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Research Ethics Committee for Wales

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15 February 2011

Professor Ivor Chestnutt
Cardiff University
Cardiff University Dental School
Heath Park,
Cardiff CF14 4XY

Dear Professor Chestnutt

Study Title:	**Seal or Varnish? A Randomised Trial To Determine The Relative Cost And Effectiveness Of Pit And Fissure Sealants And Fluoride Varnish In Preventing Dental Decay**
REC reference number:	**11/MRE09/6**
Protocol number:	**SPON766-09**
EudraCT number:	**2010-023476-23**

The Research Ethics Committee reviewed the above application at the meeting held on 10 February 2011. Thank you for attending to discuss your application with the Committee.

Ethical opinion
Professor Chestnutt attended to discuss his application with the Committee. He was accompanied by Dr. Simon Hutchings, Trial Manager.

Members present commended Professor Chestnutt on the quality of the information sheets, agreeing that in particular those for children were of a very high standard.

Explanation as to why there is no statistician on the Data Monitoring Committee (DMC).
Professor Chestnutt informed the Committee that the Chair of the DMC is a statistician.

Members present noted the comments on the application regarding the use of tick boxes on the consent form rather than initial boxes, and asked for further explanation of this.
Professor Chestnutt explained that they were trying to simulate what happens in current practice where parents are used to ticking boxes.
Members present agreed this did not present an ethical issue and that the boxes could be ticked.

Explanation as to why non-participants would be interviewed.
Professor Chestnutt explained that they were seeking to interview twenty people who had declined to take part as they wanted to understand why : is it due to the paperwork sent out deterring people or is it due to concerns regarding the use of fluoride. He further explained that they would be sensitive towards approaching these people and that it would be done via parent-teacher groups. Professor

Chestnutt informed the Committee that if they decided to go ahead with this aspect of the study they would submit the documentation as a substantial amendment.

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Ethical review of research sites
The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion
The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where the only involvement of the NHS organisation is as a Participant Identification Centre (PIC), management permission for research is not required but the R&D office should be notified of the study and agree to the organisation's involvement. Guidance on procedures for PICs is available in IRAS. Further advice should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

Clinical trial authorisation must be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA).

The sponsor is asked to provide the Committee with a copy of the notice from the MHRA, either confirming clinical trial authorisation or giving grounds for non-acceptance, as soon as this is available.

Other conditions specified by the REC

- The word "important" should be removed from the sixth line of the letter / consent form for the examination for training purposes.
- Page four of the information sheet states the study has been reviewed by South East Wales REC. This should be corrected to read the REC for Wales.

If you would find it helpful to discuss any of the matters raised above or to seek further clarification from a member of the Committee you are welcome to contact the REC co-ordinator, Dr. Corinne Scott, whose contact details can be found in the header of this letter.

It is responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

You should notify the REC in writing once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers.

Approved documents
The documents reviewed and approved at the meeting were:

Document	Version	Date
Protocol	1	11 January 2011
Participant Information Sheet: Children	1	12 January 2011
GP/Consultant Information Sheets	1	12 January 2011
REC application	signed in ink by Professor Chestnutt and in ink by Dr KJ Pittard-Davies, sponsor's representative	13 January 2011
Participant Consent Form	1	12 January 2011
Summary of product characteristics	Duraphat 50mg / dental suspension; date of revision of text - February 2003	
Annual exam follow up letter	1	12 January 2011
Participant Information Sheet: Parents	1	12 January 2011
Investigator CV	Professor Chestnutt	11 January 2011
Baseline exam follow up letter	1	12 January 2011
Evidence of insurance or indemnity	Zurich Municipal certificate of insurance - Cardiff University - expires 31 July 2011	27 July 2010
Covering Letter	signed Simon Hutchings	13 January 2011
Summary/Synopsis	Participant flow chart; version 1	12 January 2011
Letter from Sponsor	signed DR KJ Pittard-Davies, Cardiff University	11 January 2011
Medical history form	1	12 January 2011
Letter from funder - NIHR HTA programme		21 October 2009
Letter from chief investigator to NIHR HTA		06 November 2009
Interim follow up letter	1	12 January 2011
Missed treatment follow up letter	1	12 January 2011
Example participant material from current Designed To Smile programme		

Membership of the Committee
The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Dr. Brown declared an interest but remained present : Professor Chestnutt is a colleague.

