RD2 DATABASE - DATA INPUT FORM

TO: Dr Tony.

Please complete fully details of the project on the form below. Tick boxes as appropriate.

1. File No: 198/1013
   If confidential project please state reason:

2. Project Type: Initiative/Stand-Alone ☑ Unit ☐ Centre ☐ - If Centre or Unit: state name

3.

Project Title : National Registry of Hepatitis C Virus Infections

4 Contractor: PHLS

5. LeadResearcher: Dr. M. Ramsay

6. Name of Initiative - see below

(IES) Evidence Based Social Care	(IMH) Mental Health	(IME) Medical Education and Training
(IIT) Information Technology	(IVD) Vaccine	(IPL) Primary Health Care in London Lon
(ICH) Community Health Services	(IOA) OSCA	(IVH) Variations in Health
(IEP) Evaluation of Purchasing	(ICC) Child Care	(ISC) Skin Cancer
(IHR) Human Resouses and Effectiveness	(INU) Nutrition	(IHC) Hepatitis C ✓
(IHB) Individual Health Behaviour	(IPR) Prescribing	

7. Name of Theme (if not initiative) - see below

Environmental Health	Health Intervention	Health Organisation	Health Status	Lifestyle
Children/Social Care	Adults - Social Care	Cross Cutting	Prevention/Promotion	Non-theme

8. Planned Start Date: 1 April 97 Planned End Date: 31 March 2000

9. Joint funders: Home office ☐ Welsh office ☐ Scottish office ☐ OGD ☐ none ☑

10. Customer Division/s: HP

11. Budget Type: Frascati ☑ Medlink ☐ CJD ☐

12. Country: *(tick all required)* England ☑ Scotland Wales Northern Ireland
European Community ☐ International (non EC)

13. Tender basis: Resricted ☐ fully open ✓ negotiated

14. NABS Code (refer to the NABS Codes definitions previously distributed)

Human Health:		Social Structures and Relationship:	
4.0	General Research ☐	8.0	Research of General Nature ☐
4.1	Medical, Hospital Treatment, Surgery ☑	8.1	Education, Training, Recurrent Education and Retraining ☐
4.2	Preventative Medicine ☐	8.2	Cultural Activities ☐
4.3	Biomedical Eng. and Medicines ☐	8.3	Management of Businesses and Institutions ☐
4.4	Occupational Medicine ☐	8.4	Improvements of Working Conditions ☐
4.5	Nutrition and Hygiene ☐	8.7	Social Change, Social Processes and Social Conflicts ☐
4.6	Drug Abuse and Addiction ☐	8.9	Other Research with Regard to Society
4.7	Social Medicine ☐		
4.8	Hospital Structure, Organisation of Medical Care ☐		

15. Research Type:

Specific Applied Research ☑
Strategic Applied Research ☐

16. Primary Purpose Code:

Government Services ☑
Policy Support ☐
Technology Transfer ☐

17. Establishment Type:

Within the Dept. (inc RDD) ☐ Elsewhere in Central Government ☐ NDPB
Local Authorities ☐ Institutes of Higher Education ☐
Businesses ☑ Abroad ☐ Other (Non-profit Organisations) ☐

18. NRR Methodologies:

Before after trial without control ☐	Dissemination ☐	Questionnaire/s ☐
Cost Effectiveness Analysis ☐	Diaries ☐	Retrospective Study ☐
Cost Benefit Analysis ☐	Double Blind Method ☐	Secondary Analysis ☐
Case Control Study ☐	Economic Analysis ☐	Sensitivity ☐
Cohort Prospective ☑	Ethnography ☐	Specificity ☐
Cohort Historical ☑	Follow-up ☐	Statistical Modelling ☐
Crossover Trial ☐	Health Technology Assessment ☐	Survey ☐
Case Acertainment ☐	Interview ☐	Systematic Review ☐
Case Series ☐	Laboratory Study ☐	Theoretical Study ☐
Controlled Trial with Randomisation ☐	Literature Review ☐	Other - please state:
	Organisational Analysis ☐	
Controlled Trial without Randomisation ☐	Physical Sciences ☐	
	Prospective Study ☐	
Database Analysis ☐		

19. Programme Type: DoH ☑ RHA ☐ Other ☐

20. Project Funding Catergory: DH funded and managed ☑ MRC managed ☐

21. Protocol Written ☑

22. Peer Reviewed ☑

23. Intention to Publish ☑

24. Generalisable ☑

25. Finance Details - cost breakdown by calendar year:

NB: only additional funding is required for units/centres

1997	£	45 712
1998	£	57068
1999	£	52307
2000	£	
2001	£	
2002	£	

26. The above research has been agreed for funding. I have checked the **POLICY RELEVANCE** and **ABSTRACT** for accuracy and arranged for them to be entered onto the data-base.

