

Nigerian Version 01/05

A randomised double blind placebo controlled trial of oral Ephedrine and Etilefrine in the prevention of recurrent (stuttering) attacks of priapism in sickle cell disease: A multicentre International study in older children and adults.

Study Protocol

Priapism In Sickle CELL Study (PISCES)

CONFIDENTIAL

DISCLAIMER: This protocol is not intended as an *aide memoir* and is only to be used for individuals registered within the context of this clinical trial. This version of the protocol has been written solely for the purpose of the ethical approval in Nigeria.

STUDY PERSONNEL

Name	Institution/ Affiliation
Mr Adebajji Adeyoju FRCS (Urol)	Consultant Urologist, Stepping Hill Hospital. Poplar Grove, SK2 7JE United Kingdom
Professor Olu Akinyanju, MD FRCP	Professor of Clinical Haematology. Sickle Cell Foundation. Lagos. Nigeria
Mr. Jon Cartledge, MD, FRCS(Urol.)	Consultant Urologist, St James Hospital, Leeds. LS9 7TF
Professor Sally Davies MSc MB FRCP FRCPCH	Director of Research and Development, Department of Health, Richmond House, 79 Whitehall, London SW1A 2NS
Dr Jo Howard MRCP MRCPATH	Central Middlesex Hospital, London
Dr Kehinde BSc MB BS FMCP (Nig), Dip Path (lond)	Consultant Haematologist, Lagos University Teaching Hospital, Lagos, Nigeria.
Ms Julie Morris MSc	Head, Medical Statistics, Wythenshawe Hospital Manchester. M23 9LT. United Kingdom
Dr Ade Olujohungbe MD MRCP MRCPATH	Consultant Haematologist, Aintree Hospitals NHS Trust. Lower Lane Liverpool L9 7 AL
Mr Stephen Payne Mch, FRCS	Consultant Urologist, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL
Dr Moji Awogbide MRCP MRCPATH	Consultant Haematologist, Kings College Hospital. Denmark Hill. London. SE5 9RS
Dr Kate Ryan MBBS MRCP MRCPATH	Consultant Haematologist, Manchester Royal Infirmary, Oxford Road, Manchester M13 9WL
Dr Christine Wright MB ChB MRCP	Consultant Haematologist, City Hospital, Dudley Road, Birmingham B18 7QH
Dr. Josh Wright, BmedSci, MBChB, MD, FRCP, FRCPATH	Consultant Haematologist, Royal Hallamshire Hospital, Sheffield. S10 2JF
Dr Anne Yardumian MBBS MD FRCP FRCPATH	Consultant Haematologist, North Middlesex Hospital. Sterling way London. N18 1QX.
Professor Yetunde Aken'ova. FWACP FMCPATH	Professor of Haematology, University College Hospital, Ibadan. Nigeria.

TRIAL STEERING GROUP

Mr Adeyoju FRCS (Urol)	Consultant Urologist, Stepping Hill Hospital. Poplar Grove, SK2 7JE United Kingdom
Prof Olu Akinyanju MD FRCP	Professor of Clinical Haematology. Sickle Cell Foundation. Lagos. Nigeria
Dr Kofie Anie Phd	Central Middlesex Hospital.
Mr Adrian Brooks BSc (Chemistry)	Lay Person
Mr Nick George FRCS (Urol)	Consultant Urologist, University of South Manchester, Manchester. Chairman
Mrs Heather Gill Bpharm MRPS	Coordinating Pharmacist, University Hospital Aintree, Lower Lane, Liverpool L9 7AL
Dr Ade Olujohungbe MD MRCP MRCPATH	Consultant Haematologist, University Hospital Aintree NHS Trust. Lower Lane Liverpool L9 7 AL
Dr Anne Yardumian MBBS MD FRCP FRCPATH	Consultant Haematologist, North Middlesex Hospital. Sterling way London. N18 1QX.
Mrs Verna Angus Davies RGN RM	Counsellor, Manchester Sickle Cell and Thalassaemia Group Denmark Road, Manchester M13 9WL
Ms Julie Morris MSc	Head, Medical Statistics, Wythenshawe Hospital Manchester. M23 9LT. United Kingdom

INDEPENDENT DATA MONITORING COMMITTEE

Dr Iheanyi Okpala MBBS MSc FWACP	Consultant Haematologist, Department of Haematology, St Thomas' Hospital, London SE1 7EH
Mr Oluwabunmi Olaopa FRCS	Senior Lecturer in Urology, University College Hospital Ibadan. Nigeria.
Dr David Rees PhD. MRCP MRCPATH	Consultant Haematologist, Kings College Hospital. Denmark Hill. London. SE5 9RS
Mr P O'Reilly FRCS	Consultant Urologist, Stepping Hill Hospital. Poplar Grove, SK2 7JE United Kingdom
Ms T Remington BSc Hons MA	Cochrane Cystic Fibrosis and Genetics Disorders Group. Alder Hey Children's Hospital Eaton Road, Liverpool L12 2AP
Mr Christopher Roberts	The University of Manchester, Oxford Road, Manchester M13 9PT

LIST OF CONTENTS

Title page	Pg 1
Study Personnel.....	Pg 2
Trial Steering Group	Pg 2
Independent Data Monitoring Committee.....	Pg 3
Page Index.....	Pg 4
Introduction	Pg 5
Background.....	Pg 5
Objectives.....	Pg7
Methods	
Study Design.....	Pg 8
Eligibility criteria	Pg 7
Exclusion criteria	Pg 7
Sample size	Pg 9
Observation period.....	Pg 9
Patient Information and Consent	Pg12
Randomisation	Pg 10
Diary Keeping	Pg 10
Blinding	Pg 10
End Points	Pg 9
Tolerability	Pg 11
StatisticalAnalysis	Pg 11
Appendices	
Patient information leaflet	Pg13
Patient Consent Form	Pg 16
Patient Information Sheet 12 – 16 yrs.....	Pg 17
Relative/Carer Assent Form 12-16 yrs.....	Pg 20
GP Letter	Pg 21
Side Effects and Possible Drug Interaction of Study Drugs	Pg 22
Serious adverse events form.....	Pg 23
References	Pg 12
Patient Flow Chart	Pg 26
Care Pathway for the Management of an Acute Attack	Pg 24
Sample Diary	Pg 27

1. SUMMARY STATEMENT

This randomised (phase IV) double blinded placebo controlled trial aims to compare the efficacy and side effects of standard dose Etilefrine with two doses of Ephedrine in patients with sickle cell disease and stuttering intermittent attacks of priapism.

