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SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE

CONFIDENTIAL

SCOTLAND/NORTHERN IRELAND HAEMOPHILIA DIRECTORS CLINICAL TRIAL TO ASSESS THE TOLERABILITY OF HIGH POTENCY FACTOR VIII/CONCENTRATE (HPVIII) MANUFACTURED BY SNBTS IN NON-HIV INFECTED PATIENTS WITH HAEMOPHILIA A

(HP 012)

Participating Centres

Aberdeen
Belfast
Dundee
Edinburgh
Glasgow (GRI & Yorkhill)
Inverness

PROTOCOL

25 NOVEMBER 1991

R R C STEWART

GRO-C

GRO-C (Fax)

SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE

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(HP 012)

Protocol dated .....

Clinical Investigator

Name .....

Title .....

Addres .....

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Signed .....
Date .....

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Signed .....
Date .....

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1. INTRODUCTION

The treatment of patients with haemophilia A was revolutionised in 1964 following the observation by Poole et al (1) who demonstrated that a fraction of plasma precipitated on thawing (cryoprecipitate) was effective in reducing bleeding in such patients. For many years, cryoprecipitate was the mainstay of treatment of haemophilia patients, until purified Factor VIII concentrates became available.

While this further improved the treatment of haemophilia patients, it was not without its drawbacks, notably virus transmission (HIV, hepatitis B and non-A, non-B hepatitis agents) and an apparent immune disturbance in non-HIV infected individuals. The cause of this immune disturbance has not been unequivocally identified, and many contaminants of the Factor VIII concentrate have been implicated, including immunoglobulin and total protein load. This suggestion has led most manufacturers to develop Factor VIII products which have less contaminating protein in them. The Protein Fractionation Centre in Edinburgh, in collaboration with French colleagues, have developed such a product.

This surveillance study is designed to assess the safety of HPVIII with respect to transmission of potentially infectious viruses. The protocol is based on the International Committee of Thrombosis and Haemostasis recommendations but entry criteria have been broadened and follow up more prolonged in certain circumstances.

The aim of this study is to assess the tolerability of HPVIII. This will consist of the following elements.

i. Immediate (allergic-type) reactions.

ii. Virological safety - to assess HIV, non-A, non-B hepatitis and parvovirus transmission by HPVIII.

iii. To assess effect of HPVIII on immune function, by measurement of lymphocyte subset numbers.

iv. To assess the development of inhibitors to Factor VIII in patients on HPVIII.

Blood samples will be collected before infusion of HPVIII concentrate and serially thereafter. The frequency of sampling decreases with time but it is envisaged that the patients should be followed up for at least 2 years after the initial infusion. Ideally a study such as this should be undertaken only in previously untransfused patients (PUPs) but the number of such individuals in Scotland is likely to be small within any one year and it is therefore proposed to include individuals who have only been transfused with single donation products, and those patients who were entered in the Z8 PUP study and were closely monitored and shown not to have contracted hepatitis. In addition to analysis of all patients entered, the data will be analysed separately for PUPs (Group 1), those who have previously received unfractionated blood products (Group 2), and those who were Z8 PUP's (Group 3).

2. METHODS

2.1 Patients

The patients will be hospital outpatients and will be recruited by the Haemophilia Directors of Scotland and Northern Ireland.

2.2 Inclusion Criteria

Patients of either sex and any age whom the physician believes requires Factor VIII concentrate and who belong to one of the following groups:

1. Previously untransfused patients
2. Z8 PUPS
3. Partial PUPs

Both patients with Haemophilia A and von Willibrands Disease will be recruited.

2.3 Exclusion Criteria

1. Patients who have previously been transfused with fractionated pooled plasma products, other than those who were part of the Z8 PUP study.
2. Patients who are known to have liver dysfunction ie to have abnormality of liver function on routine testing at entry or clinical evidence of chronic liver disease.
3. Patients who are serologically positive for anti-HIV, anti-HCV, HBsAg, anti-HBc or anti-HBs (unless due to vaccination).
4. Patients at risk of HIV infection other than from blood products.
5. Patients with a known history of alcohol abuse.

2.4 Number of Patients

Up to 40 patients will be enrolled.