Signed: GRO-C Date: 19 March 97

27. **Please return this form to:** IAN McENTYRE.

NATIONAL REGISTRY OF TRANSFUSION ACQUIRED HEPATITIS C INFECTIONS AND OF OTHER HCV INFECTIONS WITH A KNOWN DATE OF ACQUISITION

Dr M Ramsay, Ms K Soldan, Dr ON Gill, PHLS Communicable Disease Surveillance Centre;
Dr P Mortimer, PHLS Virus Reference Division;
Dr A Robinson, Dr P Flanagan, Dr S Knowles, Dr T Wallington, National Blood Authority;
Dr D Gibb, Institute of Child Health.

1.0 Summary

A national registry of "known date" hepatitis C (HCV) infections will be established to provide a facility for future monitoring of the natural history and long term outcome of HCV infection.

Infections presumed to have been acquired through transfusion of blood or blood products will form the nucleus of the register. The initial objective will be to include all HCV infected individuals identified by Blood Centres as a result of the current National Blood Authority "lookback" exercise. In the lookback exercise recipients of blood or blood components from HCV infected donors are being traced, contacted and offered counselling and anti-HCV testing.

The register will subsequently be extended to include other types of "known date" HCV infections. These will include:

i) infections identified in individuals with a known date of exposure to a known HCV infected source, where that exposure is likely to result in transmission (eg. HCV infected organ recipients);

ii) those where seroconversion has been documented (that is, an anti-HCV positive individual for whom a negative result of an anti-HCV test of the same type has been recorded at any point in the preceding 4 years, eg. people with haemophilia, injecting drug users, blood donors);

iii) laboratory confirmed and reported cases of acute hepatitis C infection;

iv) HCV infections of imputed known date (eg. individuals who are 19 years of age or younger at the time of the first positive anti-HCV test result and who are thought to have acquired HCV infection through injecting drug use; child born to an HCV-infected mother, where HCV infection in the child is confirmed at or before the age of 5 years).

Baseline information will be collected on each registered case. Limited follow up information will be collected on an annual basis over the period of the funding. The registry will provide minimum estimates of the distribution of times from HCV infection to biochemical, histological and clinical HCV-related illness and death, and if follow up is maintained will allow continual updating of these estimates. It will be a resource to be used for future studies involving or requiring "known date" HCV infections.

The register of HCV infections presumed to have been acquired through transfusion will be administered jointly by the National Blood Service (NBS), through the National Blood Authority (NBA) and the Public Health Laboratory Service Communicable Disease Surveillance Centre (CDSC). The registry will be managed by a registry coordinator. Success of the registry will be dependent on developing close collaboration with Blood Centres and others involved in the lookback exercise, and with hepatologists, paediatricians, and other clinicians responsible for the care of patients with known date HCV infections. In addition, close collaboration with other centres, including the Institute of Child Health, is also planned. Parallel arrangements in, and collaboration with, the Scottish centres (SNBTS and SCIEH) would be desirable.

Funding for an initial period of three years will be necessary to:

