REPORT OF THE IMMUNO AG

COMMUNITY ADVISORY BOARD

Final version, September 1997

BACKGROUND OF COMMUNITY ADVISORY BOARDS

It is an established principle of research ethics that research on human subjects can only be carried out after informed consent. During the 1980s and 1990s a number of people have argued that participation of patients should be extended to the planning and actual conduct of clinical trials. This has resulted in the establishment of so-called Community Advisory Boards at different levels, mainly in the US. To our knowledge there has only been one other Community Advisory Board in Europe. These Advisory Boards are composed of representatives of the communities affected by HIV, and are typically consulted on various aspects of trial design.

BACKGROUND OF THE PRESENT COMMUNITY ADVISORY BOARD

Immuno AG decided to establish a community advisory board during the planning of its clinical trial of HIV-1 rgp-160 candidate vaccine in seropositive HIV-1 volunteers. The Board members were selected during the Winter of 1993/1994, and the Board had its first meeting in February 1994. The last meeting was held in Vienna in January 1997.

The members selected by Immuno AG were:

Ulrich Würdemann, from Köln, Germany
Hubert Hartl, from Vienna, Austria
Michael Toth, from Vienna, Austria
Reidar K. Lie, from Oslo, Norway

The Board decided to add another member, as no woman was represented on the initial Board. Consequently,

Claudia Fischer from Berlin, Germany

was added to the Board from the third meeting.

The initial selection of the members of the advisory board highlights one of the fundamental challenges of such a board: how to select a representative group of people. This has been an important topic of deliberation during the board meetings (see below).

WORKPLAN OF THE CAB

The CAB has had 10 meetings, 5 of them with the central sponsor. During these meetings, both issues relating to the clinical trial and relating to the functioning of the CAB were discussed.

Issues related to the clinical trial

During the meetings with the central sponsor the CAB raised a number of issues related to the clinical trial. These included:

1) Use of other medications during participation in the trial

2) Questions concerning reasons for drop-outs

3) Questions concerning the informed consent form

4) Information to investigators concerning the existence of a CAB

5) Questions concerning patient diaries

6) Compensation for injury

7) Information to participants after the trial

Issues related to the functioning of the CAB

The CAB spent a considerable amount of time working out a general framework for the functioning of a CAB, including proposing and getting accepted statutes governing the CAB. The statutes regulate the internal operations of the board, the relationship to the sponsor, as well as giving the main goals of the CAB. The statutes are attached to this report.

A CAB has four main functions:

1. Represent community interests during the planning of the protocol of the trial;

2. Represent community interests during the trial period, especially if adverse effects occur;

3. Facilitate the flow of information between the community, investigators and sponsor during all phases of the trial, including during the protocol planning period.

4. Advise Steering Committee and Sponsor in issues of accrual and compliance.

By the time the CAB was established, the clinical trial was well under way, and the

Community Advisory Board could consequently not influence the design of the protocol. There were also relatively few issues that arose during the clinical trial in the time period the CAB was in existence (some of these have been mentioned above). This particular trial has been characterised by high compliance by participants. There were, however, a number of more general issues that the newly established board felt that it was necessary to discuss and decide on:

1. Selection of members

2. Relationship to central sponsor and investigators

3. Flow of information and contact with the community and study participants

4. Honoraria of CAB members

1. Selection of members

The Immuno rgp-160 illustrates an important aspect of clinical trials in a European context. It is a multi-center trial carried out in 8 European countries. A Community Advisory Board will thus have to represent the interests of all the affected communities in all of these countries. This, of course, would be difficult, or impossible, to achieve. For one, the board would be too large with one representative from each of the countries. The challenge is therefore to establish a board that will nevertheless represent the interests of trial participants in the various countries, and how one should identify and select the representatives to the Board.

The members should somehow represent the various communities, and should be selected because of their knowledge of the needs, the concerns, and the life-worlds of the participants in the trial. Medical expertise is no necessary requirement. The various members of the CAB should ideally complement each other, in the sense that the CAB as a whole would have the necessary expertise with regard to representing the community interests.

The members of the CAB will ordinarily be members of various community based organizations, and may be people who have been active in issues of treatment policy in that organization. It is useful for the CAB to use such people. However, these people would not represent their respective community organizations and would not be responsible towards that organization with regard to their work in the CAB. Each member of the CAB is individually responsible to represent the various communities affected by HIV and AIDS.