3. TRIAL MEDICATION

3.1 Description

The product to be used in the study is:

HPVIII: Factor VIII in vials of approximately 250 IU with a specific activity of greater than 50 IU/mg protein. This product is prepared by the Protein Fractionation Centre, Edinburgh from plasma collected by the SNBTS and NIBTS and will be supplied gratis by the SNBTS.

3.2 Storage

Factor VIII concentrate should be stored in the dark at temperatures between +2°C and +8°C.

3.3 Resolution from the dry state

The vial of Factor VIII Concentrate and the sterile water for injections (Ph Eur) shoud be brought to room temperature before reconsitution. Remove the plastic caps from the Factor VIII Concentrate and the sterile water for injections (Ph Eur) and clean the stoppers with a spirit swab. Using a syringe, gently add te sterile water for injections (Ph Eur) to the dried Factor VIII. The contents of the vial should be mixed gently to ensure resolution. DO NOT SHAKE THE SOLUTION. The solution should then be allowed to stand without further agitation.

Performed in this way the reconstitution is generally instantaneous and should be complete within 5 minutes in the case of HPVIII Z8 may take up to 20 minutes to dissolve.

4. DOSE OF HPVIII

The dose of HPVIII given to each patient will be individualised to attempt to achieve blood levels appropriate for their clinical condition.

5. RECRUITMENT OF PATIENTS

The purpose and procedures of the study will be explained to prospective subjects and their unforced written consent obtained prior to their taking part in the study.

It must be emphasised to each prospective subject that, if they wish to withdraw their participation in the study, they are free to do so without prejudicing their clinical care.

6. TRIAL SCHEDULE

6.1 Infusion of trial medication

The material should be infused as soon as practicable after dissolution is complete. The rate of infusion should be such as to allow the infusion to be completed within 30 minutes. Continuous infusion over a long period is to be avoided.

6.2 Clinical monitoring

The patients temperature, recumbent blood pressure and pulse rate shall be noted prior to the commencement of the infusion and 15 min, 30 min and 1h thereafter. This is summarised in Appendix 1.

6.3 Sample Collection Arrangements

6.3.1 Prior to Therapy

See Appendix II

1. For emergency treatment take a single blood sample immediately before infusion of HPVIII concentrate. If possible an additional pre-treatment blood sample should be collected some time before entry for an elective procedure.
2. Give first injection of vaccine for Hepatitis B if not known to be immune.

Blood Samples

All samples will be analysed locally

At entry: 1. LFTs including ALT (or AST if ALT not available) and GGT

2. Serum stored (5ml, for children < 5 years - 1ml) at -40°C
3. Virology (HAV, HBV, HCV, EBV, CMV, HIV and parvovirus)
4. Lymphocyte subsets
5. Full blood count

6.3.2 Follow Up Samples

A. FORTNIGHTLY SAMPLES

Samples will be procured fortnightly until 16 weeks after the last infusion. For patients who took part in the Z8 PUP study, monthly sampling is acceptable.

Follow up samples:

1. LFTs including ALT and GGT. (If ALT not available locally measure AST immediately and store aliquot at -70°C for ALT measurement later if required).
2. Serum stored at -40°C (5ml, for children < 5 years - 1ml)

B. MONTHLY SAMPLES

In addition to those required in A above, a full blood count will be done.

C. THREE MONTHLY SAMPLES

In addition to the samples required in A and B above, T cell subset numbers will be determined. The following virology tests willl be performed at months 3, 6 and 12 : HAV, HBV, HCV, EBV, CMV, HIV and parvovirus.

These sampling schedules are summarised in Appendix II.

6.4 Procedure on Suspected Hepatitis Transmission

6.4.1 If ALT (or AST) > 50% over local normal range

Immediately

1. Retest sample locally
2. Recall patient for further sample. If ALT (AST) within normal range no further action required.

If ALT (AST) above normal range

a. continue to sample weekly until diagnosis of hepatitis confirmed or refuted.

b. Full clinical history and examination.

(Check list eg Alcohol
Drugs
Contact with an individual suffering from hepatitis or carrier
Abroad
Contact with other blood products
Parenteral drug abuse
Tattoo)

c. Virology to be undertaken locally. If patient develops hepatitis, serum sample to be sent to a Virology Reference Laboratory.

d. Inform Co-ordinating Centre by telephone and send written confirmation by first class post.

