

A randomised, controlled, assessor-blind, parallel group clinical trial to assess the efficacy, safety and acceptability of phenothrin mousse, phenothrin lotion and the wet-comb technique in the treatment of head lice.

CT 100

A randomised, controlled, assessor-blind, parallel group clinical trial to assess the efficacy, safety and acceptability of phenothrin mousse, phenothrin lotion and wet-comb technique in the treatment of head lice.

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CLINICAL TRIAL NUMBER: CT 100

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1. Introduction

1.1 Summary of the study

Title:	A randomised, controlled, assessor-blind, parallel group clinical trial to assess the efficacy, safety and acceptability of phenothrin mousse, phenothrin lotion and wet-comb technique in the treatment of head lice.	
Principal Investigators:	Dr. P Nair (Supervising clinician) Dr Ian Burgess Mrs Christine Brown	
Co-ordinator:	Deirdre Power	
Estimated Study Dates:	START: Apr 1997	END: Oct 1997
Subjects/Volunteers:	A total of 266 evaluable subjects will be recruited to the study. 104 subjects will be treated with the phenothrin mousse, 104 with Phenothrin lotion and 58 with the wet-comb technique.	
Type:	Children (over the age of 4), or adults who upon inspection are found to have live head lice.	
Products:	Phenothrin mousse, phenothrin lotion, head louse detection comb, shampoo and conditioner (both for dry hair, non-frequent use).	
Methods of Application:	<p><u>Phenothrin mousse</u> - the mousse is applied directly to DRY hair and is washed off with shampoo after 30 minutes. The treatment will be applied once.</p> <p><u>Phenothrin lotion</u> - the lotion is applied directly to DRY hair, and is washed off with shampoo after 2 hours. The treatment will be applied once.</p> <p><u>Wet-comb technique</u> - the hair is first washed with shampoo (for dry hair, non-frequent use). A generous amount of conditioner (for dry hair, non-frequent use) is then massaged into the hair. The hair is sectioned and combed thoroughly and systematically from scalp to tip with a head louse detection comb. The comb is wiped between strokes on paper towelling. The treatment will be repeated at half weekly intervals for two weeks.</p> <p>All three treatments will be applied/carried out by an adult carer under the supervision of (and after training from) a member of the investigating team. For the wet-</p>	

comb technique, the first combing will be supervised, and following combings will be carried out by the adult carer who was trained at the start of the trial.

Study Design:

Subjects will be recruited into the trial, and randomised to one of the three treatments described above.

The subjects randomised into the mousse and lotion groups will be assessed at day 0 (recruitment) and then treated. Further assessments will be done at days 4, 7, 10 and 14. The assessors will be blind to the treatment group. Any lice found at assessments will be taped into the Case Report Form for size analysis.

The subjects randomised into the wet-comb group will be assessed at day 0 (recruitment) and then combed. The subjects will be combed again at days 4, 8, and 12. Subjects will have a Diary Card and any lice found will be taped onto this card. Assessments will not take place during this time.

Subjects from the wet-comb group will be assessed again at day 14 and those found to have no lice at day 14 will be assessed again on day 21. If no lice are found at the day 21 assessment, they will be assessed again at day 28.

Aims of the Study:

To compare the efficacy, safety and acceptability of Phenothrin lotion and the wet-comb technique in the eradication of head lice, and to assess whether phenothrin lotion and phenothrin mousse are equivalent in terms of efficacy, safety and acceptability.

1.2 Rationale

Infection with the human head louse (*Pediculus humanus capitis*) still remains a widespread concern in the UK (1, 2).

There are many insecticidal compounds available to the subject for the treatment of lice which include carbamates, organophosphates and synthetic pyrethroids (3, 4, 5, 6, 7). All these products have the advantage of being ovicidal as well as insecticidal and show a very low toxicity in mammals (8, 9).

