APPENDIX I: Publications arising from this thesis

1. **Griffiths EA**, Pritchard SA, Welch IM, Price PM, West CML. Is the hypoxia-inducible factor pathway important in gastric cancer? *Eur J Cancer,* 2005 Dec; 41(18):2792-805.

2. **Griffiths EA**, Brummel Z, Gorthi G, Pritchard SA, Welch IM. Tumour length as a prognostic factor in oesophageal malignancy: univariate and multivariate survival analyses. *J Surg Oncol,* 2006 Mar; 93(4):258-67.

3. **Griffiths EA**, Brummel Z, Gorthi G, Pritchard SA, Welch IM. The prognostic value of circumferential resection margin involvement in oesophageal malignancy. *Eur J Surg Oncol, 2006 May; 32(4):413-419.*

4. **Griffiths EA**, Pritchard SA, Mapstone NP, Welch IM. Emerging aspects of oesophageal and gastro-oesophageal junction neoplasia – an update for the surgical oncologist. *World J Surg Oncol; In press.*

5. **Griffiths EA**, Pritchard SA, Valentine HR, Whitchelo N, Bishop PW, Ebert MP, Price PM, Welch IM, West CM. Hypoxia-inducible factor-1α expression in the gastric carcinogenesis sequence and its prognostic role in gastric and gastro-esophageal adenocarcinomas. *Br J Cancer; In press.*

6. **Griffiths EA,** Pritchard SA, McGrath S, Valentine HR, Price PM, Welch IM, West CM. Increased expression of hypoxia inducible proteins in the Barrett's metaplasia-dysplasia-adenocarcinoma sequence. *Submitted to Br J Cancer*.

APPENDIX II: Other material

Contents:

Ethical approval letters

MHRA letter

Patient information sheet

Tameside & Glossop Local Research Ethics Committee
Room 181
Gateway House
Piccadilly South
Manchester
M60 7LP

Telephone: 0161 237 2336
Facsimile: 0161 237 2383

Email: carol.ebenezer@gmsha.nhs.uk

10 June 2005

Mr Ian Welch
Consultant Gastric Surgeon
c/o Dr Jo Cresswell
Academic Department of Radiation Oncology
Christie Hospital NHS Trust
Wilmslow Road
Manchester
M20 4BX

Dear Mr Welch,

Study title: ***Heliobacter pylori infection and expression of radioresponsiveness markers as predictors of outcome following treatment for gastric carcinoma***
REC reference: **03/TG/560**
Protocol number:
EudraCT number:

Amendment number: **1**
Amendment date: ***26 May 2005***

The above amendment was reviewed at the meeting of the Sub-Committee of the Research Ethics Committee held on 10 June 2005.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

- Notice of substantial amendment dated 27 May 2005

Membership of the Committee

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

Management approval

All investigators and research collaborators in the NHS should notify the R&D Department for the relevant NHS care organisation of this amendment and check whether it affects local management approval of the research.

Statement of compliance

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.

[REC reference number]: 03/TG/560 Please quote this number on all correspondence

Yours sincerely,

Carol Ebenezer
Committee Administrator

Enclosures *List of names and professions of members who were present at the meeting and those who submitted written comments*

NHS

South Manchester Research Ethics Committee
1st Floor, Room 181
Gateway House
Piccadilly South
Manchester
M60 7LP

11 March 2005

Mr Ian Welch
c/o Dr Jo Cresswell, Scientific Administrator, ADRO
Christie Hospital NHS Trust
Withington, Manchester
M20 4BX

Dear Mr Welch

Full title of study: ***Markers of radio- and chemoresponsiveness and predictors of treatment response in oesophageal and gastric carcinoma***
REC reference number: ***05/Q1403/17***

Thank you for your letter of 04 March 2005, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered at the meeting of the Sub-Committee of the REC held on 10 March 2005. A list of the members who were present at the meeting is attached.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

The favourable opinion applies to the research sites listed on the attached form. In the meantime no study procedures should be initiated at sites requiring SSA.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document Type:	Version:	Dated:	Date Received:
Application	1	14/01/2005	17/01/2005
Investigator CV			17/01/2005
Protocol	1	11/01/2005	17/01/2005
Covering Letter	1	13/01/2005	17/01/2005
Summary/Synopsis	1	11/01/2005	17/01/2005
Peer Review	1	03/12/2004	17/01/2005

SL14 Favourable opinion following consideration of further information
Version 2, October 2004

NHS

Statistician Comments	1		17/01/2005
GP/Consultant Information Sheets	2	11/01/2005	08/03/2005
Participant Information Sheet	3	24/02/2005	08/03/2005
Participant Consent Form	3	24/02/2005	08/03/2005
Response to Request for Further Information	1	04/03/2005	08/03/2005
Other	1		17/01/2005

Management approval

The study should not commence at any NHS site until the local Principal Investigator has obtained final management approval from the R&D Department for the relevant NHS care organisation.

Membership of the Committee

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

Notification of other bodies

The Committee Administrator will notify the research sponsor and the R&D Department for NHS care organisation(s)] that the study has a favourable ethical opinion.

Statement of compliance

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.