6.4.2 Definition of Hepatitis

Hepatitis is diagnosed by finding an ALT level greater than 2 and a half times the upper limit of the normal range in two samples taken more than 14 days apart.

6.4.3 Investigation of Suspected Case of Hepatitis

All episodes of hepatitis will be reported to the Communicable Disease (Scotland) Unit who will investigate and report to the Co-ordinator and Chairman of the Independent Data Review Committee.

6.4.4 Data Review Committee

An Independent Data Review Committee is established. All episodes of Hepatitis will be reported to the Chairman of this group who will take what action is considered appropriate.

6.5 Detection of Inhibitors to Factor VIII(c)

Samples should be taken to test for the presence of inhibitors to Factor VIII(c) before the first infusion and three monthly thereafter. Factor VIII inhibitor activity will be measured in Bethesda units.

6.6 Documentation

1. Entry Registration Form (Form A) should be completed as soon as a potentially suitable patient is identified and sent to the Co-ordinating Centre. The Co-ordinating Centre will issue a letter of confirmation of receipt which will include a patient study number.

2. Report of Infusion Form (Form B) should be completed on each occasion when the patient receives HPVIII or any other blood product and sent to the Co-ordinating Centre immediately.

3. Laboratory Report Form (Form C) should be completed and sent to Co-ordinating Centre immediately the results of each blood sample are known.

4. Virology Report Form (Form D) should be completed retrospectively for each patient at time of entry and six monthly thereafter.

6.7 Adverse Events

Acute adverse events in the use of Factor VIII concentrates are rare. Some patients experience slight irritation at the site of injection. A transitory headache or nausea following the administration of Factor VIII concentrate also has been reported and for individual patients, this appears to be batch related. In the event of any patient experiencing a reaction to the infusion, the infusion should be stopped immediately and appropriate medical action taken. The infusion should be restarted in such case only when, in the opinion of the attending physician, it is justifiable to do so.

6.8 Analysis of Data

The role of formal statistical inference in all studies of this kind should be very limited. With 60 patients randomly selected, if no side effects are seen, we can state with 95% confidence that the 'population' side effect rate does not exceed 5%. This type of statement will commonly be quoted in a protocol of this kind, but it is misleading. The patients are in no way a random sample, as they are seen over a short period of time, and in consequence will be receiving a limited number of batches of the product being tested. In a situation where batch variability may be important, conventional analysis will therefore give over-optimistic confidence intervals. With side effects expected to be rare, no useful statistical inference will be obtained on batch variability. Therefore, we believe that the best approach will be to report the data obtained descriptively.

In the presentation of results it will be important to stratify according to whether or not the patient has been previously untreated with blood products (Group 1) or previously treated with unfractionated products (Group 2) or previously treated with Z8 and prospectively monitored after such treatment (Group 3). In Group 2 early evidence of non-A non-B hepatitis may be a consequence of previous treatment and all relevant previous treatment would be included in the presentation. Throughout the study, any incident of non-A non-B hepatitis, or other possible major side effect will lead to a review of the data.

7. ADMINISTRATION

7.1 Ethical Review

The protocol will be approved by the ethics committee of each of the Haemophilia Centres which supplies the haemophilia volunteers. No individual, whose respective ethics committee has not consented to the study, will be entered.

7.2 Declaration of Helsinki

The trial shall conform to the recommendations of the Declaration of Helsinki as adopted at 18th World Medical Assembly, Helsinki, Finland, 1964 and as amended by the 35th World Medical Assembly, Venice 1983, and the 40th World Medical Assembly, Hong Kong 1988. A copy is appended (Appendix IV).

7.3 Legal Category

The trial will be performed under the terms of the Clinical Trials Exemption (CTX) Scheme. It will not take place until authorisation to proceed has been received from the Medicines Control Agency.