2. INTRODUCTION

Sickle cell disease (SCD) is the commonest inherited disorder of the haemoglobin molecule worldwide with a varying frequency of affected population per country. Carrier rates range from 0.1% in Europe to 40% in sub-Saharan African. It is estimated that there are approximately 12,000 affected individuals resident in the United Kingdom (Streetly *et al* 2001). Priapism, defined as painful, persistent penile erection in the absence of sexual stimulus, is a poorly documented but recognised complication of the disease. The precise incidence is unclear and earlier reports in the literature suggested that the prevalence of this complication in SCD was of the order of 2-6% (Miller *et al* 1995). Another report from the United States reported a higher incidence of 28% on direct questioning (Mantadakis *et al* 1999). We recently conducted a multicentre international semiquantitative study (Adeyoku *et al* 2002), which showed a much higher prevalence of 35%. Both these latter studies highlight a poor knowledge of this complication in patients and families with sickle cell disease. Some of the variability in the reported incidence may arise from the reluctance of patients to volunteer this information at clinic attendances and also a lack of awareness on patients' part that priapism is a complication of SCD. Mantadakis *et al* reported that only 7% of male patients attending a clinic in Texas, USA were aware of such an association.

The acute complications of priapism include pain, dysuria and psychological distress. Priapism can also precede or follow an acute painful bone pain crisis.

The long-term sequelae of priapism are also psychologically and physically damaging. These include varying degrees of erectile dysfunction, frank impotence, and sexual dissatisfaction including a fear of engaging in sexual activity.

This trial includes older children and adult cases with sickle cell disease actively attending a designated centre for care. Its aim is to compare a treatment modality in documented use with a more easily available alternative, in terms of tolerability and efficacy.

3. BACKGROUND

There are two types of priapism recognised: -

(i) a short self limiting episode lasting up to 4 hours which tends to be recurrent, nocturnal and is not associated with organ damage itself per se, called **stuttering** priapism.

(ii) an **acute major** attack, which requires medical and/or surgical intervention, failure of which can result in impotence.

The time limit for such intervention should be within 6-24 hours of the onset of symptoms. Any age may be affected by priapism but the majority of patients are

under 40 years with 10-25% having an attack in the first decade of life. 75% of patients will have had their first attack by their 20th birthday. Some controversy exists in the literature with regards the association between the two types of priapism. We recently carried out a 5-centre questionnaire survey, which showed a 35% incidence of priapism and a clear relationship of stuttering priapism as a harbinger of an acute major attack (χ^2 ; $p < 0.001$) (Adeyoku *et al* 2002). The mean frequency of attacks was 3 per month (range 3 per year - 4 per week). The mean duration of each attack was 1.25 hours. This relationship has also been reported from the large cohort of patients reported by Emond *et al* in the Jamaican study of sickle cell anaemia (Emond *et al* 1980). It seems therefore possible that prevention of recurrent attacks of stuttering priapism may prevent an acute major attack with its catastrophic consequences.

- Mechanism of Priapism and Rationale for Therapy

Ischaemic priapism is a failure of the penile detumescence mechanism from many causes among which are excessive release of neurotransmitters, blockage of the draining venules (the presumed causative factor in sickle cell disease), paralysis of the intrinsic detumescence mechanism, and prolonged relaxation of the intracavernous smooth muscles. The outcome is a persistently increased intracavernous pressure of 80 to 120 mm Hg and a gradually worsening ischaemic state. Typically, pain will not ensue until 4-6 hours have passed. The degree of ischaemia is a function of the duration of venous occlusion. Alpha-Adrenergic nerve fibres and receptors have been demonstrated in the cavernous trabeculae and surrounding the cavernous arteries, and norepinephrine has generally been accepted as the principal neurotransmitter to control penile flaccidity and detumescence. Animal studies demonstrate that the stimulation of sympathetic nerves or systemic infusion of Epinephrine causes detumescence of the erect penis (Diederichs *et al*, 1991a, 1991b).

Ephedrine is a sympathomimetic agent with direct and indirect alpha adrenergic activity.

- Treatment modalities for priapism.

Various conservative measures have been tried to abort attacks of stuttering priapism. These include hydration, simple and compound analgesia, exercise, tranquillisers, blood transfusion, vasodilators, anticoagulants and lately hydroxyurea. This represents a lack of consensus on the best treatment for this condition.

Diethylsiboestrol, an oestrogen in doses of 5mg, has been used in treating repeated attacks of priapism. The incidence of adverse events is relatively high (20%) in a relatively small number of patients (11 in total). It has feminising side effects and compliance may be a problem.

Oral α -adrenergic agents have been used in a non-systematic fashion to treat stuttering priapism. The most widely used is Etilefrine (Okpala 2002). Most patients were established on a dose of 50 mg modified daily release and that is the dose chosen for the study. Another alpha agonist is Ephedrine, which is a common ingredient in most "off the counter preparations" for common cold and may be a suitable alternative. The minimum effective dose has not been established. The side effect profile of Ephedrine include palpitations, tachycardia, insomnia, anxiety, dry mouth, tremors and these side effects are infrequent (<5%), mild and well understood and may be limited by taking the tablets at night. Furthermore, the doses intended for the study are relatively small and will ensure that side effects are limited. Neither drug is

currently licensed for this indication. Etilefrine is imported into the UK by special arrangement through hospital pharmacies. Ephedrine is broadly available in developing countries but Etilefrine is neither available nor affordable in these parts of the world. Both drugs are not known to be myelosuppressive hence making them suitable options to be combined with other agents such as hydroxyurea, which some patients take to ameliorate the course of their disease. If this study's results are positive, we believe its benefits may be widespread to male patients with sickle cell disease in all countries.