Statement of compliance
This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review
Now that you have completed the application process please visit the National Research Ethics Service website > After Review

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

We would also like to inform you that we consult regularly with stakeholders to improve our service. If you would like to join our Reference Group please email referencegroup@nres.npsa.nhs.uk.

11/MRE09/6	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

PP **Dr Gordon Taylor**
Chairman

Email: corinne.scott@wales.nhs.uk

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments
"After ethical review – guidance for researchers"

Copy to: Dr Simon Hutchings

REC for Wales

Attendance at Committee meeting on 10 February 2011

Committee Members:

Name	Profession	Present	Notes
Dr Gail Boniface	Occupational Therapist	Yes	
Dr Paul Brown	Radiographer	Yes	
Dr Maurice Buchalter	Alternate Vice Chairman / Hospital Consultant (Cardiologist)	Yes	
Dr Kate Bullen	Psychologist	Yes	
Mrs Monika Hare	Research Fellow	Yes	
Ms Nicola Heales	Solicitor	No	
Mr HAO Hughes	Pharmacist	Yes	
Dr Meriel Jenney	Hospital consultant (Paediatric oncologist)	No	
Mr Keith Jones	Retired Probation Officer	Yes	
Dr Mohammad Obaidullah	GP	No	
Ms Susan Pope	Communications / PR	No	
Dr V. Bapuji Rao	Hospital consultant (Psychiatrist)	Yes	
Ms Paula Strong	Nurse	Yes	
Dr Gordon Taylor	Chairman / Statistician	Yes	
Mrs Wendy Turkie	Nurse	Yes	
Dr Richard Walker	Deputy Director	Yes	
Dr Pete Wall	Vice Chairman / Clinical Physiologist	Yes	
Mr Stewart Williams	Management Consultant	Yes	

Also in attendance:

Name	Position (or reason for attending)
Dr Corinne Scott	Co-ordinator
Mrs. Helen Williams	Assistant Co-ordinator

Written comments – not regarding this application - received from:

Name	Position
Dr Meriel Jenney	Hospital consultant (Paediatric oncologist)

NHS
National Patient Safety Agency

National Research Ethics Service

CLINICAL TRIALS OF INVESTIGATIONAL MEDICINAL PRODUCTS IN HUMAN SUBJECTS

After ethical review – guidance for sponsors and investigators

This document sets out important guidance for sponsors and investigators on the conduct and management of medicinal trials following ethical review. The guidance is supplementary to the ethical opinion provided in the letter from the ethics committee. However, some reporting procedures described below are statutory requirements under the Medicines for Human Use (Clinical Trials) Regulations 2004 ("The Regulations"); this is indicated in the text. Failure to comply with these requirements could lead to the committee changing its opinion and recommending to the Medicines and Healthcare products Regulatory Agency that the clinical trial authorisation should be suspended or terminated.

1. Further communications with the Research Ethics Committee

1.1 Further communications during the trial with the Research Ethics Committee that gave the favourable ethical opinion (hereafter referred to in this document as "the Committee") are generally the responsibility of the lead sponsor. However, the sponsor may delegate responsibility to the Chief Investigator or another representative.

1.2 Where there is more than one sponsor for the trial, it is recommended that the lead sponsor or its representative takes responsibility for all communications with the Committee. However, one of the co-sponsors may take responsibility for each of the following group of functions:

- Substantial amendments, modified amendments and the conclusion of the trial
- Urgent safety measures
- Pharmacovigilance reporting.

2. Commencement of the trial

2.1 It is assumed that the trial will commence (i.e. the initiation of any protocol procedures) within 12 months of the date of the favourable ethical opinion.

2.2 Under the Regulations the sponsor must obtain Clinical Trial Authorisation (CTA) from the Medicines and Healthcare products Regulatory Agency (MHRA) before the commencement of the trial. Evidence of the CTA should be forwarded when available (if not already provided to the Committee). Where the MHRA requests significant changes to the protocol before confirming CTA, or attaches any other condition requiring substantial amendments to be made to the terms of the REC application or the supporting documentation, a Notice of Amendment form must be submitted to the Committee (see section 5).

2.3 The trial must not commence at any site until the Committee has notified the Chief Investigator that the favourable ethical opinion is extended to the site and management permission or approval has been obtained from the organisation responsible for the care of the participants at the site.