7.4 Compliance with protocol and deviations

The final protocol of the study will be agreed by the clinical investigators and the SNBTS and will be signed in confirmation of such agreement. The protocol will be approved by the SHHD and the local Ethics Committee. Any variations to this protocol must be agreed in advance by the clinical invetigators and approved by the SNBTS and SHHD. The Medicines Control Agency and the local Ethics Committee will be informed of any such variations. While in normal circumstances the protocol should be adhered to, in any emergency situation, the clinical investigator(s) shall exercise their clinical judgement and safeguard the patient's interests. In such cases, deviations from the protocol shall not require the prior approval of the SNBTS and the SHHD, nor the local Ethics COmmittee. Any such deviations from the protocol, along with full details of the reasons for their occurrence should be reported to the SNBTS in writing as soon as possible.

7.5 Confidentiality

Volunteers taking part in the study will be issued with a study number, and this number and initials will be used to identify samples and in the handling of data. Volunteers taking part in the study may thus be assured that their identity will be known to as few people as possible.

7.6 Maintenance of Records

The Case Report Forms of each patient shall be retained by the SNBTS for a period of at least 5 years and shall be made available for the inspection of members of the Regulatory Authorities, or other authorised individuals only.

7.7 Indemnity of Investigators/Haemophilia Doctors

Trials of SNBTS Factor VIII products are covered by a Scottish Home and Health Department Compensation Scheme which is based on the ABPI Healthy Volunteer Study Guidelines. The Department requires to review each trial before it can proceed.

7.8 Prestudy Documentation

The study will be conducted under the Clinical Trial (Exemption) Scheme (CTX) of the Medicines Control Agency. Trial medication will not be issued until Dr R Stewart receives the following:

1. Approval of the study by Medicines Control Agency by the issue of CTX.
2. A copy of the Local Ethics Committee's letter of approval.
3. A copy of the laboratory normal ranges for the tests required by the protocol.
4. A specimen copy of the informed consent form.
5. An up-to-date copy of the curriculum vitae of each of the clinical investigators.

7.9 Monitoring Responsibility

Monitoring of the trial will be the responsibility of Dr R Stewart who will visit the Centre to review progress at least every three months. During the early phases of the trial these visits will be more frequent to ensure that any misunderstandings are cleared up quickly.

7.10 Adverse Event Reporting

Any serious adverse events which occurs subsequent to the infusion of HPVIII should be reported immediately by telephone to Dr R Stewart or his deputy (Tel No 031 220 4590). A serious adverse event includes the death of any patient in the study of whatever causes, even if apparently unrelated to the trial medication. This is necessary as the SNBTS must report such reactions to the Medicines Control Agency promptly. Minor adverse events would be reported at the next regular monitoring meeting.

7.11 Early Cessation of the Trial

The SNBTS reserve the right to stop the trial if:

a. Recruitment is too slow to allow accrual of an adequate number of patients in a reasonable length of time.

b. Evidence is gained that patients are being exposed to an unacceptable risk.

c. For any reason, it is not possible to continue to supply the trial material.

d. Advances in therapy make the protocol obsolete.

7.12 Publications

Without prejudice of the intention to publish the results of this study, the SNBTS reserve the right to review any written or oral presentation of the data prior to publication. This is to ensure that no information with potentially commercial application is disclosed prematurely.

8. REFERENCES

1. Poole J, Hershgold EG, Pappenhagen AR, 1964 Nature, 203, 312.

APPENDIX I

CLINICAL MONITORING SCHEDULE

	Blood Pressure	Pulse Rate
Pre-infusion	X	X
15 min	X	X
30 min	X	X
1 hour	X	X

APPENDIX II

SAMPLING SCHEDULE

	Prior to therapy	Week 2	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16
LFT	X	X	X	X	X	X	X	X	X
Full Blood Count	X		X		X		X		X
Serum stored (5ml)	X	X	X	X	X	X	X	X	X
Virology	X						X		
Lymphocyte subsets	X						X		
Factor VIII inhibitors	X						X		

SAMPLING SCHEDULE (Continued)

	Week 18	Week 20	Week 22	Week 24	Week 36	Week 48
LFT				X	X	X
Full Blood Count				X	X	X
Serum stored (5ml)				X	X	X
Virology				X	X	X
Lymphocyte subsets				X	X	X
Factor VIII inhibitors				X	X	X

NB: Repeat months 4 to 6 until 2 years after entry or 26 weeks after last infusion whichever is the lesser.