The treatment for an acute major attack of priapism includes outpatient penile aspiration with or without irrigation with α -adrenergic agent such as Epinephrine or Etilefrine (Virag 1996). This approach is only available in designated centres with a large number of patients and specialist urology input and is not available to many patients. Ephedrine and Etilefrine appears to be safe when taken orally, in the doses we propose to use in this study.

Study Objective

- (i) *To assess if oral Ephedrine or Etilefrine taken by patients with sickle cell disease is tolerable and if it reduces the rates of stuttering priapism and/or major attacks of priapism **compared to placebo.***
- (ii) *To see if oral Ephedrine is comparable to Etilefrine in efficacy.*
- (iii) *If it is so, to establish the minimum effective dose of Ephedrine.*

Eligibility criteria

- Must be male patients with a documented history of sickle cell disease irrespective of genotype. (α Thalassemia status will not be determined).
- Patients should be 12 years or over.
- Patients with a known history of stuttering priapism (a short self limiting episode lasting up to 4 hours which tends to be recurrent) attributable to SCD.
- Patients in active attendance at a designated care centre i.e. one visit in the last 6-12 months.
- Patients on a stable dose of hydroxyurea for over 6 months before trial entry can be included provided a baseline "event rate" (on treatment) is established before randomisation and no dose change occurs during trial period
- Patients who received a 'one off' or isolated top up transfusion greater than three months before recruitment date can be entered into study.

Initial discussions about trial entry will be established when patient is in "steady state" and *not* experiencing an acute event

Exclusion criteria

- Patients with sickle cell trait. (Hb A greater than Hb S on alkaline gel electrophoresis or HPLC) will not be eligible for randomisation.
- Patients' known to have elevated blood pressure or a history of cardiac disease.
- Patients with SCD and a documented history of stroke in the past.
- Patients with a history of vessel aneurysm in the past.
- Patient's known to be on MAOI (mono amine oxidase inhibitor drugs) or other drugs with significant interactions with study drugs e.g. tricyclic antidepressants, Reserpine, Phenelzine and Dopamine.

-
- Patient's known to be intolerant of α -adrenergic drugs.
- Patients with hyperthyroidism.
- Patients on a long-term blood transfusion programme to prevent or treat the complications of sickle cell disease.
- Patients with renal failure (serum creatinine greater than 400 $\mu\text{mol/l}$) are not eligible for the study.

Reasons for withdrawal

- A dose change in the Hydroxyurea during the study period.
- Patients transfused within the duration of the study period are also ineligible for analysis.

Once patients are recruited they will be followed up throughout the study duration on an 'intention to treat basis'.

Study Design(Appendix 1)

This is a randomised double blind placebo controlled trial between two doses of oral Ephedrine (15 mg and 30 mg) and a standard dose of Etilefrine (50 mg).

Recruitment

Patients will be told that priapism is a side effect of Sickle Cell Disease at a confidential interview during a routine clinic visit. Patient information leaflets will be handed to patients in 'steady state' by the local investigator. After 1 –2 weeks, patients who wish to participate will give written informed consent. A drop of blood will be blotted onto Guthrie cards at registration and stored for postage to a central laboratory in the UK.

Phase A. Patients will record prospectively over a six-month (6) period the frequency of attacks and any recognised precipitating event(s). Diaries will be collected at the end of phase A of the study period. Follow up will be 6 weekly in designated centres recognised for care of affected individuals under the supervision of a Consultant Haematologist/Urologist or specialist health care worker. Each centre will nominate a contact person for monitoring purposes. A completed entry form should be sent to Ms Julie Morris Medical Statistics, Wythenshawe Hospital Manchester. M23 9LT, United Kingdom, fax number: 0161-291-5816 at registration on starting Phase A.

Observation only period

The natural history of priapism is highly variable between individuals and even within the same individual over a period of time. It is very important therefore for us to establish the average "true" frequency of attacks or "event rate" before randomisation. A minimum observation period of **3 months** is required in all cases with a maximum of 6 months. There are a variety of self- help measures that patients can adopt to limit an attack or reduce its frequency such as oral rehydration, moderate exercise, simple or compound analgesia, cold or warm baths (Adeyoju et al 2003). None of these have been systematically evaluated. These should be offered in the first instance to see how

effective they are. If the frequency of attacks should increase or an acute attack should ensue during the observation period, then treatment according to local practice such as intracorporeal aspiration of blood with injection of epinephrine should be carried out or even surgery may be necessary. Thereafter, patients may be randomised to receive one of the study drugs (see suggested Care Pathway pg 21). This is at the discretion of the local physician but individualised cases should be discussed with one of the clinical coordinators:- Drs Ade Olujohungbe, Anne Yardumian, Mr Adeyoju or Dr Joshua Wright.

Phase B. Patients will then be randomised in phase B between four arms comprising of study drug, Ephedrine (in two doses 15 mg and 30 mg) and Etilefrine 50 mg and a placebo. Phase B will last 6 months. The Study tablets are white, and will include either placebo, Etilefrine 50 mg or Ephedrine in 15 mg and 30 mg formulations. They will be encapsulated and identical in appearance. Each patient will take two capsules once a day at night for the entire six months duration of phase B. If side effects appear the dosage can be reduced to one tablet for two weeks and notified to the Chief Investigator. If no further side effects occur, this dose is maintained throughout the study period. Tolerability will be assessed by evaluation of the diary for side effects. Grading of the severity adverse events will not be carried out to allow simplicity and consistency between centres. The number of patients still on the trial drug at the end of study period will be noted and the monthly “drop out” rate will be calculated from the diary returns.

Study end points.

- A change in the frequency/severity of attacks of stuttering priapism from baseline data.
- A change in the incidence of an acute (major) attacks of priapism.
- Tolerability of oral Etilefrine (50 mg) or Ephedrine at 15mg or 30mg with respect to side effect profile.

Sample Size

With 80 subjects in each group (320 in all) the study will have 80% power to detect differences of approximately 1.5 attacks per month between the active treatment groups and the placebo group, assuming the average attack rate is 5 per month under placebo, (where the attack rates quoted are geometric means and the common standard deviation of the logged attack rates is 1) The standard deviation estimate is based on data from a previous cohort study of subjects suffering from priapism.