However, there have been reports of lice resistance to these insecticides which may result from inadequate use of the products by the subject - i.e. inadequate contact time or inadequate dosing (wetting of the hair). Subject compliance with these insecticides is therefore of major concern when developing a new head lice preparation. Resistance may also be a result of continued use of one particular active ingredient in a given health authority for too long a period (largely due to pressure from customers requesting to purchase a product which had worked for them in the past), or as a result of poor formulation of a particular brand of product. Whilst shampoos may be cosmetically more appealing than some other products, the alcoholic solutions may be

more efficacious (6, 10, 11). Other additives within a formulation may also enhance the insecticidal ability of a product (12, 13).

It is advantageous to have a product containing an active ingredient which has a high lice kill-rate with a minimum contact time and which can be easily and effectively applied by the subject. This clinical trial has been designed to evaluate the efficacy of a new mousse presentation of phenothrin. This mousse formulation has been designed to facilitate application by the subject. It will be compared to a currently accepted insecticidal treatment using the same active ingredient - phenothrin - Full Marks Lotion. The efficacy of the wet-comb technique at eradicating lice will also be evaluated alongside the two product groups. The rationale behind the wet-comb technique, is that lice are physically combed out of the hair with a fine toothed comb. Conditioner is applied so that the lice can't grasp the hair shaft. The comb is not fine enough to remove the eggs, so combing must be repeated at half weekly intervals for two weeks to ensure all lice are removed as they hatch.

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13. Burgess I. Malathion lotions for head lice - a less reliable treatment than commonly believed. Pharmaceutical Journal, 1991, Nov 9, 630-632.

1.3 Aims (Objectives)

- i To test for equivalence in killing head lice between the two phenothrin formulations.
- ii To test for equivalence in eliminating viable lice eggs - i.e. no small lice noted during follow-up assessments between the two phenothrin formulations.
- iii. To compare the efficacy of wet-combing in eradicating infection with the phenothrin formulations.
- iv. To monitor the safety of the treatments in clinical use.
- v. To assess the ease of use of each treatment.
- vi. To assess the overall subject acceptability of each treatment.

1.4 Design in brief

A total of 266 evaluable subjects who following examination are found to suffer from head lice, and fit the selection criteria (see section 2.1.2 and 2.1.3) will be recruited to the trial.

The subjects and/or guardians will have the study explained to them and if they wish to be included in the trial they will give their written informed consent. The consent form will confirm that the subject is willing to be treated by any of the three methods. Also at recruitment subject details will be recorded (see section 2.3.3.2).

The subject will then be randomised to treatment. The random code will generated by a random number generator on a computer. The treatment allocations will be kept in sealed envelopes and will only be opened after consent has been received. The envelopes will be numbered sequentially on the outside with the subject number. The envelopes will be held at the study centre by the study co-ordinator, and a copy will also be kept in the central file at Seton. Research Investigators will be given a block of subject numbered envelopes (e.g. subjects 1-10), and will recruit all these subjects before picking up another block of subject numbered envelopes from the study

centre. The next subject will be treated with the appropriate treatment following randomisation using the next sequential number from the randomisation code (see section 2.3.3.2).

Subjects who were randomised to the phenothrin mousse and phenothrin lotion groups will be treated only once at day 0. Subjects who were randomised to the wet-comb group will be combed at days 0, 4, 8 and 12. See summary below;

Subjects randomised to the phenothrin mousse and phenothrin lotion groups will be assessed at days 4*¹, 7*¹, 10*¹ and 14*². Subjects that were randomised to the wet-comb group will be assessed at day 14*² and again at days 21*² and 28*² (see section 2.3.3.3). See summary below;

Design Plan:

Day No.	Phenothrin mousse		Phenothrin lotion		Wet-comb technique	
	Treat	Assess	Treat	Assess	Comb	Assess
0	✓	✓	✓	✓	✓	✓
4		✓		✓	✓	
7		✓		✓		
8					✓	
10		✓		✓		
12					✓	
14		✓		✓		✓
21						✓
28						✓

All adverse events will be monitored during the study (see sections 2.3.5 and 2.3.6). In addition, all changes in concomitant medication will be recorded (see section 2.3.4).

¹ *¹ - The assessors will be blind as to whether the treatment was phenothrin mousse or phenothrin lotion.

² *² - The assessors will be totally blind to treatment group (a new assessor will be used).