2.4 Should the trial not commence within 12 months, the sponsor should give the Committee a written explanation for the delay. It is open to the Committee to allow a further period of 12 months within which the trial must commence.

2.5 Should the trial not commence within 24 months, the Committee may review its opinion and may recommend to the MHRA that the CTA should be suspended or terminated.

3. Duration of ethical opinion

3.1 The favourable opinion applies for the duration of the trial. If it is proposed to extend the duration of the trial as specified in the application form, the Committee should be notified.

3.2 Where the trial involves the use of "relevant material" for the purposes of the Human Tissue Act 2004, authority to hold the material under the terms of the ethical approval applies until the end of the period declared in the application and approved by the Committee.

4. Progress reports

4.1 Research Ethics Committees are required to keep a favourable opinion under review in the light of progress reports and any developments in the trial. A progress report should be submitted to the Committee 12 months after the date on which the favourable opinion was given. Annual progress reports should be submitted thereafter until the end of the trial is declared.

4.2 Progress reports should be in the format prescribed by NRES and published on the website at http://www.nres.npsa.nhs.uk/applicants/after-ethical-review/.

4.3 The Committee should be kept informed of any significant findings or recommendations by an independent Data Monitoring Committee or equivalent body established for the trial.

4.4 The Chief Investigator may be requested to attend a meeting of the Committee or Sub-Committee to discuss the progress of the trial.

5. Amendments

5.1 If the sponsor proposes to make a substantial amendment to the clinical trial authorisation, the Regulations require that a Notice of Amendment form must submitted to the Committee and the MHRA. In the case of multi-site studies, there is no requirement to submit notices of amendment to RECs undertaking site-specific assessment (SSA).

5.2 A substantial amendment is any amendment to the terms of the request for clinical trial authorisation, or to the terms of the application for ethical review, or to the protocol or other supporting documentation approved by the Committee, that is likely to affect to a significant degree:

(a) the safety or physical or mental integrity of the trial participants

(b) the scientific value of the trial

(c) the conduct or management of the trial

(d) the quality or safety of any investigational medicinal product used in the trial.

5.3 Notices of Amendment should be in the format recommended by the European Commission at Annex 2 to *"Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of a trial"* (ENTR/CT1) and available at http://eudract.emea.eu.int/document.html#guidance. The form should be signed by the person submitting the notice.

5.4 A substantial amendment on which an ethical opinion has been requested must not be implemented until a favourable ethical opinion has been given by the Committee, unless the changes to the trial are urgent safety measures (see section 7). The Committee is required to give an opinion within 35 days of the date of receiving a valid notice of amendment.

5.5 Amendments that are not substantial amendments ("minor amendments") may be made at any time and do not need to be notified to the Committee.

5.6 Further guidance on amendments is available at http://www.nres.npsa.nhs.uk/applicants/after-ethical-review/ .

6. Changes to sites

6.1 Where it is proposed to include a new site in the trial, the Site-Specific Information Form (SSI Form) together with the Principal Investigator's CV should be submitted to the relevant REC for site-specific assessment (SSA). If the site was not included in the list of proposed trial sites in the original REC application and request for CTA, a Notice of Amendment form must also be submitted to the Committee under the Regulations. A copy of the Notice of

Amendment must be sent to the MHRA for information only.

6.2 Where it is proposed to make significant changes in the management of a site (in particular, the appointment of a new PI), a Notice of Amendment form must be submitted to the Committee (and to the MHRA for information) *and* a revised SSI Form for the site should be submitted to the relevant REC for SSA, together with the CV for the new PI if applicable.

6.3 The Committee should be notified when a site is closed or withdrawn prematurely.

7. Urgent safety measures

7.1 The sponsor or the Chief Investigator, or the local Principal Investigator at a trial site, may take appropriate urgent safety measures in order to protect the trial participants against any immediate hazard to their health or safety.

7.2 The Regulations require that the Committee and the MHRA must be notified within 3 days that such measures have been taken, the reasons why and the plan for further action.

8. Pharmacovigilance

8.1 Safety reporting requirements are set out in *"Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials of medicinal products for human use"* (ENTR/CT3) issued by the European Commission and available at http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-10/21_susar_rev2_2006_04_11.pdf. Guidance is also available on the NRES website.