The study will also have 80% power, using a one-sided test at the 5% level, to demonstrate equivalence in the attack rate per month between the active treatment groups, assuming the average attack rate is 4 per month under active treatment, that an average difference in attack rates of less than 1.5 per month indicates effectiveness (where the attack rates quoted are geometric means, the common standard deviation of the logged attack rates is 1, and the true difference in attack rates is zero).

The sample sizes above take account of the multiple comparison tests required with the active treatment groups and also assume an attrition rate of 5%.

Randomisation

This will be carried out using a separate randomisation schedule for each centre, created by the Department of Medical Statistics; South Manchester NHS Trust using computer generated randomised blocks (which will be used to prepare opaque, sealed, consecutively numbered envelopes, each containing the single allocation of a patient to one of the drug groups). The principal investigator at each centre will be responsible for enrolling patients into the study. The pharmacist at those centres will select sequential envelopes to assign patients to designated therapies

It is expected that randomisation will take place near the end of phase A.

Blinding

This will be a double blind placebo controlled study, neither the patient nor the clinician assessing the outcome will be aware of the drug allocation. The study drugs will be packaged by DHP Ltd (Clinical Trial Supplies, Waller House, Elvicta Business Park, Crickhowell, Powys, NP8 1DF) who will be responsible for the provision of the drugs in three monthly child resistant tamper evident caps according to cGMP. The study statistician and the company QP will be the only individuals with access to the codes.

The outcome will be analysed by the Statistician (JM) in Manchester, UK.

Clinical & Laboratory study

Blood pressure will be measured at the beginning of the study, two weeks into Phase B and then six weekly until study completion. A rise in systolic and/or diastolic blood pressure of greater than 20 mm Hg above baseline or above 130/80 mm Hg should lead to discontinuation of study drug and notification to the Trial office.

At recruitment a drop of patient's blood will be blotted on Guthrie cards to confirm diagnosis of sickle cell disease prospectively and to measure variant haemoglobins present. This card will be stored in a waterproof sealed bag and sent to the centres chief investigators laboratory for HPLC analysis.

No specific laboratory monitoring is required throughout the study period.

Diary Keeping

A colour-coded diary (blue) will be issued on entry into trial for collection of baseline data on frequency rates. This will be Phase **A**. Diaries will be reviewed 6 weekly in clinics by designated personnel for a total period of 6 months.

Upon randomisation: - start of phase **B**, a separate diary of a different colour (yellow) will be issued and also reviewed 6 weekly for a total of 6 months marking end of study. All diaries will be collected at the end of each phase and sent to the medical statistics department, South Manchester. The diaries will **not** differ in each centre but each centre will have a unique centre number allocated to it. As many centres that

demonstrate a willingness to randomise patients and collect data systematically in both countries will be encouraged to participate.

Data Management

Patient demographic data and completed diaries will be processed by the Department of Medical Statistics, South Manchester NHS Trust and entered onto a computer spreadsheet. Patient identifiers will not be included on the computer file, and all patient demographic data and diaries will be kept in a locked filing cabinet.

Data Monitoring

An independent data monitoring has been set up to follow the trial progress. The data committee will monitor the data 3 monthly. The trial statistician will be asked to submit a summary of the data three months into phase B for adverse events and tolerability of study drug. Data will be analysed at the end of Phase A and on study completion.

Statistical Analysis

Comparison of changes in attack rates over the period of the study between the active treatment groups and the placebo group will be carried out using analysis of covariance to adjust for baseline rates and a limited number of possible confounding factors.

Equivalence will be assessed by the calculation of confidence intervals for the difference in attack rates.

The analysis will be on an ITT basis, with subjects who discontinue treatment (only a very small number of withdrawals is expected) being followed up as far as is feasible.

Tolerability.

Common side effects of Ephedrine and Etilerfrine have been listed in check boxes on a weekly basis. Other unexpected side effects can be written in manually. How often these side effects occur per week will be noted in the diary by ticking the appropriate box or writing in space provided in phase B diaries.

Serious Adverse Effects

Definition

A serious adverse event (SAE) is defined as any undesirable experience occurring to a patient, whether or not considered related to the investigational drug, which results in:

- a) death
- b) immediate risk of death at the time the observation was made
- c) hospitalisation or prolongation of hospital stay
- d) persistent or significant disability or incapacity
- e) a congenital anomaly or birth defect

Serious adverse effects should be reported within 24 hours of the first full working day or after the weekend to the trials office by filling in the appropriate documentation and faxing it to Julie Morris (Fax: 0161-291-5816) and Dr Ade Olujongbe (Fax: 0151-529-3310).

3. REFERENCES

1. Streetly A., Maxwell K and Mejjic A. 1997
Sickle Cell Disorders in Greater London.
needs assessment of screening and care services. The Fair shoes for
London for London Report. London.
Department of Public Health Medicine UMDS and St Thomas's
Hospital.
2. Miller S.T., Rao S.P., Dunn E.K., Glassberg K.I. Priapism in children
with sickle cell disease J Urol. 1995; 154: 844-47
3. A.B. Adeyoju, A.B.K. Olujongbe, J. Morris, A. Yardumian, D.
Bareford, A. Akenova, O. Akinyanju, K. Cinkotai, P.H. O'Reilly
Priapism in sickle cell disease: Incidence, risk factors and
complications; An international multi-centre study. British Journal of
Urology 2002 90; 898-902
4. Mantadakis M.D., Cavender J.D., Rogers Z.R., Ewalt D.H., Buchanan
G.R. Prevalence of priapism in children and adolescents with sickle
cell anaemia. J. pediatric haematol./Oncol. 1999; 21(6): 518-22
5. Virag R., Bachir D., Lee K., Galacteros F. Preventive treatment of
priapism in sickle cell disease with oral and self administered
intracavernous injection of Etilefrine Urology 1996: 47(5): 777-81.
6. Okpala I., Westerdale N., Jegede T., Cheung B. Etilefrine for the
prevention of priapism in adult sickle-cell disease. Br. J. Haem 2002:
118(3):918-21
7. Diedericks W, Stief CG, Bernard F, et al: The sympathetic role as
antagonist of erection. Urol Res 1991a;19:123-126.
8. Diedericks W Stief CG, Lue TF, Tanagho EA: Sympathetic inhibition
of papaverine induced erection. J Urol 1991b;146:195-198
9. Emond AM, Holman R, Hayes RJ, Serjeant GR. Priapism and
Impotence in Homozygous Sickle Cell Disease. Arch Intern Med.
1980 Nov;140(11):1434-7.