2. Relationship to central sponsor and investigators.

One of the persistent worries by community representatives has been that CABs will turn out

to have no real influence, but will be used by sponsors of clinical trials as a token of community involvement. This is a real worry and can only be met by showing that concerns voiced by the CAB are taken seriously by investigators and sponsors. How to best achieve this has been discussed by the present CAB.

Initially, the CAB wanted a representative on the Steering Committee of the trial. This Committee is the one formally in charge, and makes all decisions concerning the trial. It is composed of 7 members with a medical background, and one representative from the central sponsor. The CAB felt that it should have a representative on this committee because the conduct of clinical trials not only requires scientific expertise, but also expertise from the affected communities. The Steering Committee for example makes the decision concerning premature termination of the study, which is a decision that not only requires scientific expertise.
This demand was, however, not met by the Sponsor. The reason given for this decision was that the Steering Committee was a body that made decisions concerning the scientific aspects of the study, and that community representation therefore was not necessary. Community concerns would, however, be made available to the Steering Committee, who would consider them together with the other relevant aspects of a particular decision. It was also agreed that in the future a member of the CAB would be a fully voting member of the protocol team.

The CAB continued to believe that a place on the Steering Committee was essential, but it felt that it would nevertheless not be necessary to press this point in the context of the present trial. One reason for this was that the Board felt that at present there is very little experience with regard to CABs that it would be better to press this particular point at a later date, when a number of different CABs have had a chance to function in a variety of different settings.

The Statutes adopted by the CAB and the sponsor stipulated that

- the CAB would meet regularly with representatives of the Steering Committee and the Central Sponsor

- a representative of the CAB would be present at the Investigators' meeting as a fully entitled member

- a representative of the CAB would be part of the Protocol Team as a fully entitled member (including voting).

It was also decided that the CAB will be in consultation with the Steering Committee regarding revisions of the protocol and respective proposals (before any decision is reached on such matters). The CAB will be informed regularly regarding information on serious and unexpected adverse experiences, recommendations by the Oversight and Scientific Advisory Committees (if any).

During the period of this CAB there have been some problems with regard to relationship between the CAB, the sponsor and the investigators. The CAB in agreement with the sponsor wanted a letter sent to all investigators stating that a CAB was in existence and giving information as to how the CAB members could be contacted. This letter was sent out after a

considerable delay, and after several reminders. The CAB also requested that information about the CAB was forwarded to the participants in the trial; the CAB has reason to believe that this has not been done in the majority of the study centers.

There have also been a number of problems with regard to the operations of the CAB, such as invitation to investigators' meeting, and dispatch of information concerning the clinical trial. There was also a delay in the approval of the statutes.

All of these problems were corrected after they were brought to the attention of the sponsor, although after some delay.

These problems in the relationship to the sponsor could point to a problem of sincerity by a sponsor with regard to the existence of a CAB. Clearly, a pharmaceutical company has publication relations interests in the existence of a CAB, and there is a continuing danger that this is seen as the only reason by the sponsor. We recommend strongly that a sponsor creates mechanisms within its corporate structure to take care of the concerns of a CAB. This includes, but is not limited to, making one person responsible for the relationship between the company and the CAB, creating means to deal with internal conflicts within the company which may affect the operations of the CAB, clearly defining the duties of the CAB liaison officer, and ensuring that there is a smooth flow of information concerning the CAB within the company.

This CAB started without much experience with running such a board. It would have been desirable to be able to draw on the experience of other CAB, for example those which are in existence in the US. Such contacts between CABs should be encouraged.

Finally, we would like to mention the usefulness of the monthly Medline searches on vaccine trials sent by the sponsor to CAB members. These have been important in the education of CAB members.

3. Flow of information and contact with study participants

One of the most important tasks of a CAB is to ensure a flow of information between study participants, the community, the investigators and the sponsor. As mentioned above, there have been some problems in this regard in the present trial. It is, for example, essential that study participants know of the existence of a Community Advisory Board. It is, however, also important that mechanisms are in place which will ensure that concerns in the community reaches the CAB. We propose the following structure to facilitate this.

One main goal of this particular CAB has been to establsih mechanisms and structures which can be taken over by future CABs, and which ensure that the general goal of communication between the community and the investigators is reached. We would like to suggest that the following should be done.