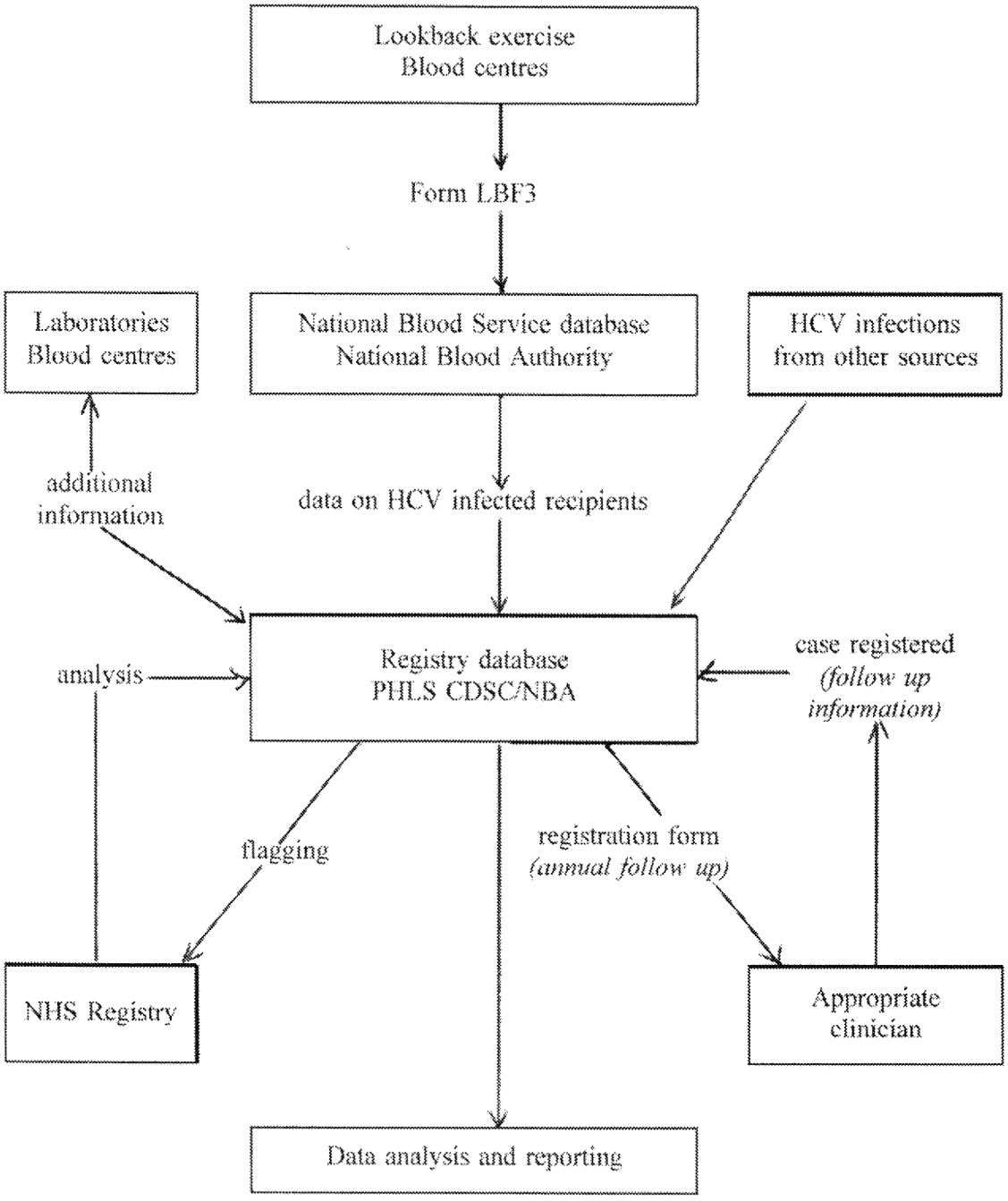
1. Establish the registry
2. To pilot recruitment mechanisms and methods for tracking patients
2. Explore the problems of ascertainment bias
3. Pilot the collection of follow up data
4. Determine the early outcome of HCV infection

This can be achieved for approximately £50,000 pa over the first three years.

Further long term support at an estimated £50,000 pa will be required to reap long term benefits from the project.

NATIONAL REGISTRY OF TRANSFUSION ACQUIRED HEPATITIS C INFECTIONS AND OTHER HEPATITIS C INFECTIONS WITH A KNOWN DATE OF ACQUISITION

SUMMARY ALGORITHM



2.0 Background

Knowledge about HCV infection has increased dramatically in the last six years, but important questions about the natural history of infection, the efficiency of sexual and perinatal transmission, and the effect of host and virus genotypes, co-factors (eg alcohol, infection with other hepatitis viruses), treatment and reinfection on outcome remain unanswered.

Anti-HCV screening of donated blood was introduced in the United Kingdom in 1991. As a result a number of anti-HCV positive donors were identified, of whom some donated blood before the introduction of screening. In early 1995, the UK Health Departments announced that a "lookback" at recipients of blood or blood components derived from anti-HCV positive donors would be undertaken. In the course of this exercise recipients are being identified from local hospital records, and those who are not known to have died are being contacted and offered counselling and serological testing for HCV infection. A high proportion of the recipients of HCV infected blood are expected to be infected with HCV, and, though most are likely to be asymptomatic at present, all infected recipients are being referred to clinicians with an interest in hepatic disease for assessment and clinical follow up.

Cases of HCV infection acquired following transfusion and identified by the lookback will be unusual in having a known date of acquisition, an identifiable source, and in having been identified relatively early in the course of infection. The introduction of screening, and the consequent exclusion of those found to be HCV infected from the donor panel, will have considerably reduced the incidence of transfusion acquired HCV infections, and only a few cases of hepatitis C infection diagnosed now or in the future will be due to receipt of HCV screened blood or blood products. Other than infections transmitted by transfusion, most known HCV infections have been diagnosed as a result of the investigation of patients with chronic liver disease or through testing those with recognised risk behaviours (eg. injecting drug use). For most of these infections the date of acquisition of infection or period of exposure is not even approximately known. Infections for which the source of infection is identifiable are ascertained even less frequently.