APPENDIX A

A randomised placebo controlled study of Ephedrine/Etilefrine for prevention of recurrent (stuttering) attacks of priapism in sickle cell disease.

PATIENT INFORMATION SHEET

Dear Patient

You are being asked to take part in a multi-centre randomised trial this is being conducted in many hospitals throughout the UK and two centres in Nigeria. It has been subjected to ethical approval by your local hospital.

Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

REASONS FOR THE STUDY

Priapism is a persistent, painful erection of the penis. It can be caused by a variety of diseases but it is a well-recognised side effect of sickle cell disease. Things that bring on attacks are poorly understood, neither is there an agreed best way to treat this problem locally or internationally. We have some evidence that an acute severe and major attack is preceded by recurrent, short lasting (less than 4 hours) *stuttering* attacks. An acute attack can lead to severe pain, sexual dissatisfaction and impotence and may require major surgery.

We are carrying out a clinical study comparing two drugs Ephedrine and Etilefrine for preventing frequent attacks of stuttering priapism and its other long-term problems such as impotence and sexual dissatisfaction. We do not know if by preventing such frequent attacks medically, whether we can prevent a major attack thus reducing the number of people who may have to undergo a surgical operation to relieve it or be treated for impotence.

Cont....

Why have I been offered entry to the study? : You have been offered to take part because you are a male patient with sickle cell disease who has stuttering priapism.

We would be grateful if you would consider participating in our trial, which consists of two stages. An initial stage 'A', which lasts 6 months, consists of filling in a diary on how frequently you have these attacks. We will look at your diary every 6 weeks during a normal clinic appointment. At the end of six months, you will then be asked to submit the diary and to enter into stage 'B' to be randomised into one of four treatments arms these being; (1). Ephedrine 15 mg (2). Ephedrine 30 mg (3). Etilerfrine standard dose and (4). Placebo (dummy drug) You will be seen initially after two weeks and then every six weeks for a period of 6 months. You will be asked to fill in the study diary.

Neither you nor your Doctor will know what tablets you are taking.

What do we know about the study drugs: Ephedrine is a common nasal decongestant present in most common cold preparations bought over the counter in the UK and in some developing countries. Ephedrine is also licensed for the treatment and prevention of asthma. We are testing two strengths, 15mg and 30 mg of the Ephedrine tablet to see which effective dose will have the least side effect(s).

We are also testing Etilerfrine (a drug with a similar action) at a dose of 50 mg, which is less widely available but has been used in managing low blood pressure in hospitals and more widely used for treating priapism in the UK. This drug is licensed for the treatment of low blood pressure in other European countries such as Germany and Spain. The tablets to be used in the trial are identical in appearance. Neither drugs are licensed for this use but both have been used occasionally in sickle cell disease.

What side effects can I expect? Both drugs side effects are similar and only occur occasionally. Side effects include; tachycardia,(strong heart beat) anxiety, sweating. You may become easily annoyed. In people who are prone; chest pain and a rise in blood pressure can very rarely occur. The elderly are more likely to develop these effects on the heart. The side effects are usually mild and can be limited by taking the tablets just before going to bed at night. We are also using a very low dose of both drugs, which should still be effective. Your local doctor will monitor you for any side effects you may be having during that period and how often you are still getting the attacks and may advise you to stop if you are not tolerating the drugs. You will be asked to fill in your diary.

What happens at the end of the study? There may be a time period between the end of your participation in the study and the analysis of results. During that time you will receive the best care as decided by your Doctor in discussion with you. We will write to your Doctor. He or she will then discuss subsequent treatment with you either based on the results of the analysis or his suggestion. We hope that the results of this study will enable your Doctor to come a good decision about your care. Despite this fact, the best drug may not be subsequently available for your Doctor to prescribe for you.

Cont....

What else would be involved in the study? We would take a drop of blood from your normal blood sample taken at your clinic visit onto a special (filter) paper to re-confirm your exact sickle cell type. There are **no** extra blood tests needed for the purpose of the study. We will check your blood pressure at each clinic visit and review your diary.

What other treatments can I have? There are other treatments available for priapism but none of these have been agreed by everyone. These include drainage of blood in the erect penis by a needle and injection of a similar drug to cause flaccidity or surgery. You could have a long period of blood transfusion.

What happens if anything goes wrong? You are free to participate or not and this will in no way affect your subsequent care in the hospital you attend. There is no payment for doctors or patients as this trial is not sponsored by any drug company. If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence or wrong doing, then you may have grounds for a legal action but you may have to pay for it. You may withdraw from the study at any time without explaining why.

Will the information be confidential? Yes. Only those involved will be able to look at any records. Specific details which identify you will be available to your local doctor, the trial Medical Statistician and nominated members of the study on written request.

What benefits may I get from the study? The study may or may not benefit you. We hope that by preventing short 'stuttering attacks', we may prevent a major attack and/or reduce the number of patients requiring which can lead to impotence.

If further information is required, you can contact your local investigator or the Chief Investigator.

We hope you will agree to participate.

Many thanks for your anticipated co-operation

Chief Investigator

Dr Adebayo Olujongbe
MD MRCP MRCPATH
Consultant Haematologist
University Hospital Aintree NHS Trust.
Lower Lane, Liverpool L9 7AL
United Kingdom

Email: ade.olujongbe@aht.nwest.nhs.uk
Tel [0151-529 2837/3375](tel:0151-5292837)

Name and Address of local investigator

Professor Yetunde Akenova
Haematology Department
University College Hospital
Ibadan
Nigeria

Email: yetundeakenova@yahoo.com

APPENDIX B

PATIENT CONSENT FORM

Centre Number _____

Patient Number _____

A randomised placebo controlled study of Ephedrine/Etilefrine for prevention of recurrent (stuttering) attacks of priapism in sickle cell disease.

