SCOTTISH NATIONAL BLOOD TRANSFUSION SERVICE

CONFIDENTIAL

CLINICAL TRIAL OF COMPARING HIGH POTENCY FACTOR VIII CONCENTRATE (HPVIII) WITH AN INTERMEDIATE PURITY FACTOR VIII CONCENTRATE (Z8) IN THE TREATMENT OF BLEEDING IN PATIENTS WITH HAEMOPHILIA A

(HP014)

PROTOCOL

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Dr R R C STEWART

Tel No GRO-C
Fax No

SNBTS Headquarters
Medical Unit
Livingstone House
39 Cowgate
Edinburgh

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Protocol dated .....

Clinical Investigator

Name .....

Title .....

Address .....

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Signed .....

Date .....

Monitor Dr R R C Stewart
SNBTS Headquarters Medical Unit
Medical Unit
Livingstone House
39 Cowgate
Edinburgh
EH1 1JR

Signed .....

Date .....

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 time 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. One such product is HPVIII prepared by the Protein Fractionation Centre of the SNBTS. This product is prepared from plasma collected by the SNBTS and NIBTS.

The aim of this study is to demonstrate that HPVIII is effective in the treatment of bleeding in patients with haemophilia A.

2. METHODS

2.1 Study Design

The study shall be an open controlled study.

2.2 Patients

There will be no limit to the number of patients entered into the study. All patient who fulfil the entry criteria below and who, in the opinion of the Haemophilia Directors require to be treated with Factor VIII should be enrolled.

2.2.1 Inclusion Criteria

Patients should satisfy the following criteria:

1. be suffering from haemophilia A (WHO Disease Classification Number 286.0)

2. are at least 12 years of age.

3. have an active bleed, or require factor VIII replacement to cover surgery or dental extraction.

In the early phases of the study, patients will be hospital outpatients who present at the local Haemophilia Centre with acute bleed, which may be of the following type, haemarthrosis, post dental treatment. As experience with HPVIII increases, patients who are 'self administering' at home will be included in the study.

2.2.2 Exclusion Criteria

The following will be excluded from the study:

1. Patients whose bleed is considered to be potentially life threatening.

2. Patients with a history of severe reactions to blood products.

3. Patients who possess inhibitors to Factor VIII.

4. Any other patient whom the physician thinks is unsuitable for inclusion in the study.

2.3 Location of Study

The study shall take place at the Haemophilia Centre, Royal Infirmary, Edinburgh, the Department of Medicine, Royal Infirmary Glasgow, Department of Haematology, Royal Hospital for Sick Childrem, Glasgow and the Department of Haematology, Royal Victoria Hospital, Belfast.

3. TRIAL MEDICATION

3.1 Description

The products to be used in the study are:

HPVIII: Factor VIII in vials of approximately 250 IU with a specific activity of about 150 IU/mg protein.

Z8: Factor VIII in vials of approximately 200IU containing anti-haemophilic factor A at a specific activity of 0.5-1.0 IU/mg protein.

These products are produced 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) should be brought to room temperature before reconstitution. Remove the plastic caps from the Factor VIII Concentrate and the sterile water for injections (Ph Eur) to the dried Factor VIII. The contents of the vial should be mixed gently to ensure resulution. 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 FACTOR VIII CONCENTRATE

The dose of Factor VIII given to each patient will be individualised to achieve blood levels appropriate for their clinical condition. For a minor bleed, initial treatment should be with 500 IU. More severe bleeds will require increased doses.

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

Patients will be monitored for a 4 month period while being treated with Z8 and the efficacy of Z8 in treating any bleeds which occur in this time will be recorded. Thereafter the pateint will be switched to HPVIII and the efficacy of this product in treating bleeds will be recorded.

6.1 Clinical monitoring

When the patient is being treated in hospital, temperature, blood pressure and pulse rate shall be noted prior to the commencement of each infusion and 30 min, 1hr and 2 hourly thereafter until the patient leaves the unit or until 7 hours post infusion. (See Appendix I)

6.2 Infusion of trial medication

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

6.3 Measurement of efficacy

This is outlined in Appendix II.

6.3.1 Inpatients

The efficacy of the Factor VIII concentrates in treating bleeds in inpatients will be assessed as follows:

1. Severity of pain (assessed by rating scale, see Appendix I) at time zero and 5-6 hours (if appropriate).
2. Quantity and nature of analgesics required.
3. Circummference of muscle or joint at time zero and 5-6 hours (if appropriate).

4. Personal assessment of efficacy by the patien by selecting the one from the list which best described the outcome.

i. Extremely helpful
ii. Very helpful
iii. Helpful
iv. Only helped a bit
v. Did not help at all

5. Degree of restriction of joint mobility (assessedd by goneometry) at time zero and 5-6 hours.
6. Cessation of opening bleeding (if appropriate).
7. Failure of bleed to recurr within 48 hours (if appropriate).