2. Materials and Methods

2.1 Subject Selection

2.1.1 Total Numbers of Subjects and Study Duration

A total of 266 evaluable subjects will be recruited to the study. The duration of the trial will be 14 days for the phenothrin groups and 28 days for the wet comb group.

2.1.2 Inclusion Criteria

1. Male and female subjects over the age of 4 who are suffering from head lice.
2. Subjects who give written informed consent, or if the subject is under 18 years of age whose guardians give written informed consent to participate in the study.
3. Subjects who will be available for visits from the research investigators over the next 28 days.
4. Subjects who have an adult carer/guardian who will be able to treat or comb the hair (depending on the allocated treatment group).

2.1.3 Exclusion Criteria

1. Subjects with a known sensitivity to pyrethroid and/or chrysanthemums.
2. Subjects who have been treated with other head lice products within the last 4 weeks.
3. Subjects who have any persistent skin disorder of the scalp (i.e. eczema, chronic dermatitis, psoriasis).
4. Subjects receiving treatment for asthma.
5. Subjects who have bleached hair, or hair which has been colour treated or permed within the last 4 weeks.
6. Pregnant or nursing mothers.
7. Subjects who have participated in another clinical trial within 1 month prior to entry to this study.
8. Subjects who have already participated in this clinical trial.
9. Subjects who have been treated with antibiotics within the last 4 weeks.

2.2 Clinical Supplies and Materials

2.2.1 Physical Forms of the Study Supplies

Phenothrin Mousse

Phenothrin mousse contains phenothrin 0.5% in an aqueous/alcoholic base plus propellant (butane).

Full Marks Lotion

A clear, colourless, alcohol-based lotion containing phenothrin 0.2% w/v.

Wet-comb technique

Bug Busting Kit containing plastic comb, 1 bottle of shampoo (for non-frequent use on normal to dry hair) and 4 bottles of conditioner (for non-frequent use on normal to dry hair).

2.2.2 Packaging and Labelling

Phenothrin mousse is supplied in a canister, phenothrin lotion in a bottle and the wet-comb technique will be supplied as a pack. For the wet-comb technique 1 bottle of shampoo (for non-frequent use on normal to dry hair) and 4 bottles of conditioner (for non-frequent use on normal to dry hair) will also be supplied. All samples will be weighed and numbered prior to despatch. All samples will be labelled with appropriate clinical trial labelling, including the bottle/canister number, subject number and subject initials.

2.2.3 Care of Supplies

All supplies used in the study must be maintained securely, under the direct responsibility of the principal investigator or under that delegated by the investigator.

All supplies shall be dispensed in accordance with the investigator's prescription and it is the investigator's responsibility to ensure an accurate record of supplies issued and returned is maintained.

All supplies should be stored at room temperature, out of direct sunlight and protected from humidity and moisture.

All supplies will be used only while participating in the trial and returned at the end of the study for weighing.

2.2.4 Study Materials

All clinical trial materials will be supplied by the Sponsor. Sufficient supplies will be forwarded for the duration of the trial. In addition, case report forms will be supplied for each subject.

2.2.5 Compliance

All supplies used, partly used or unused will be maintained for collection by the Study Monitor.

2.3 Procedures and Investigations

2.3.1 Treatment Regimen/Allocation

This is a randomised, controlled, assessor-blind parallel group study of phenothrin mousse, phenothrin lotion and wet-comb technique in the treatment of head lice. Each subject who satisfies the inclusion/exclusion criteria will be randomised into one of three groups. One group will be treated with phenothrin mousse, the second group with phenothrin lotion, and the third with the wet-comb technique.

2.3.2 Randomisation

The randomisation code for treatment will be generated by an independent statistician on behalf of Seton Healthcare Group plc. The random numbers will be generated by a random number generator on a computer. Treatment allocations will be kept in sealed envelopes numbered sequentially on the outside with the subject number.

