that the study "represents the withholding of a potentially life-saving service." These admissions alone should be enough to stop the study in its tracks.

We would also point out that it is the very marginalization of injection drug users (IDUs) that has allowed this study to proceed this far. No one would seriously consider randomizing gay men to receive or to not receive free condoms. Even though there is no randomized controlled trial documenting condom efficacy in preventing HIV transmission, the well-organized gay community would never permit it. Unfortunately, the ad hoc committee you have convened to consider our request to cancel the study reinforces the notion that IDUs are excluded from critical decisions affecting their health: not a single IDU or IDU representative is included on the 10 person committee. Instead it is comprised primarily of academics, some of whom are recipients of grants from the NIH and whose interests may be very different from those of IDUs. The

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funding of this study, as we noted in our October letter to you, clearly represents a deferral to the alleged needs of researchers as opposed to the clear demands of public health. The exclusion of IDUs from the ad hoc committee merely serves to highlight this tilt.

Space and time preclude addressing all of Dr. Fisher's misstatements, so we have concentrated only on the most egregious.

"There is no state law prohibiting needle/syringe sales in Alaska." (Page 1 of Dr. Fisher's letter)

This statement intentionally ignores something Dr. Fisher well knows: the city of Anchorage, where the study would be conducted, has a paraphernalia law very similar to those that exist in the great majority of states in this country. (This is not mentioned in the body of the grant application or in the informed consent form for his study, but is apparent only upon close inspection of the material to be used by study staff to inform IDUs about the study.) Thus, the situation in Anchorage is similar to most jurisdictions in this country: pharmacists are expected to determine whether the purchaser intends to use the syringe for a "legitimate medical purpose," effectively putting a limit on syringe sales through pharmacies.

"Lurie and Wolfe do not mention...secondary or indirect exchanging." (Page 1)

Here Dr. Fisher is trying to have it both ways: on the one hand he claims to be advancing the field by conducting an unprecedented randomized, controlled trial (forcibly denying access to an NEP to half the subjects), while on the other hand he says that the phenomenon of secondary exchange (where syringes obtained at the NEP by those randomly assigned to the NEP arm of the study may make their way/be given to those assigned to the pharmacy condition) addresses our ethical concerns. Obviously, to the extent that secondary exchange occurs (and it is likely to be substantial–although still not enough to render the study ethical), it will seriously undermine the randomization process. Furthermore, there is every reason to believe that secondary exchange will introduce bias into the study and make it extremely difficult to interpret, particularly because Dr. Fisher does not plan to track syringes. It is doubtful, as Fisher claims, that they will be able to accurately measure the extent to which this secondary exchange occurs.

"Lurie and Wolfe are not aware that we removed a... 'compassionate arm' condition, termed a 'declared crossover'..." (Page 2)

We were quite aware of this decision. It is clear from the first pages of Dr. Fisher's December 1995 grant application that an earlier version of the grant included the "declared crossover" group, but NIH reviewers objected on the grounds that it would ruin the randomization. Faced with a decision between a less unethical

approach (allowing crossover for those who had not been randomized to have access to the NEP *if the IDU requests it*) and one that would be more likely to capture the research funds (answering the reviewers' objections and deleting the crossover option), Dr. Fisher predictably chose the latter: he removed the "declared crossover" group. While this decision makes the randomization procedure more vigorous (by reducing crossover, at least from the pharmacy to the NEP), it requires NEP workers to turn away IDUs assigned to the pharmacy condition should they request syringes at the NEP. Now Dr. Fisher hints that the "declared crossover" group may be making a comeback in that he has "had conversations with NIDA's Community Research Branch Chief" about this. This presents two problems. First, declaring one's desire to cross over to the other condition is no substitute for unrestricted access to both conditions, particularly if the IDU is seeking to please the researcher. Second, it is highly unlikely that the crossover so generated is going to be random, and the bias thus introduced will undermine the very basis for a randomized controlled trial. This highlights the unresolvable problem that plagues this research proposal: there is no way of providing adequate access to all syringe services–NEP and pharmacy–without undermining the randomized nature of the study.

We have surveyed and attempted syringe purchase at all of the pharmacies within the Municipality of Anchorage..." (Page 2)

It is interesting that, despite having surveyed these pharmacies, Dr. Fisher does not mention any results of this survey in his grant application or in his November 12 letter. Thus the only available data on actual syringe sales are those we brought to your attention in our letter of November 18, which described our early-November 1996 survey of pharmacy sales practices in Anchorage. In our survey, only 14% of pharmacies consistently, without encumbrance, sold syringes to IDUs, a far cry from the easy availability claimed by Dr. Fisher.