Any CAB will have to establish a means by which concerns of the community can reach the

CAB, and thereby the investigator/sponsor. This is a particular challenge because European trials take place in a number of different countries, and the CAB members are only from a few of these countries. The members of the CAB will of course hear things in the course of their daily activities, and may be contacted by the individual trial participants. Such information will, however, be somewhat limited, in particular it will be limited to the the cities where CAB members live. The CAB should therefore, in addition, identify specific individuals in the different European countries who can be a source of information for community concerns in their respective countries. The individuals should be selected because they occupy a specific position in a community organization to ensure that there is a permanency to the structure. These individuals will be asked to approach the members of the CAB if they get information which may be important for the CAB, the investigators or the central sponsor. Other people, including trial participants, can of course also contact the CAB members, but by setting up a structure such as this one with individuals who see it as their special responsibility to give important information, one will ensure that more potentially useful information will reach the CAB, the investigators and the Central Sponsor, which in turn will result in changes that will benefit the community.

Not only will the CAB not represent all countries, but may not represent all affected communities. Special attention therefore needs to be made to ensure that the needs of communities not represented in the CAB will be brought to its attention.

Another important function of the CAB is to provide information to the community. This has also been discussed at length by the present CAB. We do not think that individual members of the CAB, or the CAB as a body, should provide information directly to the trial participants. Information to trial participants should be the primary responsibility of the individual investigators. The question is whether the CAB should have a special role in ensuring that information important to actual and potential trial participants are being provided. We believe that the CAB should have such a role, and we propose the following ways that this can be achieved.

There should be a meeting between the CAB and the investigators taking part in the trial before the trial begins. One should also organise a meeting in each trial center where the CAB is introduced to the clinical trial participants who would want information about the CAB. In these meetings the reason for the existence of the CAB should be given and information about how to contact the CAB should the trial participants want to do so. The existence of the CAB should be clearly stated in the informed consent form, with information about how to contact the CAB.

The individual members of the CAB should have a special responsibility in organising information meetings in the various communities about the goals of the CAB.

Mechanisms should be in place to inform the participants after the completion of the trial of the results of the trial. This was done in at least one of the centers participating in this trial. The CAB recommends that such information be provided in all centers taking part in the trial.

4. Honoraria for CAB members

The CAB felt that the members of the board performed a service to the sponsor in that a CAB is essential for the successful performance of a clinical trial. It also felt, however, that it would be a problem if individual members depended financially on the honoraria received for the service on the committee. This could create conflicts of interests and impede the a critical stance towards the proposals by the sponsor. The CAB therefore decided after a lengthy discussion that the sponsor should pay a specific amount to the CAB for the service performed, and that the funds generated in this way should be used for community projects. It was agreed that the sponsor should pay DEM 2000.- per CAB member per meeting. The sum was calculated on the basis of a reasonable compensation for the time involved in participation and preparation for a meeting. The CAB would decide how to best utilise these funds for this purpose.

Initially, the CAB announced that it had funds available for community projects and received some proposals. During the review of the proposals the CAB experienced problems with regard to criteria for deciding which proposals the CAB should fund and how the CAB should ensure that the projects were carried out in an appropriate way. A substantial amount of CAB meeting time were used to discuss funding proposals. Based on this experience, the CAB concluded that its initial idea of receiving honoraria to fund community projects should be abandoned. It is a misuse of the CABs time to be a funding agency. Instead, a company should only provide generous funding for the necessary infrastructure and expenses for the CAB to carry out its activities.

The funds received from Immuno were used to organise a workshop during the Spring of 1997.

RECOMMENDATIONS FOR FUTURE CABS

- The CAB should be in existence before the process of designing the protocol has been started. A representative of the CAB should be a member of the protocol team

- a representative of the CAB should be a member of the Steering Committee

- the goals and tasks of the CAB should be clearly defined at the outset. The statutes worked out for this CAB could be used as a model

- there should be contact between the CAB and the trial participants in the sense that all trial participants should be informed about the existence of the CAB. This should be done in the following way:

- information about the CAB should be written into the informed consent form

- there should be an information meeting at the beginning of the trial where the CAB is introduced to the trial participants. At this meeting the goals of the CAB should be explained as well as information about how individual participants can contact the CAB members should they wish to do so.

- the CAB should be encouraged to draw on the experience of other CABs.

- the CAB members should not receive honoraria for their work, neither in the form of personal honoaria nor in the form of funding for community projects

- the CAB should receive sufficient and generous funding for the necessary infrastructure and expenses to carry out its activities.

