URGENT

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DEPARTMENT OF EPIDEMIOLOGY AND POPULATION SCIENCES

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FAX MESSAGE

To Dr JOHN TOY
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From ANDY HALL

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Date 20/11/96

No of pages including this: 5

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Message:

I will phone to check you got this.

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EPIDEMIOLOGY AND POPULATION SCIENCES DEPARTMENT
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December 20, 1996

Dear John,

Re: National Registry of HCV infections

This proposal now contains more detail of the methods to be used but to my mind "ducks" the difficult questions. These are of two kinds a) questions related to the quality of the information on follow up - will it be possible to get reliable and valid data on subsequent illness and on other risk factors and b) the question related to the reason for transfusion in the look back study. Although they now claim that follow up is not the primary objective of the registry this must surely be the primary reason for setting it up (although as they state there will be possibilities of other important studies such as familial transmission). The recruitment of an appropriate control group is almost certainly going to have to come from other transfused patients (and perhaps those found HCV negative in the lookback study) and the logistics of this would be much simpler if they are done at the same time as the recruitment to the registry. My feeling is that the proposal must include this element.

In addition I feel that the investigative team needs to be supplemented in two areas. First there should be a hepatologist (or more) as an investigator to advise on clinical aspects. It should also be noted that the selection of the hepatologist(s) is critical to success given the competitive nature of hepatitis research in the UK with the accompanying acrimony. Secondly the group have limited expertise in cohort studies of chronic diseases (which this essentially is or will become) and they should include in the team an epidemiologist with experience in this area as well as naming a statistician who will be responsible for the work.

Clearly this is an important study which must be done. However I would suggest that only a pilot phase is funded with the requirement that a more detailed protocol being developed during this phase. The overall level of funding is modest currently but if the real value of the study is to be harvested then it will be considerably more costly. This will require a more detailed plan and costing.

I have attached detailed comments separately should you wish to forward them to the investigators.

I hope you have a good Christmas.

Yours sincerely

GRO-C

Dr A J Hall
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Reader in Communicable Disease Epidemiology

Referee's comments: National registry of HCV infections

This proposal is a little confusing in that in the accompanying letter it is stated that a natural history study of HCV is not feasible and then describes the setting up of a register which must surely have that as a primary aim. In addition there is in the proposal a discussion of a control group without any commitment to what it should be or how recruited. Whilst this is clearly a very important study if it is really not feasible to carry out a proper natural history study then one wonders if it is worth funding. Some of the issues will only be addressed by trying to do it and it would therefore seem sensible to pilot the procedures whilst developing a detailed protocol.

Some specific points:

1. It is not clear if deaths that have occurred in those transfused with HCV positive blood that have occurred before the look back will be included - it would seem important that at least death certificates on these are obtained to inform the generalisability of the study.
2. Under 3.1 it is unclear if there will be controls for this step in the study or will standard laboratory normal ranges be used? One critical issue is the reason for the transfusion - all of these subjects must have some prior disease or trauma and this will need to be recorded and analysed. This may also make interpretation of the liver disturbance pattern difficult without comparable controls.
3. Under 3.2 it is suggested that health planners will need to adjust the results appropriately to other routes of transmission and patient groups - it is quite unclear to me how this could be done without comparable studies in other groups.
4. The addition of other "new infections" - it is unclear how many of these there might be. It is not included in the sample size calculation. They will need to be treated separately from the look back subjects since they will have a quite different provenance - may be healthy at entry, may be IVDUs etc and hence may need additional control groups. The monitoring of new infections is surely a duty of CDSC anyway?
5. The inclusion of drug users under 19 and those with less than 3 years use represents inclusion of a quite different (and potentially large group). Since IVDUs have many other reasons for developing liver disease and a quite different pattern of morbidity and mortality to the general population a control group of uninfected IVDUs will be essential.
6. In 4.2 patient registration the reason for transfusion and prior illness will be critical information.
7. The sample size in the lookback study is clearly adequate but nothing is said about the other groups to be included.
8. Selection bias does no occur in cohort studies so the discussion of ascertainment bias refers to generalisability.
9. It is noted that flagging at Southport will still occur but how will this be interpreted with no control group??
10. The method of collecting information on additional risk factors is not specified in any detail. This is potentially a very difficult area and in order to get reliable standardised information is almost certain to require approaches to the subjects themselves directly either by postal questionnaire or interview. Reliance on clinicians to provide this information is unlikely to generate useful data.
11. It is unclear how "symptomatic liver disease" is defined. Since these subjects will have been told that they are HCV positive this form of subjective outcome is likely to be biased. Much more objective criteria are needed to define outcomes.

12. The proposal needs more development. It would probably also be beneficial to include both hepatologist(s) and epidemiologist(s) with experience in classical chronic disease cohort studies in the investigative team.