It is proposed, therefore, that a register of HCV infections presumed to have been acquired through transfusion of blood or blood components should be set up. This register will form the nucleus of a national central registry of "known date" HCV infections. An initial aim will be to register all HCV infections identified by Blood Centres during the current lookback exercise. Individuals who received potentially HCV infected blood or blood components but who, when tested, have no virological evidence of HCV infection when tested will not be entered in to the register; nor will those who are known as a result of the exercise to have died and not to have been tested for HCV prior to death.

The register of HCV infections presumed to have been acquired through transfusion in England will be administered jointly by the National Blood Service (NBS) and the Public Health Laboratory Service Communicable Disease Surveillance Centre (CDSC). It will require the collaboration of Blood Centres and others involved in the lookback exercise, and of those involved in the provision of continuing care to patients found to be infected.

3.0 Objectives

3.1 To describe the current biochemical, histological and clinically apparent liver disturbance in cases of HCV infection. To relate current status to the interval since presumed infection and other potential prognostic factors.

Information on natural history is needed to help determine the current and future burden of hepatitis C related disease on health care services, and to assess the impact of currently available treatments and those which may become available in the future. Other factors which may affect the outcome of HCV infection include the infecting genotype, initial viral load, transmission route/ exposure category, infection with other hepatitis virus(es) or HIV, age at infection, host genotype and alcohol intake. Although complete information will only become available after many years of follow up, baseline and short term follow up information collected during the period of establishment will help to ascertain the early outcome of infection, to provide prognostic information to patients and to inform shorter term health service planning.

3.2 To determine the representativeness of the registered population in relation to the total population of HCV infection in the UK

Although infected patients identified via the lookback exercise will form a unique cohort of individuals, the usefulness of the data generated will depend upon how representative this group of the total population of HCV infected individuals. This information will help to establish the appropriate resources to use on future follow up of this group and the future recruitment of patients to the register. If HCV infections acquired through transfusion progress more rapidly to disease than infections acquired through other routes, they may also provide an indicator of the maximum rate of progression, and health service planners will need to correct any projections appropriately.

3.3 To pilot and establish the appropriate methods for registration, follow up, and tracking of patients on the register

Establishment of the register will require the ability to identify the appropriate clinician to contact, the co-operation of that clinician and access to suitable baseline information. This pilot will help to determine the mechanisms which maximise the response rate, compliance, and completeness of clinical information. This process will inform the conduct of any future follow up and establish what future resources will be required.

3.4 To monitor the number of known new infections

Extension of the register to include categories other than transfusion acquired HCV will provide information on the trends in numbers of new infections in the UK, provided that consistent efforts are made to maximise case ascertainment, and provided that the way in which the infections have been ascertained (eg. tested during investigation of acute viral hepatitis; symptomatic chronic liver disease; tested after exposure to known HCV infected source) is recorded. As the register will contain only individuals with a "known date" of infection, it may not provide an unbiased estimate of such trends, since changes in testing patterns may affect the numbers identified even in the absence of any true change in

incidence. However, given the limitations and expense of other methods, the register will make a very useful contribution to knowledge.

3.5 To provide a shared national (or international) resource for use by those designing future studies

A number of future studies can be envisaged which would benefit from linkage with, and access to, the register. These include studies of sexual, vertical and household transmission; clinical trials of new antiviral drugs; further evaluation of existing antivirals and of alternative treatment protocols; determination of the relationships between viral load, genotype, and treatment and disease progression; and study of markers prognostic for progression to disease. Clinical investigators whose studies it was agreed to support would be provided not with direct access to registered individuals, but with access to the clinicians responsible for the continuing care of those individuals.

4 Plan of Investigation

4.1 Case definitions

4.1.1 Definition of a known date transfusion/transplant/tissue acquired infection

An individual with virologically confirmed HCV infection who received blood or blood components, or an organ or tissue from a known anti-HCV positive donor, where the date of receipt is known and the individual has neither a history of injecting drug use nor of receipt prior to 1985 of blood products for the treatment of haemophilia.

4.1.2 Definition of a seroconverter*

An individual with virologically confirmed HCV infection for whom a negative result of a test of the same type for HCV infection has been recorded at any point in the preceding 4 years. The "window" of five years has been chosen for two reasons. First, those who are frequently tested for HCV may be unrepresentative of the majority of HCV infected individuals, and selection of a narrower window would therefore restrict registration to a selected, and possibly unrepresentative, group. Second, analyses may be performed using a definition based on less than five years, by excluding those with a wider window, and the possible effect of the width of the window on the rate of disease progression can be studied.