- | | | |
|-------------------------------------------------------------------------------------------------------|-----|----|
| I FREELY AGREE TO PARTICIPATE IN THIS STUDY | Yes | No |
| I have read the Patient Information Sheet provided | Yes | No |
| I have had the opportunity to ask questions about the study | Yes | No |
| I understand that my medical care will not be affected if I do not participate in the research study. | Yes | No |
| I give consent form my case records to be looked at if necessary for purposes of the study. | Yes | No |
| I can withdraw at any time without giving a reason | Yes | No |
| I give permission for my GP to be informed | Yes | No |
| I am happy to take the drugs for six months | Yes | No |

Name and signature of Participant:

..... **Date:**

Name and signature of Principal Investigator: .

.....**Date:**.....

APPENDIX C

A study of two different medicines [Ephedrine and Etilefrine], testing to see if one or both work, to reduce attacks of ‘priapism’ in boys and men with sickle cell.

PATIENT INFORMATION SHEET (12 – 16 YRS)

Dear Patient

Introduction.

Priapism is a persistent erection of the penis, which can last for minutes or hours, and which can occur especially in people with sickle cell. It can affect boys as young as 5 or 6 years of age. It is different from a normal erection in that it is painful. Often it settles down itself, or comes and goes over a period of time (‘stutters’). But sometimes it lasts such a long time that medical treatment, or even an operation, might be necessary. We know that if an attack goes on too long, it can cause damage to the penis so that having normal erections after a bad attack can be difficult or impossible. We are therefore trying to look for better ways of managing the problem.

What am I being asked to do? You are being invited to take part in a study which is happening in many hospitals throughout the UK and in two centres in Nigeria. The study involves writing in a diary over a period of six months when you have an attack. Then, for a further 6 months, you will be given some tablets to take every day. These may contain either one of the two medicines which we think might help reduce or stop priapism happening, or may be inactive dummy or placebo tablets. All the tablets look the same, and neither you nor your doctor will know what it is that you are taking, so none that what we see happening cannot be ‘twisted’ by what we think might happen. The people who are organising the study record which person gets which tablets, so we will know in the end which of the treatments is best. You will need to keep recording any attacks or symptoms in the diary we give you. We will therefore be able to find out if the treatments reduce the number of ‘stuttering’ attacks, and if they reduce the number of people who suffer bad, long attacks too.

Before you decide whether or not to take part, please read the following information carefully and discuss it with friends, relatives and your own GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. You will need to show this to your parent(s) or guardian, and discuss it with them too, as they will need to ‘sign’ to say it is OK for you to take part

Cont.

Why have I been offered entry to the study? You have been offered to take part because when we talked about it, we learned that you do have attacks like this.

What do we know about these medicines? Ephedrine is used by some people, in tablets or medicine they buy at the chemist's, when they have a cold to reduce having a blocked-up nose. Etilerfrine works in the same sort of way, and has been used to good effect in some sickle cell clinics to treat priapism, but it has never been compared to the first drug, nor to dummy treatment, to check how good it is, or which is best.

What unwanted effects can I expect? Side effects are expected only to occur occasionally. They might possibly include: being aware of your heart beating strongly, faster than usual heartbeat, sweating, or feeling a bit anxious. The side effects are usually mild and can be limited by taking the tablets just before going to bed at night. We are also using a very low dose of both drugs. Your local doctor will monitor you for any side effects you may be experiencing during that period and how often you are still getting the attacks and may advise you to stop if you are not getting on well with the medicine. You will be asked to fill in your diary regularly all the time through the study, so we know how you are and can see what difference the treatment is making.

What happens at the end of the study? At the end of the study, you will have your usual care as decided by your Doctor in discussion with you and your family. After the results have been studied, which can take some time; all the results will be communicated back to your Doctor. He or she will then discuss your subsequent treatment with you. We hope, but cannot promise, that we would be able to carry on giving you any treatment which you had found helpful, after the study has finished.

What else would be involved in the study? We would take a drop of blood from a normal blood sample onto a piece of paper to re-confirm your exact sickle cell type. There are **no** other additional blood tests required for the purpose of the study. We will check your blood pressure at each clinic visit (every 6 weeks) and look at your diary.

What other treatments can I have? other treatments are tried for priapism if it does not go away on its own, but none is very good. Urgent blood transfusions sometimes help, or some sort of operation may be necessary. Other tablets, which block the male hormones, can work but can have nasty side effects.

You are free take part or not and this will in no way affect your medical care, for this or any other problems, in the hospital you attend. There is no payment for doctors or patients as this trial is not funded by any drug company.

You may withdraw from the study at any time without explaining why.

Cont.....

Will the information be kept private? Yes. Only the staff involved will be able to see any records. Your personal details will be available only to your local doctor, and the study staff.

What benefits may I get from the study? The study may or may not benefit you yourself, but we hope that from the results overall we will find out which treatment is best for the majority of people, and this may help in choosing your treatment in the future.

Please think about what you have read, and if you have any questions or parts that you would like to have explained to you directly, just ask the clinic doctor who gave this to you.

With thanks,

Chief Investigator

Name and Address of local investigator

Dr Adebayo Olujohungbe
MD MRCP MRCPATH
Consultant Haematologist
University Hospital Aintree NHS Trust.
Lower Lane, Liverpool L9 7AL
United Kingdom

Email: ade.olujohungbe@aht.nwest.nhs.uk

APPENDIX D

Please print on appropriated hospital letterhead notepaper

Centre Number: :

Patient Identification Number for this trial:

**PARENT/GUARDIAN CONSENT FORM
AGE (12 – 16 YRS)**

A randomised placebo controlled study of Ephedrine/Etilefrine for prevention of recurrent (stuttering) attacks of priapism in sickle cell disease.

Name of Researcher:

Please initial box

1. I confirm that I have read and understand the information sheet dated (version....) for the above study and have had the opportunity to ask questions.