APPEXDIX III

INFORMATION FOR PATIENTS
Clinical Trial Of High Potency Factor VIII

Trial Number: HP 012

You are invited to take part in a clinical trial of a new preparation of Factor VIII. This product is prepared by the Protein Franctionation Centre of the SNBTS from plasma collected by the SNBTS and NIBTS from unpaid Scottish and Northern Irish blood donors. These donors are all tested for the presence of Hepatitis B surface antigen. The factor VIII concentrate is of a higher potency than that previously produced by the Scottish National Blood Transfusion Service (having a specific activity of over 50 IU per milligramme of protein). It has been suggested that such higher potency factor VIII concentrates may enhance patient care. The most noticable difference which you as a patient will detect is that the product is made up in a smaller volume and it is likely to go into solution more quickly than other products which you have used.

A similar product (made from plasma from French blood donors) is in routine use in France and there is considerable experience with it. However, as this product has not been widely used within the UK, the Haemophilia Directors and the Scottish National Blood Transfusion Service have agreed that, in the meantime, it should only be used on a clinical trial basis.

The purpose of the trial is to closely monitor recipients of the high potency factor VIII concentrate to ensure that the use of the product is not associated with any

unexpected side effects. This will require that samples are taken at specified times for specified tests. This will mean that you attend the Haemophilia Centre more frequently than at present. Travelling expenses for such additional visits will be re-imbursed. The data gained will be very valuable and will assist in the improvment of haemophilia care in Scotland and Northern Ireland.
If you have any questions about the purpose or procedures of the trail, your Haemophilia director will attempt to answer them.

You are invited to take part in this trial, but should be clear that you may choose not to do so. Having agreed to take part in the study, you may withdraw at any time without being required to give a reason. You may be assured that refusal to take part or withdrawal will not prejudice your medical care in any way, although, obviously, you will not be able to continue to receive the high potency factor VIII concentrate.

The Haemophilia Director and the staff of the Centre will take responsibility for your clinical care during the study. They will halt your participation if it is felt that continued participation would be detrimental to your wellbeing.

The Scottish Home and Health Department has agreed to indemnify the Haemophilia Directors and their staff for any claims for compensation for damage or loss which paients suffer as a consequence of the use of Scottish National Blood Transfusion Service Products during clinical trials. This indemnity is in line with that which is normally offered by pharmaceutical companies in the UK (so called ABPI Guidelines: see British Medical Journal, volume 287, page 675).

All efforts will be made to ensure that information that

is obtained with this study which can be identified with you will remain confidential. In any written reports and pubications, you will be referred to by a code number only. It however is possible that representatives of the Scottish National Blood Transfusion Service or of governmental regulatory agencies may wish to examine your records and in signing this consent you give permission for such examination.

Some insurers treat participation in medical studies as a material fact which should be mentioned when making any proposal for health-related insurance and that accordingly participation in the study should be disclosed if the patient is in the process of seeking or renewing any such insurance and the patient should check that participation does not affect any existing policies (including endowment mortgages) held by the patient. A form to send to your insurers will be supplied.
This information for patients is intended to assist the patient in deciding whether to take part in the clinical trial. If the patient agrees to do so, they should sign the consent form which should be presented along with this document.

APPENDIX IV

DECLARATION OF HELSINKI

Recommendations Guiding Physicians
in Biomedical Research involving Human Subjects

Adopted by the 18th World Medical Assembly,
Helsinki, Finland, 1964
and ammended by the 29th World Medical Assembly,
Tokyo, Japan, October 1975
35th World Medical Assembly,
Venice, Italy, October 1983
and the
41st World Medical Assembly,
Hong Kong, September 1989

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge annd conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, 'The health of my patient will be my first consideration', and the International code of Medical Ethics declares that, 'A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient'.

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedureds involve hazaards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving hujman subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design annd performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically coompetent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportioon to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessmment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of sciencce and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimise the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians

should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should bot be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of theis official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are compiled with.

II MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgment it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic methods.

4. The refusal of the patient to participate in a study must never interfere witn the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (1,2).

6. The physician can combine medical research with professsional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-clinical biomedical research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interests of science and society should never take precedence over considerations related to the wellbeing of the subject.