4.1.3 Definition of an HCV infection of imputed known date

An individual with virologically confirmed HCV infection in whom seroconversion has not been documented but who:

a) first received blood products (FVIII/FIX) for the treatment of haemophilia between 1980 and 1984, or who received transfusion(s) of blood or blood components within a defined time period not exceeding 5 years and who has no other identifiable risk for HCV infection.

or

b) acquired HCV infection through injecting drug use and was aged 19 years or under at the time of diagnosis,

or

c) acquired HCV infection through injecting drug use, where the period of use of drugs by injection lasted for an identifiable period of less than three years,

or

d) a child of an HCV-infected mother, where HCV infection of the child is confirmed at or before the age of 5 years.

4.2 Patient registration

4.2.1 Transfusion associated infections

In the process of monitoring the lookback at recipients of blood components from HCV infected donors, the NBS is setting up a database of all the recipients who were traced and subsequently tested for HCV infection. The database contains information derived from lookback form LBF3 (which contains patient identifiers and information gathered during pre-testing discussion with the recipient), augmented by results of laboratory tests. Recipients found to be HCV infected will be reported by export of data from the NBS database to the central national registry database at three monthly intervals until the lookback exercise is complete. The data exported will include patient identifying information and details of the clinician responsible for the continuing clinical care of the patient.

Clinicians responsible for the care of recipients who fulfil the registry case definition will be contacted by letter, in which the purposes of the registry will be explained. They will be asked to register their patient and to provide information about the outcome of the initial assessment and the current clinical condition of the patient by completing and returning a standard report form to the national registry (Appendix B). The final format of the standard report form will be approved by an appropriate ethics committee.

4.2.2 Patient registration: other infections

There are a number of sources, or potential sources, of reports of HCV infections which may satisfy the other definitions above. These include the national surveillance system, to which laboratories report confirmed HCV infections; notifications to ONS of acute viral hepatitis specified as "non A non B hepatitis"; the NBS/CDSC infected blood donor and blood recipient surveillance system; the British Paediatric Association Surveillance Unit (an application to include HCV infection on this scheme is pending); local or regional registries of infected patients; and clinicians responsible for the care of patients with liver disease or for the care of individuals in identifiable risk groups. Where the surveillance systems receive reports of HCV infections which might be appropriate for inclusion in the register, the clinician responsible for the continuing care of the patient will be contacted and invited to register the infection. Participating clinicians, and others known to be likely to be responsible for the continuing care of individuals with HCV infections will also be invited to register other patients under their care who have transfusion acquired infection or who satisfy any of the other definitions above. In addition, the Epidemiology Department at the Institute of Child Health plans to conduct a study, through the BPASU, of HCV infection in children, which will include children born to mothers with HCV infection. The investigators will work with the registry to ensure data comparability. Data exchange between the two projects will be of benefit to both.

4.3 Sample size

As at August 1996, the NBA had identified approximately 6,500 components from donors known to be anti-HCV positive. For approximately 40% of these components there will be no infection traced (for example because the component was not transfused or the recipient has died). A total of 850 recipients have been identified and tested so far and approximately

60% of recipients have been anti-HCV positive (personal communication, Kate Soldan). With time the proportion of recipients traced is likely to decline but it is anticipated that 1000 people (adults and children) with transfusion acquired HCV will be identified as a result of the lookback investigation. The precise response rates from clinicians and the numbers of other "known-date" infections are unclear but will be estimated during the period of the study. This will allow more accurate planning for long term follow up and maintenance of the register.

By the end of 1996, 55% of anti-HCV positive patients identified so far by the lookback will have acquired infection seven or more years previously. Extrapolating from this, by the end of 1999, 553 of 1000 patients recruited will have acquired infection at least 10 years previously. Previous long term follow up of persons with HCV infection suggest that approximately 20% develop chronic liver disease after 20 years,[1] and a higher proportion would be expected to have biochemical liver abnormality. If we assume that by 10 years the proportion of patients with symptomatic liver disease will range between 2 and 5%, and the proportion with abnormal liver function will range between 10 and 50% this number of patients will allow precise estimation of these parameters (table). Even if the number of patients recruited is lower, fairly precise estimates can be obtained.