"There are several limitations to the [hepatitis B case-control] study." (Pages 3-5)

While no study is perfect, the importance of the Tacoma case-control study was recognized in the University of California and National Academy of Sciences studies, which relied heavily upon it in their determinations that NEPs can reduce the transmission of HIV. Even in the absence of a randomized controlled trial, six groups of federally funded researchers were able to use the great variety of NEP studies that provide consistent information on NEP effectiveness to conclude that NEPs are effective. One simply cannot do a randomized controlled trial to demonstrate effectiveness for all interventions in public health, particularly if to do so would be unethical, as in the present case. There is not a single behavioral intervention that has been proven to reduce the incidence of HIV in a randomized controlled trial: not condoms, not bleach disinfection of syringes, not HIV counseling and testing, not HIV prevention posters, etc., etc. The current impasse on federal NEP policy has nothing to do with the absence of a randomized controlled trial and everything to do with

politics. It is unfortunate that Dr. Fisher has chosen to exploit this unsavory state of affairs in order to further his career.

"[A research study] found that a majority of IDUs felt that over the counter purchase of syringes in pharmacies would be more effective than a needle exchange in reducing sharing." (Pages 5-6)

This still unpublished study speaks only to IDUs' opinions of effectiveness and provides no evidence that they are actually correct. The real point is this: some IDUs prefer NEPs, some prefer pharmacies and some will use both given the choice. In Dr. Fisher's study design, no IDUs will use both (unless crossover occurs, undermining the study) and many IDUs who would prefer one source of syringes will be assigned to the other condition.

"Contrary to the St Louis data, we have not been able to detect any ethnic bias to needle selling by pharmacists in Anchorage." (Page 6)

Again, no data are provided to back up this assertion. In our study of Anchorage Pharmacy sales, an African American woman was turned down at all five pharmacies she visited, including two pharmacies that had sold to non-African Americans the day before.

"Both groups will have increased access to needles, not decreased." (Page 8)

Whereas this is true, it is really a statement about the appalling state of clean needle access in Anchorage, manifested in extremely high rates of needle sharing among IDUs in that city. The absence of any needle exchange program in Anchorage until now reflects poorly on the Anchorage Health Department in that approximately 100 other communities in the United States have used state, county, local or private funds to start NEPs, despite the irrational continuance of the prohibition on the use of Federal funds. None of these restrict access to sterile syringes as does the proposed Anchorage one. Dr. Fisher has chosen to exploit the failures of local public health officials rather than working together with them to improve sterile syringe access for all IDUs–which would have a much greater impact on the public than Dr. Fisher's unethical experiment. Thus, although there will be some increased access to clean needles, limited to those who sign up for the study, all other IDUs (most IDUs in Anchorage) will not be able to benefit from the NEP. A real NEP would provide a much greater degree of access than the contrived experimental one proposed in this study and so it is unclear if the results of this study would even be applicable to other NEPs.

"It is common for needle exchange programs to be established so that the funding is contingent upon an evaluation being performed." (Page 8)

"If we did not have this kind of a strict research design [a randomized controlled trial], then we would not be able to have the Anchorage needle exchange program survive." (Page 9)

These are self-serving distortions of the history of the development of NEPs in this country. There is not a single NEP that has opened in this country (or elsewhere) with a requirement that a randomized controlled trial be conducted. In fact, many have opened with little or no evaluation component. There is no indication from the supporting materials for Dr. Fisher's grant application that any group's support was contingent upon conducting an evaluation with a randomized design.

"The Indian Health Service will provide vaccination to all Alaska Native referrals from this research project." (Page 9)

"The non-Alaska Native participants will be referred to the ... [sexually transmitted disease] clinic for administration of the vaccine. We will provide a coupon that our participants can present to the STD clinic." (Page 10)

Because there is no mention of these services–including the provision of vouchers to obtain hepatitis B vaccine–in the December 1995 grant application or in the informed consent sheet, and because one of the services is documented only with a reference to a personal communication dated October 31, 1996 (after our initial letter to you), this is obviously another "cover your tracks" measure similar to the reinsertion of the "declared crossover" group. The plain fact is this: the researchers have little desire to successfully vaccinate their subjects, as to do so would obliterate the study endpoint (conversion from hepatitis B negative to positive when the IDUs contract hepatitis B) and make the study meaningless. Given this obvious conflict of interest, and the researchers' insensitivity to other ethical concerns, we have little confidence that hepatitis B vaccination levels in this study will be substantial. This is particularly unfortunate as the prospective nature of the proposed study would provide an excellent opportunity for completing the three-injection regimen (particularly for those assigned to the NEP). Clearly, hepatitis B vaccination levels are proportional to the amount of effort given to the vaccination program. Again, if the meager hepatitis B vaccination program now contemplated by Dr. Fisher comes to pass, it may well undermine the randomization if IDUs assigned to the NEP, for example, are more likely to get vaccinated.