PERSONAL STATEMENTS FROM CAB MEMBERS CONCERNING THEIR MOTIVATION TO PARTICIPATE IN A CAB

Claudia Fischer

Within Europe "Community Advisory Boards" are nearly unknown as an instrument of representation of the interests of people living with HIV and AIDS. Therefore, in 1994, I was more than astonished when I was asked to participate in a Community Advisory Board. It very quickly became clear that participation is not a question of pleasure but of necessity after I was concerned with the tasks of a Community Advisory Board more deeply. The fact that the already existing board was exclusively staffed with men made it even more necessary. They did not see themselves as able to take female aspects and problems into consideration. The position of women in general requests an inclusion. They have problems demanding their rights, ask questions or just be difficult, because of their female socialization. It is rare that women demand something for themselves or articulate their needs. Taking into account the already difficult relationship between doctors and patients in which they seldom have equal rights, a partial representation of women becomes even more necessary.

Of course it is difficult to be **the** representative for all HIV-positive women and women who are sick with AIDS. These women are extremely different, they have different backgrounds and living situations. They are not a homogenous group. Sometimes it is overwhelming for one single representative to bear all the different aspects of women's life in mind. Therefore the burden of adequate representation is huge. For this reason another women in the Community Advisory Board would have been a great help.

Fundamentally, I would plead for a balanced gender relation in future Community Advisory Boards. Further it should be recognized that all communities affected by HIV and AIDS should be represented on the board. Very often I felt uncomfortable with the fact that no representative of the drug-using community was a member of the board. In my opinion it is also important that no community is overrepersented as it is now the case.

During my work in the Community Advisory Board I, personally, learned a lot. The cooperation with my fellow members was very productive and solid. I understnad the confrontation with the other side, the pharmaceutical industry and their representatives and the resulting discussions as a progress. I am convinced that both sides have learned a lot. After this period of cooperation there is a better understanding of each others' needs.

I see it as my task to get more women involved and active in this kind of representation of interests. Especially HIV-positive women and women who are sick with AIDS should have a say and the right to make decisions on all levels of the HIV/AIDS. Nobody knows their situation better than they do.

Hubert K. Hartl

When I was asked to be a member of the "Community Advisory Board of Immuno European AIDS Vaccine Trials" (CAB) in February, 1994, I had no idea about the work, or obligations, of this kind of patient representation. The first meeting in early 1994 convinced me to participate in this board and I tried to be a representative of the hemophilia community/the hemophiliacs who were study participants.

In the first meeting with the Company chosen representatives of the gay community and one professor of medical ethics, we first decided to ask a woman to become a member of the CAB, as a representative of women's concerns. We discussed the independence of this CAB from the central sponsor as a very important factor, elected the Chair of the CAB, and decided to be "pioneers" in this, especially in Europe, very new field of community representation.

European patients with hemophilia look back at more than 25 years of self-help organizations, the Austrian Haemophilia Society (ÖHG) has a 30 year old history. Representation of patient interests as well as teamwork with nurses, doctors and the pharmaceutical industry are very common; or were very common in the time before AIDS. The HIV-infection changed the doctor-patient relationship; especially HIV-infected hemophiliacs had communication problems with their treatment centers, and their treatment centers with them. Hemophiliacs have, and had, problems with other HIV-communities like gay people or i.v.drug users; there was no contact between AIDS-support organizations and the ÖHG, for example.

These contacts developed during the last five years and the benefits for both need not be discussed here. So my input into this CAB was the experience in patient representation of an experienced self-help organization and I wanted to be a partner of study participants who have communication problems with representatives of other risk groups.

From the first meeting of the CAB we have not heard anything about problems between study participants and investigators; there were no questions from particiapnts to CAB-members, and especially there were no serious adverse events or similar study problems that we had to deal with.

Let me finish with some criticism. The communication with the other boards of the study and the clinical investigators could have been better; the function of the CAB-Liaison-Officer was not well defined for a while. As a result unnecessary problems arose. The CAB first met at the start of the study and there was no possibility to influence the study protocol. Information about patient compensation came at the end of the trial.

But at least it was a great experience for me. I learned a lot from and with my fellow members, and I think this CAB was a good and important step in patient representation.

Reidar K. Lie

There are two reasons why I wanted to take part in a Community Advisory Board. First, in

my academic work in Medical Ethics I have been particularly interested in ethical issues raised by clinical trials and in ethical issues in drug development. Second, as a gay activist I have been interested in policy issues with regard to AIDS in general.