Table: 95% confidence interval for various outcomes at 10 years

Outcome	**Expected proportion**	**95% confidence interval**	
	at 10 years	n = 553	n = 400
Symptomatic liver disease	2.0%	1.0-3.5%	0.8-3.9%
Symptomatic liver disease	5.0%	3.4-7.2%	3.1-7.6%
Abnormal liver function	10.0%	7.6-12.8%	7.2-13.4%
Abnormal liver function	50.0%	45.9-54.3%	45.1-54.9%

4.4 Analysis

Baseline clinical information on the current virological, biochemical and clinical status of infected recipients will be analysed and compared according to years since presumed acquisition, age at acquisition, and other potential co-factors. Linkage of data on the infected (source) donor can also be linked to data on these infected recipient(s) on the register (Appendix C).

The ascertainment biases associated with this subset of infections are likely to be complex, because infections have been acquired via a single route, and only a selected proportion of infections acquired by this route will be available to the registry. To understand how the registered cases relate to the entire cohort of recipients, registry data will be compared with

any available data on the donor (source) and recipients of **all** presumptively infected blood components which were transfused. Basic data, such as age, sex and cause of death should be available for all recipients who have died or who could not be traced. Registered cases will then also be compared with available data on HCV infections acquired by other routes and in other risk groups (including donors). This information will become increasingly available over the next few years as seroprevalence studies, description of genotypic variation, clinical status of infections in other groups, and as surveillance of HCV infection becomes established.

Analysis of early outcome will be performed by a nominated statistician at CDSC, using standard techniques, including survival analysis. Where possible, if sufficient abnormality is detected, times to onset of abnormality will be compared by factors such as age at acquisition, sex, genotype, alcohol consumption, and co-infection with other hepatitis viruses and HIV.

4.5 Initial follow up

Although the period of follow up during this study will be small, it is important to establish the mechanisms for obtaining follow up information. As the current management of HCV infection is variable, and as this management is likely to change in the short term it will be inappropriate for the registry to prescribe regular investigation for this group of patients who are likely to be largely asymptomatic. In addition, patients on the register are likely to be recruited to local studies of investigation and treatment. It will therefore be impossible to follow all patients to a standardised protocol. This proposal will therefore seek to glean any available information in a standardised format from clinicians, accepting that clinical data may be incomplete.

Initial mechanisms employed will be as simple and flexible as possible to establish the feasibility of these methods, the appropriate clinician to contact (eg GP or hepatologist), and the completeness of information obtained. The proposed methods are:

a) Annual follow up of registered cases via the clinician responsible for their care.

Clinicians responsible for the continuing care of registered patients will be asked to complete and return a follow up form annually on each patient (Appendix B). Clinicians will also be asked to copy discharge summaries and details of medical out patient care to the registry.

b) Alternative sources of data for annual follow up

For those clinicians who decline to complete annual follow up forms for individual cases, a list of registered patients will be sent annually with a request for a simplified data set (date of last clinical contact, diagnosis of liver disease and/or death) as appropriate. For patients not under follow up with a hepatologist, request for this simplified clinical data may be made to the GP. Alternatively, arrangement could be made to export data electronically from local databases of patients receiving care for HCV-related disease to the registry.

c) "Flagging" of all registered cases at NHS Central Registry (ONS)

All cases on the register will be flagged at the NHS registry to allow follow up after movements within the UK and to capture deaths.

4.6 Formation of a resource for future study

The explanation of the purposes of the register which will be provided to clinicians in the letter inviting them to register their patient(s) will inform many clinicians with a research interest in HCV infection (and therefore potential investigators) about the registry and its potential. In addition, the existence and purposes of the registry will be made known, through existing networks and publications, to regional infectious disease epidemiologists, public health physicians, consultants in communicable disease control, consultant microbiologists, virologists, haematologists and paediatricians, and other groups or national bodies (eg. Medical Research Council) which might be expected to include potential investigators.

It is hoped that clinicians will perceive that the benefits of participation in the registry will include potential access to broader groups, and larger numbers, of patients than available within a single centre, and will wish to develop proposals for further studies. If large scale trials of therapy for HCV infection in both children and adults were set up, the register would provide a valuable resource. Close collaboration with, and data exchange between the registry and any "trial centre" would be beneficial to both, and could also avoid duplication of work involved in follow up by participating clinicians. The main areas of potential interest are outlined in appendix D.

All studies involving the use of registered patients would be approved by the steering committee and funding body and would require approval by an appropriate ethics committee.

4.7 Data Protection Act

The purposes for which PHLS CDSC and the NBA are licensed under the Data Protection Act cover such data collection and analysis.