"Acute Hepatitis B infection has a case fatality rate of 1% (Page 10)

This is part of Dr. Fisher's ongoing efforts to downplay the seriousness of hepatitis B infection and thus justify his failure to provide hepatitis B vaccine. As he presumably knows, most hepatitis B mortality is not from acute infection, but from its chronic sequelae, including cirrhosis and liver cancer. In approximately 5-10% of patients who contract acute hepatitis B, the disease progresses to chronic hepatitis,

according to *Harrison's Principles of Internal Medicine*. And anyone who has contracted acute hepatitis can testify to how unpleasant it is. It is for these reasons that hepatitis B was recommended by the Centers for Disease Control and Prevention for all susceptible IDUs in 1991, the standard of care that Dr. Fisher plans not to observe.

"In the Tuskegee study, the men were actively prevented from obtaining treatment from other sources." (Page 12)

Of course, the IDUs randomized to the pharmacy condition will be "actively prevented" from obtaining access to free syringes through the NEP, so the Tuskegee analogy seems appropriate. And while the Tuskegee researchers observed their untreated subjects develop the complications of tertiary syphilis without intervening, Dr. Fisher plans to observe these IDUs as they develop sometimes-fatal hepatitis B even while he has the ability to prevent it (his inadequate and after-the-fact claim to be providing referrals to the vaccine notwithstanding.)

"In the Tuskegee study, no information was given to subjects about the true nature of the study..." (Page 12)

This attempt to distance the present study from Tuskegee ignores how manifestly inadequate the informed consent form for this study is. As one person who has written to you has noted (letter from Mark Hochhauser, Ph.D. to you, October 26, 1996), the informed consent form requires a reading level equivalent to 15 years of schooling, even though Dr. Fisher's own research demonstrates that Anchorage IDUs read at a 9th grade level. The informed consent form describes the randomization procedure as follows: "Those who are in the first study group will receive the benefit of information on how to purchase needles and syringes from Anchorage's pharmacies. Those who are in the second study group will be given the benefit of information on how to exchange their syringes at the syringe exchange." Here are some elements omitted from this wholly inadequate consent form: 1. If you are assigned to the pharmacy condition, you cannot attend the NEP; 2. If you are assigned to the pharmacy condition and attempt to exchange syringes at the NEP, you will be turned away; 3. If you don't sign up for the study you cannot attend the NEP; 4. The syringes at the NEP are free; 5. The NEP will provide other free services such as condoms, bleach, alcohol wipes, sterile water and HIV prevention literature; and 6. The researchers will be monitoring to see if you develop potentially fatal hepatitis B infection, even though they have a vaccine that could prevent it (in fact, there is no mention of hepatitis B vaccine at all in the informed consent form). This informed consent form is in clear violation of principle one of the Nuremberg Code, which requires adequate informed consent. These enormous holes in this misleading informed consent form make it clear that Dr. Fisher's description of that aspect of Tuskegee applies equally to his own study.

"If the criteria that Lurie and Wolfe are using to attack this proposal were applied to other studies, then no phase III clinical trial would have ever taken place." (Page 13)

As anyone who has followed our involvement in FDA affairs knows, we are among the most vocal proponents of randomized controlled trials to evaluate drug efficacy. Where we, unlike Dr. Fisher, draw the line is when the data from other studies are sufficient to support efficacy and subjects are not adequately protected from potential harm. As principle 5 of the Nuremberg Code states, " No experiment should be conducted where there is an *a priori* reason to believe that death or disabling injury will occur..."

The expected outcome of this study is a significant number of hepatitis B infections in those not randomized to the NEP. Aside from the flawed methodology–especially the revised version which seriously compromises the randomization and thus the sole alleged purpose of the experiment–these violations of the Nuremberg Code are more than sufficient to permanently stop this study.

Sincerely,

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Director