2. I understand that sections of my relatives/child’s medical notes may be looked at by responsible individuals involved in the study. I give permission for these individuals to have access to my relatives/child’s records.

4. Participation in this study is entirely voluntary and there is a right to withdraw from the study without giving a reason and in the knowledge that treatment following withdrawal will not be affected.

5. I have no objection for my relative/child to be included in the above study.

Name of Relative/Carer

Date

Signature

Relation to Child

Date

Signature

Name of Person taking consent
(if different from researcher)

Date

Signature

Verbal assent obtained Yes ___ No ___

1 copy for patient; 1 for researcher; 1 to be kept with hospital notes

APPENDIX E

Local Hospital Letterhead

GP/PHYSICIAN LETTER

Dear Doctor

Your patient with sickle cell disease volunteers a history of **stuttering priapism** (a self limiting episode of penile erection lasting up to 4 hours which tends to be recurrent) and has asked to be considered for entry into a international multi-centre randomised trial, comparing a placebo with two drugs, Ephedrine and Etilephrine. This will involve male patients from the ages of 12 to 65 years. The drugs are to be taken at nighttime and we expect them to have very little or no side effects. There are four arms and your patient has been assigned to Patients will be reviewed every six weeks at the study centre and they can withdraw at any time without giving an explanation. Your patient has been given an information sheet before registration.

If you require any further information, please contactyour local investigator or the Chief Investigator, Dr Ade Olujohungbe, tel: 0151-529-2837.

Yours faithfully

Side Effects and Possible Drug Interactions of Study Drugs:-
PISCES Study

EPHEDRINE	ETILEFRINE
Tachycardia	Tachycardia
Anxiety	Anxiety
Nausea	Nausea
Restlessness	Restlessness
Tremors	Tremors
Hypertension	Hypertension
Cardiac Arrhythmias	Cardiac Arrhythmias & angina
Dry mouth	cannot be excluded
Circulatory disturbances	Circulatory disturbances
Headache	Headaches or pressure in the head

These side effects are rare and the elderly are more susceptible. These adverse effects can be abolished with dose reduction.

Possible Drug Interactions:-

Ephedrine should be avoided in patients on monoamine oxidase inhibitors such as moclobemide, tranylcypromine and phenelzine, which are antidepressants.

It should be avoided in patients on other catecholamines such as Norepinephrine.

It may also increase the effects of Dexamethasone.

Increased risk of arrhythmias with volatile liquid anaesthetics and tricyclic antidepressants. Alcohol may antagonize the effects of Ephedrine but causes no adverse reactions.

Etilefrine may have an increased effect with guanethidine (blood pressure tablets), steroids and other tricyclic antidepressants and monoamine oxidase inhibitors. Beta blockers abolish its effects partially or completely.

APPENDIX F

SERIOUS ADVERSE EVENT REPORT FORM

In this trial it is important that unexpected serious adverse events are reported immediately to the principal investigators.

A **serious adverse event (SAE)** is defined as any undesirable experience occurring to a patient, whether or not considered related to the investigational drug, which results in:

- f) death
- g) immediate risk of death at the time the observation was made
- h) hospitalisation or prolongation of hospital stay
- i) persistent or significant disability or incapacity
- j) a congenital anomaly or birth defect

Serious adverse effects should be reported within 24 hours of the first full working day or after the weekend to the trials office by filling in the appropriate documentation and faxing it to Julie Morris and Dr Ade Olujohungbe.

DESCRIPTION OF ADVERSE EVENT

Signature Date

Name Position

Please fax to:-

Mrs Julie Morris fax: 0161-291-5815
e-mail: Julie_M@FS1.with.man.ac.uk

Or

Dr Ade Olujohungbe fax: 0151-529-3310
e-mail: ade.Olujohungbe@aht.nwest.nhs.uk

Suggested care pathway for the management of an acute attack of Priapism during PISCES study period

Acute Priapism is an intractable painful erection lasting more than 4hours, which fails to resolve despite optimal medical management.

In order to standardise its treatment in all PISCES study centres, the following is recommended. Treatment should be by a multidisciplinary team with a Urological Surgeon skilled in intracorporeal aspiration and instillation of intracavernous pharmacotherapy. **This treatment algorithm can however be overruled at the discretion of the primary physician of the patient.**

TIME OF STUDY	TREATMENT OPTION
<u>PHASE A</u>	<p>If a patient gets stuttering Priapism during phase A, they should be taught “<i>self- help</i>” measures which can abort or ameliorate an attack such as moderate exercise, rigorous oral hydration with fluids, warm baths. It is important to try to establish a “true event rate” before randomisation into phase B. A minimum observation period of 3 months is recommended. If however the frequency and/ or severity of attacks increases, the individual can be randomised earlier to phase B by discussing with the clinical coordinators or withdrawn from the study. It must be emphasised that this is at the discretion of the patient and local doctors and in the best interest of the patient. We would still collect data on the chosen treatment thereafter and its outcome in relation to the frequency of attacks for all recruited patients in the study. If the attacks become prolonged (more than 4 hrs) they should present to the hospital where penile aspiration of blood within the corpora should be carried out with instillation of diluted solution of Phenylephrine. A 19-gauge needle is inserted into one corpus cavernosum. Blood is aspirated and sent for blood gas analysis to document the degree of ischaemia. Blood is then aspirated from the corpora (10-15ml), discarded and replaced with an equal amount of normal saline. This process is repeated until the aspirate is bright red. A solution of phenylephrine is prepared by taking 1ml containing 10 mg and diluting it to 100ml with normal saline. 3-5ml of this dilute solution is then injected into the corpora and this process is repeated at 10-minute intervals until the erection subsides. The patients pulse and blood pressure should be monitored during this procedure. A competent Urological surgeon in collaboration with the study physician should only undertake this manoeuvre.. The date of the attack should be noted and the patient should then be randomised between the four arms of the study drugs and continue as in phase B.</p>
<u>PHASE B</u>	<p>If a patient gets an acute attack during phase B while receiving one of the study drugs, the patient should have intracorporeal aspiration and instillation of a diluted solution. A competent Urological surgeon in collaboration with the study physician should only undertake this manoeuvre. The date of the attack should be recorded in the diary and notified to the study statistician or chief investigator through the local investigator. This event will be classed as a “treatment failure”. The code of the randomised treatment arm will be “broken” and the patient should receive subsequent care as determined appropriate by their local physicians/surgeons. We will still be interested in following up the patient long term by filling in the diary with notification of chosen second line treatment option and its outcome.</p>

References

(1)Virag R et al (1996)

Preventive treatment of priapism in sickle cell disease with oral and self-administered intracavernous injection of etilefrine.