2.3.3 Study Methodology

2.3.3.1 Pre-recruitment

Potential subjects will be identified through schools. Letters will be sent to schools in the Bedfordshire area from the Bedfordshire Health Authority. These letters will ask the schools if they would like to take part in a clinical trial (see Appendix 5). When the time is appropriate (not all schools can take part at once), the school will be sent letters to hand out to the pupil's parent/guardian (see Appendix 6). These letters will be handed out one class at a time to avoid problems of Research Investigator shortage. Within these letters will be a pre-written reply. Any suitable pupils or family members (suitable being people with an active head lice infection), will be asked to send their letter in the envelope provided to the study co-ordinator. Alternatively, they may contact the co-ordinator by phone. A recruitment meeting will then be arranged by the study co-ordinator.

2.3.3.2 Recruitment

First the potential subject will be assessed to ensure that they are suffering from an active head louse infection by the research investigator. This will be done by a head louse detection comb. Any lice found will not be removed. After, the subject will have the nature of the trial explained to them again. If they wish to continue, and they meet the inclusion and exclusion criteria, the subject or guardian will be given an information sheet explaining in full the nature of the trial (see Appendix 1). A consent form will be attached to the information sheet and this must be signed before participation in the trial.

commences. The subject's GP will be informed via letter from the Principal Investigator / Supervising Clinician that the subject will be taking part in a clinical trial (see Appendix 7), and the Subject Record Form will be completed.

The following details will then be checked and recorded in the case report form;

1. Subject's initials, sex, date of birth, race, relevant medical history, any concurrent illness and any current medication.
2. Details of the last time the subject had head lice. Dates of infection, details of the treatment used and details of the outcome will be recorded.
3. The subject's hair will be test combed to confirm infection. Lice will not be removed.
4. Details will be taken of the type of hair: length, thickness, straight or curly etc.

The research investigator will carry with them a block of sequential subject numbered envelopes. Each envelope will contain a random treatment. The random numbers will be generated by a random number generator on a computer.

After consent has been received, the next sequential subject numbered sealed envelope will be opened and the treatment allocated. All the study products used in the trial (including the shampoos and conditioners) will be weighed before the start of the trial. They will have a sticky label on them identifying the bottle/canister number and a blank section for completion at the recruitment visit. All relevant details (i.e. subject number and recruitment date), will be added to the label. The label will clearly state "FOR CLINICAL TRIAL USE ONLY".

The relevant treatment will then be applied to the hair by an adult carer under the supervision of a member of the investigating team. The Research Investigator will instruct the adult carer on application as detailed in the product instructions and in a standard way. The treatments will be applied in the following ways;

Phenothrin mousse - Shake the can well and invert to expel the mousse. Apply sufficient mousse to saturate the hair and scalp. Apply the mousse directly onto DRY hair. Wash the mousse off with shampoo after 30 minutes. The treatment will be applied once.

Phenothrin lotion - Shake the bottle well. Apply sufficient lotion to saturate the hair and scalp. Apply the lotion directly onto DRY hair. Wash the lotion off with shampoo after 2 hours. The treatment will be applied once.

Wet-comb technique - the hair is first washed with normal shampoo. A generous amount of normal conditioner is then massaged into the hair. The hair is sectioned and combed thoroughly and systematically from scalp to tip with a head louse detection comb. The comb is wiped between strokes on paper towelling. The combing will be repeated at half weekly intervals for two weeks.

All three treatments will be applied/carried out by an adult carer under the supervision of (and after training from) a member of the investigating team. For the wet-comb technique, the first combing will be supervised, and following combings will be carried out by the adult carer who did the first combing.

During the treatments/combing the research investigator will complete a checklist.

Other family members can be inspected for lice. If they are found to be infected, they will be asked if they would like to participate in the trial. If so, consent may be obtained and they may be recruited, randomised and treated in the same way.

The research investigator will bring away the recruitment book (and remaining study product in the case of the two phenothrin groups).

The subjects that have been randomised to the wet-comb group will be left Diary Cards and asked to fill them in each time they comb their hair following the wet-comb technique.

2.3.3.3 Further Assessments / Treatments

Phenothrin Mousse and Phenothrin Lotion

Assessments will be done on days 4, 7, 10 and 14 (for details of the day 14 assessment - see section 2.3.3.4). At assessments, the subjects hair will be combed with a head louse detection comb, and any lice found will be taped (with clear tape) into the subjects Case Report Form. This assessment will be carried out by a member of the investigating team (but not the person who supervised the treatment at the recruitment visit). At assessments the research investigator will complete an assessment booklet. Subject details will be completed at each assessment ("P" No., date of birth and initials).