6.3.2 Patients on Home Therapy

The efficacy of the Factor VIII concentrates in treating bleeds in patients on home therapy will be assessed as follows:

1. Severity of pain (assessed by rating scale, see Appendix III) at time zero and 5-6 hours (if appropriate).
2. Quantity and nature of analgesics required.
3. Personal assessment of efficacy by the patient by selection the one from the list which best described the outcome.

i. Extremely helpful
ii. Very helpful
iii. Helpful
iv. Only helped a bit
v. Did not help at all

4. Failure of bleed to recurr within 48 hours (if appropriate).

6.3.3 Patients requiring dental or other surgery

The efficacy of the Factor VIII to conncentrates in control of bleeding inpatients requiring dental or other surgery will be assessed by noting whether bleeding occurred and, if so, the extent of bleeding.

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 revised by the 41st World Medical Assembly, Hong Kong 1989. A copy is appended (Appendix II).

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 Permitted Deviations

The final protocol of the study will be agreed by the clinical investigators and the SNBTS and will be signed in confirmationof 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 clonical investigators 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 15 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. This is based largely on the ABPI Guidelines for Healthy Volunteer Studies. The Department requires to review each trial before it can proceed. They will issue a letter of indemnity to each major clinical investigator. Also, clinical investigators are indemnified against claims arising from their participation in the study.

In addition each major investigator will be required to sign an Investigator's Agreement.

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.
6. A copy of the Letter of Indemnity signed by the major investigator in that centre.

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 event 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 whatever cause, of any patient in the study, 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. REFERENCE

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

APPENDIX I

INPATIENT CLINICAL MONITORING SCHEDULE

	PRE-INFUSION	30 MIN	1 H	3 H*
TEMPERATURE	X	X	X	X
BLOOD PRESSURE	X	X	X	X
PULSE RATE	X	X	X	X

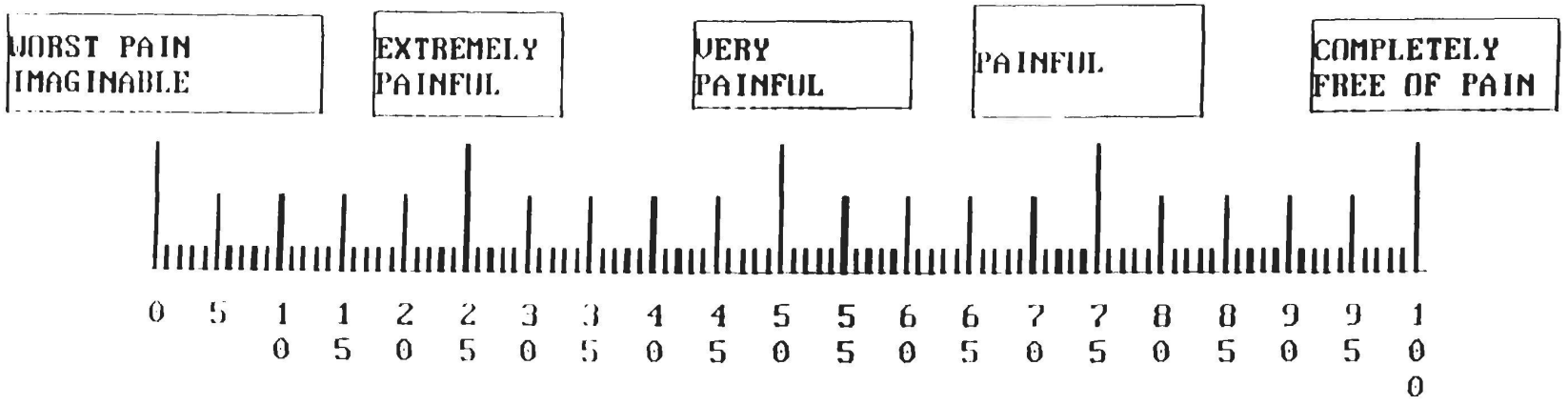
* Repeat at 2 hourly intervals until patient leaves unit, or until 7 hours post-infusion whichever is shorter.

APPENDIX II

GUIDE TO EFFICACY ASSESSMENT PARAMETERS

	Pain Severity Rating Scale	Circumference of joint or muscle	Goneometry	Analgesic Usage	Personal assessment	Cessation of open bleed	Bleed recurrence
INPATIENTS							
Joint or muscle bleed	X	X	X	X	X		X
Open Bleed					X	X	X
PATIENTS ON HOME THERAPY							
Joint or muscle bleed	X			X	X		X
Open bleed					X	X	X

PAIN SEVERITY RATING SCALE



APPENDIX III

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.