4.8 References

1. Van der Poel C, Cuypers HT, Reesink HW. Hepatitis C virus six years on. Lancet 1994; 344: 1475-1479.

5.0 Management of the registry

It is proposed that a steering committee be set up to oversee the running of the registry and to act as both guardians and guarantors of access to the resource. A registry coordinator will be employed to coordinate the study and will initially work part time at PHLS CDSC and part time at the NBA, Watford. Close liaison with the Institute of Child Health will also be required. Statistical analysis will be provided by PHLS CDSC, and performed by a nominated statistician. Reports will be provided to participating centres/reporters, the NBS and the UK Health Departments, via the steering committee, at regular intervals. These reports will, in the first year, cover progress in setting up the registry, estimate completeness of recruitment of transfusion acquired HCV infections identified through the lookback exercise, and estimate coverage of the registry of patients with known date HCV infections whose continuing care is provided by clinicians in major UK liver units. If progress permits, initial analyses of data on registered patients will be presented. Subsequent reports will cover continuing recruitment and maintenance of the registry, and provide more detailed analyses of data on registered cases.

6.0 Funding

Funding for an initial period of three years would enable the establishment of the registry, and would be necessary in order to pilot recruitment, explore the problems of ascertainment biases in depth, pilot the use of data and monitor the early outcomes of HCV infection. If the initial phase is successful, continued support will be required to reap long term benefits from the project.

6.1 Staff

A full-time registry coordinator will be required. This person will have scientific or nursing qualifications with epidemiological and organisational skills and experience necessary to set up the registry. They will work partly at the National Blood Authority and partly at PHLS CDSC, and will collaborate closely with the Institute of Child Health. S/he will be responsible for all the day to day management of the registry; eg managing the export of data from the NBS database, compiling data from Blood Centres and laboratories, sending out and checking registration forms and annual follow up forms to clinicians, and attempting to track down patients lost to follow up. In addition, some extra support for part-time data entry will be required.

6.2 Other expenses

Computer hardware and software is necessary for storage of data, statistical analysis, graphics and word processing. Participating centres will be paid £6 for each registered patient and £3 for each completed follow up form received in order to cover local clerical and postal costs. The registry coordinator will need to keep in close contact with the many participating clinicians by telephone and fax. Data entry support is required to provide assistance to the registry coordinator in entering the forms onto computer; each form will need to be entered twice as a means of verification. Postal costs are to cover communications from the registry to participating centres. Travel costs are for the registry coordinator to travel to participating centres, blood centres, and laboratories to check on problems and to provide, if necessary, help with data extraction. Flagging cases at the NHCR, or use of ONS records to trace those lost to follow up are services which have to be paid for; estimates are provided.

Appendix A

Information to be provided by export of data from NBS database/other source

Surname (to be converted into soundex code, all cases have register number in addition)
Other names
Date of birth
Gender
Ethnic origin (census categories)
Country of birth
BTC of report

Donation number(s)
Component type(s)
Date of receipt
Donated since receipt?

Other reported risk exposures?

Previous transfusions
Occupational exposure to blood
History of skin piercing
Injecting drug use
Other (specify)

Laboratory test results

Laboratory name
Specimen number & date(mo/yr)
anti-HCV EIA
HCV RIBA
HCV PCR
anti-HBc
Known to be HCV infected?
Initial LFT results (AST, ALT, Bilirubin, Albumin): ND/normal/abnormal
Initial clinical assessment (prior to test)
  Well, with no symptoms
  Symptomatic liver disease
  Other medical problems

Name of clinician to whom case referred for clinical assessment
Title
Address

Appendix B

Information to be sought from clinician responsible for initial assessment

Case identifier/Hospital number
NHS number
Consent of clinician to include case on the register
Ascertainment method

Management in last 12 months

Results of most recent LFTs (BR, AST, ALT, Alb; normal/abnormal, date [mo/yr])
Liver biopsy (date & result: Scheuer/HAI/Knodell/other; not done)
Liver imaging (date, technique, normal/abnormal; not done)
Antiviral treatment started in last year (drug name(s), schedule, dates; none)
Trial entry (yes/no; name of trial; registration/code number, entry date)
Assessment drug treatment outcome:
- early cessation, side effects
- immediate/initial response(PCR neg on completion)
- sustained response (PCR negative 6/12 post completion)
- long term response (PCR negative >12/12 and after)

HCV genotype (type/not determined)

Current clinical status: alive/dead

if alive:
- well, asymptomatic
- symptomatic HCV related disease
- liver failure
- HCC
- on transplant list
- transplanted
- other liver disease no/yes (cause)
- other medical problem no/yes (specify)

Current clinical management
- out patient care only
- inpatient care intermittent (<2 x 12/12)
- inpatient care frequent (>3 x 12/12)

if dead: date, and cause (HCV related disease/not) of death

Other information

Alcohol intake units/week
Cigarette smoker number/day
HIV status (pos/neg/nk)
HBV & HDV status

Sexual partner
- Tested neg anti-HCV
- Tested pos anti-HCV
- Not tested
- No partner

Number of children
- Age/sex
- Test results

Name/address of clinician responsible for continuing care.