Any lice found will be sent to the Medical Entomology Centre at a later date and studied under the microscope to establish their stage in development. A small number of large lice may indicate reinfection, whereas a mixture of lice of different ages probably indicates treatment failure (nymphs do not so readily transfer to a different host).

The following flow chart can be used as a guide to establish treatment success or failure;

Day 4	Day 7	Day 10	Day 14	Outcome
No lice →	→ No lice →	→ No lice →	→ No lice →	→ Treatment success.
Large louse →	→ No hatchlings →	→ No hatchlings →	→ No hatchlings →	→ Treatment success / re-infection?
No lice →	→ Hatchlings →	→ Hatchlings →	→ Hatchlings →	→ Treatment failure.
Different sized lice →	→ → → → →	→ → → → →	→ → → → →	→ Treatment failure Withdraw from trial. Use different treatment.

If it is established that the treatment failed, the subjects will be withdrawn from the trial and given an alternative method of treatment (e.g. Suleo M).

Wet-comb Group

The wet-comb group will be combed on days 0, 4, 8, and 12 following the wet-comb technique. On these days, any lice found will be taped (with clear tape) into the Diary Cards that were handed out at recruitment. These will then be studied under a microscope at a later date at the Medical Entomology Centre in Cambridge, and their stage of development noted. The subjects will be assessed at days 14, 21 and 28 only (see section 2.3.3.4).

The following flow chart can be used as a guide to establish combing success or failure;

Day 14	Day 21	Day 28	Outcome
No lice ⇒	⇒ No lice ⇒	⇒ No lice ⇒	⇒ Combing success.
Large louse ⇒	No hatchlings ⇒	No hatchlings ⇒	Combing success / re-infection?
No lice ⇒	⇒ Hatchlings ⇒	⇒ Hatchlings ⇒	⇒ Combing failure.

Any adverse events, or changes in concomitant medication will be detailed in the Case Report Form and if necessary any investigator concerns for the subjects welfare will be reported to the Sponsor.

2.3.3.4 Final Assessment

Phenothrin Mousse/Lotion subjects

An assessment will be undertaken at day 14. All subjects will be assessed in exactly the same way and by an investigator who is blind to the treatment given (i.e. a totally new investigator).

Wet-comb group only

Any subjects that had no lice at day 14 will be assessed again on days 21 and 28 to see if there are any newly emerged nymphs.

Any lice found will be collected in the same way as before for analysis.

The person who carried out the treatment/combing, and the subject will be asked to complete a questionnaire on the treatment they used. This will include questions about the ease of use, associated odour, comfort, and general acceptability of the treatment (e.g. did it cause or stop itching).

Any adverse events and changes in concomitant medication will be recorded.

The completion/withdrawal form will then be completed.

All supplies will be returned to Seton Healthcare Group for weighing on completion of the trial.

2.3.4 Concomitant Medication

The subjects should not be prescribed any other form of pediculicide treatment whilst taking part in this clinical trial. If the use of such treatment is required, the subject should be withdrawn from the study.

2.3.5 Adverse Events

The assessment booklets will provide space specifically for recording observed and

reported adverse events. All unwanted effects, whether considered to be caused by the study medication or not, will be reported to the Sponsor by completing the All Events form.

2.3.6 Serious Adverse Events

If the adverse event is serious, it shall be reported immediately, by telephone, to the study monitor:

0161-652-2222

Serious means fatal, life-threatening, disabling or incapacitating, causing hospitalisation or prolonging hospitalisation, overdose (of any kind, with or without symptoms), newly diagnosed cancer or clinically abnormal laboratory values (with or without symptoms).

A full written report will then be forwarded to the Sponsor, by fax, within 3 working days.