8.2 Under the Regulations, Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring during the trial in the UK must be notified to the Committee and the MHRA in expedited fashion. A SUSAR which is fatal or life-threatening must be reported as soon as possible and in any event within 7 days after the sponsor became aware of the event. Any additional relevant information must be reported within 8 days of sending the first report. A SUSAR which is *not* fatal or life-threatening must be reported as soon as possible and in any event within 15 days after the sponsor first became aware of the event.

8.3 There is no requirement to notify SUSARs occurring in the trial outside the UK or in other trials of the investigational medicinal product (IMP) in an expedited fashion.

8.4 There is no requirement to notify serious adverse events occurring in the trial, other than SUSARs.

8.5 For each IMP being tested in the trial, the Regulations require the sponsor to provide the Committee and the MHRA with an annual safety report of the safety of the subjects in clinical trials of the IMP for which it is the sponsor (whether in the UK or elsewhere). The report should include an aggregated

global listing of all Suspected Serious Adverse Reactions (SSARs) occurring in those trials in the reporting period.

8.6 Where a commercial sponsor is conducting one or more trials of the IMP outside the UK, it is also requested to provide the Committee with 6 monthly safety reports, including a global line listing of all SUSARs occurring in relevant trials during the reporting period. This is not a requirement of the Regulations.

8.7 In the case of double-blinded trials, all reports of adverse reactions must be unblinded.

8.8 Pharmacovigilance reports may be provided to the Committee by either the sponsor, or the sponsor's representative, or the Chief Investigator. All submissions should be accompanied by the cover sheet for safety reports published on the NRES website. A single cover sheet may be used for the submission of several reports.

8.9 The Chief Investigator and representatives of the sponsor may be requested to attend a meeting of the Committee or Sub-Committee to discuss any concerns about the health or safety of trial participants arising from pharmacovigilance reports.

8.10 Reports should not be sent to other RECs in the case of multi-site trials.

9. Conclusion or early termination of the trial

9.1 Under the Regulations, the sponsor must notify the Committee and the MHRA in writing that the trial has ended within 90 days of the conclusion of the research. Unless otherwise specified in the protocol, the conclusion of the trial is normally defined as the last visit of the last participant or the completion of any follow-up monitoring and data collection described in the protocol. Any change to the definition of the conclusion of the trial should be notified to the Committee and the MHRA as a substantial amendment.

9.2 If the trial is terminated early, the sponsor must notify the Committee within 15 days of the date of termination. An explanation of the reasons for early termination should be given.

9.3 Declarations of conclusion or early termination should be on the form issued by the European Commission at Annex 3 to ENTR/CT1 and available at http://eudract.emea.eu.int/document.html#guidance.

10. Final report

10.1 The sponsor or Chief Investigator should provide the Committee and the MHRA with a summary of the clinical trial report within 12 months of the conclusion of the trial. The Committee should also be notified of the arrangements for publication or dissemination of the research including any feedback to participants.

11. Review of ethical opinion

11.1 The Committee may review its opinion at any time in the light of any relevant information it receives. It has no power to legally withdraw the opinion it has given but may draw the attention of the MHRA to any serious concerns and may recommend that consideration is given to suspending or terminating the CTA.

11.2 The sponsor or Chief Investigator may at any time request that the Committee reviews its opinion, or seek advice from the Committee on any ethical issue relating to the trial.

12. Serious breaches of Good Clinical Practice or the protocol

12.1 Under the Regulations the sponsor must notify the MHRA of any serious breach of the conditions or principles of Good Clinical Practice (GCP) or of the protocol, within 7 days of the matter coming to its attention. A breach should be regarded as serious if it is likely to affect to a significant degree the safety or physical or mental integrity of the subjects of the trial, or the scientific value of the trial. It is requested that the sponsor should also notify the Committee of such breaches within the same timescale. There is no requirement to notify minor breaches of GCP or the protocol.

12.2 A minor deviation from the protocol to deal with unforeseen circumstances is not considered to be a serious breach of the protocol provided that it is approved by the Chief Investigator, either in advance or after the event. However, if the deviation would meet the criteria for a substantial amendment it must be notified to the Committee under the Regulations.

12.3 There is no statutory provision for the Committee to approve proposed deviations from the protocol for individual subjects. It is the responsibility of the sponsor to consider whether protocol amendments should be made in such cases. Where the amendment is substantial, it must be notified.