It is now accepted that research on human beings cannot take place without their explicit consent. However, prospective particiants are today only to a small extent able to influence decisions concerning what trials are carried out, and decisions concerning trial design. AIDS activism has to a large extent questioned this state of affairs, and also within the field of research ethics there has been a growing recognition of the need to involve prospective participants in clinical trials in the protocol planning stage. The establishment of Community Advisory Boards is one such way of ensuring that concerns of affected communities are translated to concrete proposals of changes in the way clinical trials are carried out.

There is, however, also no question that we are only at the very beginning stage of ensuring real community input to the research policy and planning process. One of the fundamental challenges today is to establish a network of a group of people in Europe who are committed to work in this area, and who will be able to exercise real influence. I regard it as one of my personal goals during the next few years to assist in establishing such a network.

Michael Toth

The concept of "community representation" admittedly poses a problem for me as a representative of the "gay community". Hardly any other target group relating to HIV/AIDS poses such difficulty when it comes to specifying the term "community". To think that this is a clearly defined group is a mistake: Who is gay, after all?

Homosexuality is basically spread evenly among the total population. However, the way homosexuality is acted out and manifests itself openly depends on social and legal circumstances. For example, in Austria there was a total prohibition until 1971, meaning that homosexual behaviour and practices were generally punished or threatened with prison sentences of up to five years. But even today there are special laws discriminating homosexual women and men (higher age of consent for gay men, ban on advertisement and associations). Even though homosexual practices are now exempt from punishment, they are not socially adequate behaviour for the larger part of society. Naturally, only few of those concerned acknowledge their inclinations as part of their personality or even admit them.

Concealed homosexuals have become interesting for social studies primarily only after the occurrence of AIDS, because an efficient primary prevention of AIDS has to take into consideration the indivdual lifestyle in order to gain acceptance. The results of those studies showed it exactly: The more a gay person is socially integrated (as such), the closer he is within reach for AIDS prevention messages.

This raises the following questions: Is the concealed homosexual "gay" as well? Even if he possibly leads a double life, is married, perhaps even a father and only secretly indulges in his inclinations under the protection of anonymity?

Because of the growing pluralism in our society it seems to get more and more difficult to differentiate groups or even to define them. By their own definition many socially integrated gay men reject the label "gay", because the sexual identity is always only a partial aspect of one's whole personality. This is especially the case with bisexual men.

In conclusion it can be said that men who are - even though not exclusively - attracted to men basically form a target group for the sphere of HIV/AIDS. I have not yet brought the term "community" into play. This seems to me to be even more difficult to define, as it isn't so easy in a more and more open society moving away from ghettoization to tell who "belongs" to the community and who doesn't.

What does this mean for me as a representative of the "gay community"?
There are "matters of gay interest" as such. They concern a great number of people, but are - through reasons explained above - recognized by only a part and acted out by an even smaller part. But this doesn't affect their importance! I see my membership in CAB and my related function as a way to partially exercise these interests.

Ulrich Würdemann

Why do I work on a Community Advisory Board? It is really for personal reasons. First, there is Jean-Philippe, a very close friend of mine. When he was in the hospital, severly ill, I experienced how he was sitting in front of cups full of pills, not knowing or understanding why he should take what, and nobody cares. That he cannot eat crackers with an oesophagus full of fungus does not seem to bother anybody in the hospital. Accidentally I find out when asking about a new drug that he is taking part in a study (without being asked about that, or having been informed). An acceptance of his rights, of his concerns, and of his wishes did not take place. Then, the second reason, in the Spring a study of a therapeutic vaccine is terminated in Germany, not because of medical reasons, but because of commercial and management reasons. Only after pressure from the outside, and weeks after the premature termination of the study, are the asymptomatic positives informed that the study is terminated and that there will be no further access to the trial drug.

Taking the needs of people with HIV or AIDS seriously, taking into consideration the personal situation and and demands, seem to be increasingly more difficult for both the pharmaceutical industry as well as for the clinical researcher. Patients are often solely regarded as objects in the study, who should ideally behave quietly and with compliance. Independence, personal wishes or demands are regarded as disturbing.

I found, and still find, these conditions to be unacceptable. I would not want to experience these things myself. And I find that Community Advisory Boards is one possibility for changing these conditions, to influence the design and conduct of clinical AIDS research. And also a chance to use a critical dialog. To make protest and AIDS-activism creative and productive. That we still are far away from a true Community-Collaboration is surely correct, but this is challenge to continue to work on Community Representation.