The contact for all serious adverse events is:

Clinical Research Manager
Seton Healthcare Group plc
Tubiton House
Oldham
OL1 3HS
Tel: 0161 652 2222
Fax: 0161 633 2375

2.3.7 Withdrawals

Subjects may be withdrawn from the study at any time for the following reasons:

a) Adverse Event

The subject is withdrawn from the study by the investigator because of an adverse event, whether or not the investigator believes it to be serious or caused by the study medication, and provided that the investigator considers it is in the subject's best interest to be withdrawn. There must be a corresponding entry on the All Events and/or the Serious Adverse Events form in this instance.

b) Non-compliance

The subject is withdrawn because of failure to comply with the treatment regimen, or comply with the investigations as required, but is still accessible to the investigator.

c) Drop Out

The subject withdraws consent to continue in the study, but the investigator would otherwise consider it appropriate for him/her to continue. The subject remains accessible to the investigator.

d) Lost to Follow-up

The subject without explanation, fails to keep appointments as scheduled for study assessments and is not seen again despite the investigator's effort (letter, telephone, home visit etc.) to re-establish contact.

e) Death

All deaths will be treated as Serious Adverse Events and the Sponsor must be informed within 24 hours and all associated documentation must be completed within 3 working days. Full details will be required including a post-mortem examination if possible.

f) Lack of Efficacy

The subject is withdrawn by the investigator, or elects to withdraw, because the study medication is not adequately effective and other therapeutic intervention is required.

3. Analysis and Reports

3.1 Definition of End Points

3.1.1 Safety

Subjects will be observed and all untoward effects should be recorded, whether or not they are thought to be related to the study treatment.

Details of the recording of adverse events is shown in section 2.3.5. and 2.3.6.

3.1.2 Efficacy

The primary measure is the between treatment comparison of the number of subjects with evidence of active head lice infestation 14 days after treatment.

Sample Size Determination

Sample sizes were determined on the basis that one wished to have 90% power to detect as significant at the 95% confidence level a difference in efficacy between the wet-combing group and the phenothrin lotion group and equivalence between the two phenothrin groups to within 20%. The sample sizes were determined assuming the underlying rates of efficacy would be 80% in the phenothrin groups and 50% in the wet-combing group, that differences would be observed using the chisquared test, and that equivalence to within 20% would be determined based on 95% confidence limits derived from the normal approximation to the binomial distribution. The sample size calculations involved an algorithm which estimated, for a given sample size, the probability of occurrence of each possible set of observed efficacy rates in the groups being compared given the underlying efficacy rates, and hence the total probability of demonstrating a difference or equivalence, and then searching using the algorithm, to find the minimum sample size where this probability exceeded the power of 90%.

3.2 Definition of Populations to be analysed

a) The Efficacy Population

Includes all randomised subjects who are treated/combed according to the study protocol. Premature terminations, due to treatment failure, adverse events etc., are also included.

b) "Intention-to-treat" Population

Includes all randomised subjects who are treated at least once. Protocol violators are included in this population.

3.3 Proposed Primary and Secondary Analyses

See section 3.1.2 for primary efficacy analysis.

Secondary assessments of efficacy will be:

The eradication of lice in the wet-comb group.
The safety of all three treatments.
The ease of use of all three treatments.
Subject acceptance of all three treatments.

3.4 Statistical Methods

The statistical analysis will be undertaken by an independent statistician on behalf of the Sponsor. Differences between groups will be tested based on the "intention-to-treat" population, while equivalence will be tested based on the "efficacy" population. Equivalence between groups in efficacy will be determined based on 95% confidence limits derived from the normal approximation to the binomial distribution. Differences between groups in efficacy and other yes/no variables will be tested using Fisher's exact test and unstratified chisquared tests as appropriate. Differences between groups in ranked variables will be tested using Kruskal-Wallis test, while changes over time will be compared using Wilcoxon Signed-Ranks test.

3.5 Clinical Report

A Clinical Report, integrating the statistical analyses will be prepared for the study and agreed by the investigator, statistician and the study monitor. A copy of this final report will be forwarded for signature by the principal investigator, the statistician and the study monitor.

4 Administrative Procedures

4.1 Regulatory Documentation

Any required legislative procedures will be undertaken prior to the commencement of the study. The study will not proceed without granted written approval.