Information to be sought from clinician responsible at annual follow up

Management in last 12 months

Results of most recent LFTs (BR, AST, ALT, Alb; normal/abnormal, date [mo/yr])
Liver biopsy (date & result: Scheuer/HAI/Knodell/other; not done)
Liver imaging (date, technique, normal/abnormal; not done)
Antiviral treatment started in last year (drug name(s), schedule, dates; none)
Trial entry (yes/no; name of trial; registration/code number, entry date)
Assessment drug treatment outcome:
- early cessation, side effects
- immediate/initial response(PCR neg on completion)
- sustained response (PCR negative 6/12 post completion)
- long term response (PCR negative >12/12 and after)

Assessment current clinical status: alive/dead

if alive:
- well, asymptomatic, normal/minimally abnormal histology
- symptomatic HCV related disease
- liver failure
- HCC
- on transplant list
- transplanted
- other liver disease no/yes (cause)
- other medical problem no/yes (specify)

Current clinical management
- out patient care only
- inpatient care intermittent (<2 x 12/12)
- inpatient care frequent (>3 x 12/12)

If dead: date, and cause (HCV related disease/not) of death

Name/address of clinician responsible for continuing care.

Appendix C

Information required for linkage of infected recipient to infected donor

1: At registration the following recipient information will be recorded

Donation number*
BTC of donation origin

2: The NBA/CDSC infected donor surveillance system holds the following information about HCV infected blood donors detected after 1/10/95

BTC of donor test
Soundex**
Gender**
Date of birth**
Ethnic origin/ country of birth
Exposure category
Date of first positive anti-HCV test/donation
Donation numbers of most recent previous donations, date
Archived specimen? Yes/No

Blood transfusion centres (BTCs) will be asked to link, through their local records, lookback donation numbers for the infected recipient (1* above) to infected donor identifiers (2** above) and to provide all the above information for donors found to be HCV infected prior to 1/10/95. Donor and recipient identifiers will then be held on related source donor/recipient reports. BTCs will also be asked to provide details of the clinician responsible for the continuing care of the infected donor, and, if eligible, the infected donor would also be registered as a known date HCV infection.

Appendix D: Options for further data collection

Long term follow up and maintenance of the registry

Prospective follow up of newly identified HCV infections for which the date of exposure is known ("known date" infections), which includes monitoring of virological & serological factors and clinical course, offers the best prospect for further defining the natural history of hepatitis C infection. As current knowledge suggests that progression to disease is usually slow, and that less than 10% of those infected will die from HCV-related causes in the first two decades after infection, such a study will require a long term commitment.

Recruitment of controls for long term follow up

Prospective follow up will offer the prospect for defining the natural history of hepatitis C infection, but the majority of patients on the register will have received a transfusion. As it is known that transfused patients have a high mortality, this study could over-estimate the adverse outcomes attributable to HCV infection. This problem could be circumvented by recruitment of a control group of transfused patients who did not acquire HCV infection and by conducting a similar follow up on those patients. Controls could be identified via the blood centres but such a study would require additional resources and careful planning. The establishment of the registry will pilot the mechanisms of recruitment and follow up and provide estimates on which to assess the power of such a case control study and the possible resources required.

Linkage of data on registered cases to specimens from the case obtained at initial assessment (and at regular intervals thereafter) and archived in a central repository, or to specimens obtained from the infection source at a known date and stored in a central repository.

Storage of sequential specimens from registered cases in a central repository would provide a national resource for use in the evaluation of tests which will be developed in the future. Only a very simple protocol is likely to be operable in practice. Should this option be selected specimen collection will probably be restricted to inviting the clinician responsible for the care of the case to provide a 10ml (adults) or 2-5ml (children) sample of blood at the time of registration or thereafter and at annual follow up. This could be achieved by including appropriate specimen packs with the registration and follow up forms, and requesting the return of either a fresh 10ml specimen by post (which would be spun down, labelled appropriately, and archived in 1ml aliquots at the central repository) or the return of an existing sample of recently stored serum.

For special studies which required fresh specimens, or as an alternative to the formal storage of specimens as discussed above, the registry would be able to provide access, via the clinicians responsible for cases' continuing care, to groups of cases defined by variables of interest eg time period since infection. This facility will be of maximum use in the longer term only if newly diagnosed known date HCV infections continue to be recruited.