05/Q1403/17	**Please quote this number on all correspondence**

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

Yours sincerely,

Isobel Davies

p.p. **Dr Philip Haji-Michael**
Chair

E-mail: Isobel.Davies@gmsha.nhs.uk

Enclosures *List of names and professions of members who were present at the meeting and those who submitted written comments*

Standard approval conditions

Site approval form (SF1)

An advisory committee to Greater Manchester Strategic Health Authority

MHRA

Medicines and Healthcare products Regulatory Agency
Market Towers
1 Nine Elms Lane, London SW8 5NQ

Mr Ewen A Griffiths MRCS
South Manchester University Hospitals NHS Trust
Wythenshawe Hospital
Southmoor Road
Wythenshawe
MANCHESTER
M23 9LT

Telephone: +44 207 084-2487
Facsimile: +44 207 084-2443
Email: martyn.ward@mhra.gsi.gov.uk

05 April 2005

Dear Mr Griffiths

Re: Markers of radio- and chemo-responsiveness and predictors of treatment outcome in gastric and oesophageal carcinoma

(LREC Reference 05/Q1403/17)

Thank you for your letter of 24 March and attached protocol. I can confirm that your proposal is not a clinical trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC. You therefore are not required to submit a Clinical Trial Authorisation (CTA) to the MHRA.

Yours sincerely

DR MARTYN WARD
Head of Clinical Trials Unit
Room 12-204

South Manchester University Hospitals NHS
NHS Trust

PATIENT INFORMATION SHEET

MEASUREMENT OF OXYGEN LEVELS IN OESOPHAGEAL/GASTRIC CARCINOMA USING PIMONIDAZOLE

You are being invited to take part in a research study. Before you decide, it is important for you to understand why this research is being done, and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything which is not clear, or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of the study?

The purpose of the study is to measure oxygen levels in oesophageal and gastric cancers. We feel this research is important as it may give further information to help improve our knowledge of these cancers. By measuring markers of low oxygen in the cancer cells we may be able to predict how the cancer will behave and respond to treatment. It is hoped that this extra knowledge will improve treatment for future generations of patients.

Why have I been chosen?

You have been chosen because of your attendance at Wythenshawe Hospital for treatment of your tumour.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

Whilst you are being admitted to hospital before your operation, we will take an extra blood sample in addition to routine blood samples. We would like to store this blood sample for future analysis to help our research.

A hollow plastic cannula (drip) will be positioned into one of your arms the night before your planned operation. You will probably have had one of these inserted for previous medical procedures, such as endoscopy. This will be used to give you a medication called pimonidazole, but is also necessary before your anaesthetic and the anaesthetist will be able to use it the following morning.

Pimonidazole will be given via your cannula from a small bag of fluid over 20 minutes and will be started the night before your planned surgery. It allows the identification of areas of your tumour which are low in oxygen to help with our research. We give a very small dose of this substance and there are no reported serious side effects using this dose.

After your operation tissue samples will be taken from your tumour. These samples will be sent as standard to the Wythenshawe pathology lab for your records, and the others will be taken to the research laboratory at the Paterson Institute for Cancer Research, Christie Hospital for further investigation. The whole procedure will be done while you are attending hospital for your treatment. Afterwards we will keep an eye on your progress by your attendance at outpatient clinics, where you will be seen routinely by the doctors looking after you.

Because cancer research is continually developing, it may be possible to test blood and tissue samples for other tests in the future. We would ask you to allow us to keep your specimens stored in the laboratory for other future research on this or a related project. They will be coded so they will be kept anonymous. Your specimens will not be used for any commercial research.

What do I have to do?

There is nothing specific that you have to do.

What are the possible disadvantages and risks of taking part?

There are no known serious side effects from the pimonidazole at the dose that would be given to you in this study.

Small pieces of tissue will be taken from the surgical specimen after your operation. There are no additional risks to you as the samples are taken from the surgical specimen after it is removed.

If you have any concerns regarding this procedure, please do not hesitate to discuss this with the Clinician responsible for your care.

If you have health insurance you may need to check your company is happy for you to take part in research projects at the same time as having your treatment.

What are the possible benefits of taking part?

There are no direct benefits to you, but we expect this research to help patients in your situation in years to come.

What if something goes wrong?

This technique has been used in many patients worldwide with no reports of any harm occurring to these patients. If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed by someone's negligence, then you may have grounds for a legal action, but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have

been approached or treated during the course of the study, the normal National Health Service complaints mechanisms should be available to you.

Will my taking part in the study be kept confidential?

All information will be kept strictly confidential and your name will not appear on any documents.

What will happen to the results of the research study?

When the study is complete the results will be published in medical/scientific journals and also presented at medical and scientific meetings. All data are anonymised (that is, your name will not be held on computer nor be disclosed in journals or at presentations). The results from this study may also be submitted for a postgraduate university degree (MD qualification).

Who is organising and funding the research?

The Department of Gastrointestinal Surgery at Wythenshawe Hospital, the Academic Department of Radiation Oncology and the Paterson Institute for Cancer Research are organising and funding this research.

Who has reviewed this study?

The South Manchester Local Research Ethics Committee has reviewed the study and agreed it may go ahead.

Contact for further information

Mr Ewen A Griffiths
Surgical Research Fellow
Department of Gastrointestinal Surgery
South Manchester University NHS Trust
Wythenshawe Hospital
South Moor Road
South Manchester
M23 9LT

0161 291 6650 (Directline)
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egriffiths@picr.man.ac.uk (email)

Thank you for your participation in this study.