This study will be conducted according to the recommendations of the European (CPMP) Guidelines on Good Clinical Practice for Trials on Medicinal Products and with the European Standard, EN 540, 1993; Clinical investigation of medical devices for human subjects.

4.2 Ethics Committee Approval

The investigator will be required to obtain written approval of his local Ethics Committee before commencing the study. In accordance with Good Clinical Research Practice a copy of this together with the constitution of the ethics committee should be forwarded to the Sponsor prior to the release of study supplies from Seton Healthcare Group plc.

4.3 Informed Consent

This study will be conducted in accordance with the principles laid down in the Declaration of the World Medical Assembly of Helsinki, as amended in Tokyo, Venice and Hong Kong (see Appendix 2).

Each subject will be requested to give written informed consent after receiving written information and an explanation of what the study involves.

An informed consent form is supplied in the case report form (see Appendix 1). The original consent form will be retained by the investigator, but both the investigator and the witness will complete the declaration section of the form, the original of which will be held by the Sponsor.

As Seton Healthcare Group plc does not maintain a record of subject names it is essential that the investigator shall arrange for the retention of subject identification codes for at least 15 years after the completion or discontinuation of the study.

4.4 Insurance Policy

Seton Healthcare Group plc confirms that this specific clinical trial is protected by insurance cover which provides an indemnity to the investigators and their co-workers, subject to the Policy terms, conditions and limitations and provided always that the study is conducted and the data as reported agree to the standards fixed by the protocol.

4.5 Compensation

Seton Healthcare Group plc maintain in force a "no fault" compensation insurance indemnity in accordance with the current version of the ABPI Guidelines on Clinical

Trials: "Compensation for Medicine Induced Injury".

In the event that the compensation on a "no fault basis" is unacceptable to the claimant, the Policy will, subject to its terms, conditions and limitations, respond to an action for legal liability arising out of this clinical trial.

4.6 Investigator's Responsibilities

i. Good Clinical Practice

It is the responsibility of each and every investigator to ensure that this study is carried out in accordance with this protocol in respect of ethical, legal and technical aspects and conforming to both the European (CPMP) Guidelines on Good Clinical Practice for Trials on Medicinal Products (see Appendix 3) and also the European Standard, EN 540: Clinical investigation of medical devices for human subjects (see Appendix 4). In this context, the investigator shall arrange for the retention of subject identification codes for at least 15 years after completion or discontinuation of the trial. The sponsor will render all support necessary to assist the investigator in discharging this responsibility.

ii Replacement of Principal Investigator

In the event of a Principal Investigator being unable to continue the study, another responsible person will be designated investigator and documentation testifying to this will be submitted to the study monitor within 10 days. The new investigator must be appropriately qualified and be approved by the sponsor and local ethics committee before the study can be continued.

iii Study Report

The Principal Investigator will submit a summary trial report within approximately 1 month of completion of the study. This report will include:

1. Details of the investigative procedures involved
2. The numbers of subjects entered, completed and withdrawn from the study.
3. Deviations from the study protocol on a general basis and for individual subjects, with explanations.
4. Explanations for each subject withdrawn from the study
5. Methodology and normal ranges for laboratory investigations (where appropriate).
6. Summary of demographic details for each treatment group, e.g. sex, age etc.
7. Summary of the safety and tolerance data, including:

Details of all Adverse Drug Events (ADE) including any follow-up. Case histories of all serious ADEs or ADEs leading to withdrawal.

8. If appropriate, details of any statistical analysis carried out by the investigators, and a summary of efficacy data including clinical observations.

9. Conclusions

4.7 Curriculum Vitae

In accordance with international standards, and Good Clinical Research Practice, a signed copy of the curriculum vitae of each investigator and co-worker will be provided to the Study Monitor.

4.8 Case Report Form

The investigator is required to prepare and maintain adequate and accurate case records which have been designed by the Sponsor to record all observations and other data pertinent to the clinical investigation. All record forms should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data. Black ball-point pen should be used to ensure the clarity of reproduced copy of all case report forms.

The original case report forms, signed by the investigator, will be given to the designated monitor at each monitoring visit, but the investigator will retain a copy together with other source data for his own files.