Urology: 47(5): 777-781.

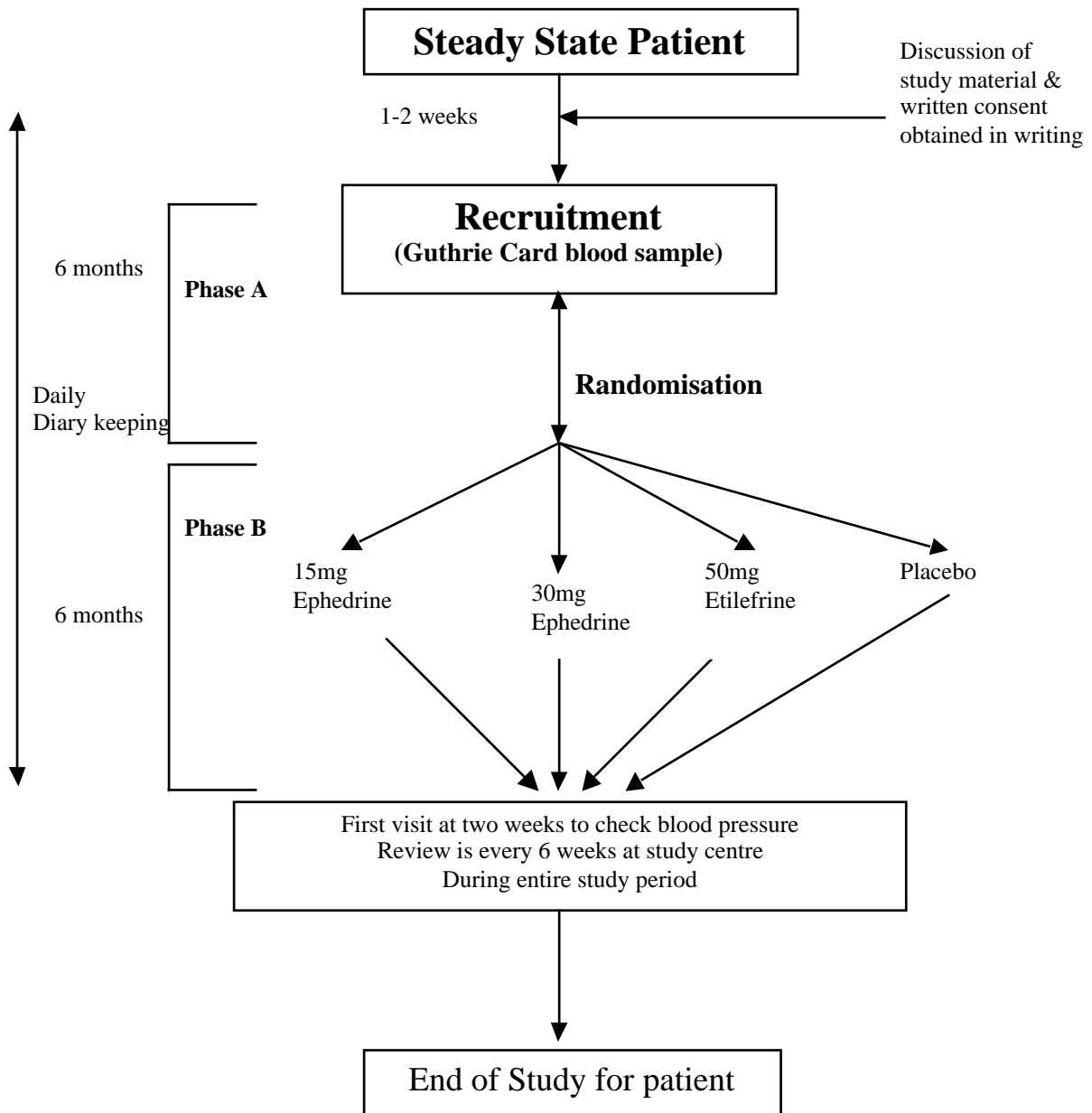
(2)Elpis Mantadakis, David H Ewalt, Joe Don Cavender, Zora R Rogers, and George R Buchanan (2000)

Outpatient penile aspiration and Epinephrine Irrigation for Young Patients with Sickle Cell Anemia and Prolonged Priapism

Blood, 1 January 2000. Volume 95, Number 1

APPENDIX G

Trial of Oral Ephedrine/Etilefrine in Priapism Secondary to Sickle Cell Anaemia



Appendix H

Phase A

PLEASE COMPLETE EACH DAY ENTRY

Baseline BP

Week 1 of 52

Patient Name

	Priapism Attack	Duration	Pain score	What did you
Day 1	Yes / No	hrs		SAMPLE
Day 2	Yes / No	hrs		
Day 3	Yes / No	hrs		
Day 4	Yes / No	hrs		
Day 5	Yes / No	hrs		
Day 6	Yes / No	hrs		
Day 7	Yes / No	hrs		

PLEASE COMPLETE EACH DAY ENTRY

Phase B

Week 27 of 52

Patient Name

SAMPLE

BP

	Priapism Attack	Duration	Tablet taken	Pain score
Day 1	Yes / No	hrs	Yes / No	
Day 2	Yes / No	hrs	Yes / No	
Day 3	Yes / No	hrs	Yes / No	
Day 4	Yes / No	hrs	Yes / No	
Day 5	Yes / No	hrs	Yes / No	
Day 6	Yes / No	hrs	Yes / No	
Day 7	Yes / No	hrs	Yes / No	

Please tick any side effects

- Strong heart beat
- Fast heart beat
- Lack of sleep
- Anxiety
- Dry mouth
- Hand shaking
- Others..... 27
-