The CPMP Guidelines on Good Clinical Practice for Trials on Medicinal Products in the European Community require that the investigator shall arrange for the retention of the subject identification codes for at least 15 years after the completion or discontinuation of the trial. Subject files and other source data shall also be kept for the maximum period of time permitted by the hospital, institution or private practice but not less than 15 years.

4.9 Monitoring of the Study

At regular intervals during the study, the study centre will be visited by a representative of the monitoring team of the Sponsor. At each monitoring visit, the investigator and the Sponsor's monitor will review study progress, compliance to the study protocol, case report forms and any emergent problems. Case report forms may be collected by the monitor at this visit.

4.10 Quality Assurance

In accordance with Good Clinical Practice Guidelines and recommendations, the Sponsor may undertake a quality assurance audit of the clinical trial and related documentation during the course of this trial.

The purpose of the QA audits is to check on the monitoring of studies and to try to reduce inconsistencies such as transcription errors and errors in logical sequence. To undertake these effectively it will usually be necessary to check the Seton Healthcare Group plc case report forms against source documents, for example laboratory reports, x-ray reports and actual subject notes. It is important for investigators to maintain an accurate set of his/her subject notes. This is essential material for auditing purposes. At any stage during the trial, the investigator has the responsibility to make all data available to the sponsor and/or relevant authority (where required) for auditing purposes. Such audits will at all times be conducted in accord with national, legal and ethical requirements.

4.11 Protocol Appendices

It is specified that the appendices attached to this protocol, and referred to in the main text of this protocol, form an integral part of the protocol.

4.12 Protocol Amendments

No changes or amendments to this protocol may be made by the investigator or by Seton Healthcare Group plc after the protocol has been agreed to and signed by both parties unless such change(s) or amendment(s) have been fully discussed and agreed upon by both the investigator and Seton Healthcare Group plc. Any change or amendment agreed upon will be recorded in writing, the written amendment will be signed by the investigator and by Seton Healthcare Group plc and the signed amendment will be appended to this protocol.

Any changes will be forwarded to the local research ethics committee and to the appropriate regulatory authority for approval prior to implementation of the amendments.

4.13 Publication Policy

Submission of results for publication will not take place without prior discussion with Seton Healthcare Group plc, allowing the company sufficient time to analyse such results and provide written agreement to publication which will not be unreasonably withheld. Seton Healthcare Group plc reserve the right to use the results and reports of this study for any purpose.

4.14 Early Termination of the Trial

By agreement between the Study Sponsor and the Principal Investigators the study may be terminated at any time if recruitment rate is such that the required number of subjects will not be recruited.

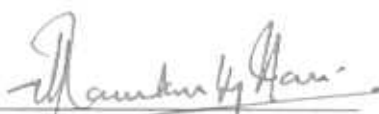
5. Investigator's Agreement

We have read this Seton Healthcare Group plc approved protocol, number 100, dated 6th March 1997, entitled "A randomised, controlled, assessor-blind, parallel group clinical trial to assess the efficacy, safety and acceptability of phenothrin mousse, phenothrin lotion and the wet-comb technique in the treatment of head lice", and have discussed it to our satisfaction with the Sponsor's monitor.


We agree to conduct the study according to this protocol and to comply with its obligations, subject to ethical and safety considerations.

We understand that should we be in breach of any of the terms of this protocol, or if we are negligent, that Seton Healthcare Group plc, would not be held responsible for any resulting losses, damages, costs and expenses of whatever kind made by or on behalf of a volunteer.

Principal Investigators:


Dr P Nair


Dr I Burgess

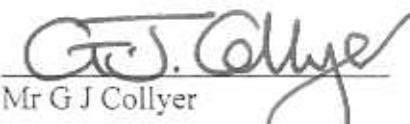

Mrs C Brown

Seton Healthcare Personnel

Study Monitor:


Miss S L Gray

Technical Director:


Mr G J Collyer

Should the decision be made by Seton Healthcare Group plc to terminate the study at any time, such decision will be communicated to the investigator in writing, and appropriate arrangements will be agreed upon and specified in writing. Conversely, should the investigator decide to withdraw from execution of the study he/she will communicate immediately such decision in writing to the Sponsor.