"A RANDOMISED, PARALLEL, OPEN LABEL STUDY TO DETERMINE THE EFFICACY OF A NEW ORAL-NASAL OXYGENATING DEVICE (TWINGUARD^{TM}) COMPARED TO STANDARD BITE BLOCK PLUS NASAL CANNULAE"

Protocol No.: CDD05/C05

Clinical Study Report

Version 1 (22 June 2007)

Study Initiation Date: November 2006
Study Completion Date: March 2007

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Co-Investigators: Dr Sanjay Ramrakha, Dr John Saxon

Archiving: The Centre for Digestive Diseases is responsible for the archiving of all essential study documentation for the total of 15 years from the date of completion above.

Note: This study was performed in compliance with Good Clinical Practices (GCP) TGA July 2002

SIGNATURE/APPROVAL PAGE

Study Title: "A Randomised, Parallel, Open – label study to determine the efficacy of a new oral-nasal oxygenating device (Twinguard™) compared to standard bite block plus nasal cannulae."

Report Author(s): Prof Thomas Borody (Principal Investigator) Dr Sanjay Ramrahka (Co-Investigator), and Kylie Peters Study Manager) from the Centre for Digestive Diseases Pty Ltd

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Investigator: Thomas J Borody **Signature:**

Affiliation: Study Site

Date: 22/06/2007

SYNOPSIS

Name of Sponsor:	**Name of Finished Product:**	**Name of Active Ingredients:**
Trawax Pty Ltd	TwinGuard™	N/A

Title of Study:

A Randomised, Parallel, Open – label study to determine the efficacy of a new oral-nasal oxygenating device (TwinGuard™) compared to standard bite block plus nasal cannulae.

Investigators:

Principle Investigator: Prof Thomas Borody Co-Investigator: Dr Sanjay Ramrakha

Study Centre:

Centre for Digestive Diseases, Level 1, 229 Great North Road, Five Dock, NSW, 2046, AUSTRALIA

Study period:	**Phase of development:**
November 2006 to March 2007	Phase II

Objectives:

Primary Objective - To determine the efficacy of the TwinGuard™ in oxygen delivery during and post procedure. To determine if the TwinGuard™ achieves and/or surpasses the level of quality of the standard nasal cannulae oxygenation with bite block during the procedure

Secondary Objective - To determine cardiorespiratory perimeters of the TwinGuard™. To assess the comfort of the TwinGuard™ device.

Methodology:

A comparative study which compares the end-tidal CO_2 and oxygen saturation levels of patients during endoscopy which have used either the new oral-nasal oxygenating device (TwinGuard™), or a standard bite block plus nasal cannulae using an equivalent flow rate of oxygen.

Number of Patients (planned and analysed):

The protocol stated that 200 patients were to fully complete the study. However, 151 patients completed as per protocol (PP) and 1 patient withdrew, and was therefore not included in the analysis. The recruitment target was reduced to 150 based on reduced timeline for completion.

Diagnosis and main criteria for inclusion:

Male and female patients aged 18 to 75 years that where scheduled for an endoscopic procedure at the Centre for Digestive Diseases, who did not have any clinically significant respiratory conditions.

Investigational product, dose, mode of administration and batch number:

TwinGuard™ versus Standard Bite block plus nasal cannulae. Used during endoscopic procedure.

Dose, Mode of administration and batch number are N/A.

Duration of treatment:	**Concomitant Medication specified in protocol:**
Single endoscopic procedure	N/A

Criteria for evaluation:

Oxygen saturation levels, End tidal CO_2 levels, Respiratory rate and Heart rate changes through the various stages of sedation during the procedure, and through to recovery. Adverse Events.

Statistical methods:

The mean oxygen saturation at baseline, following sedation and administration of supplemental oxygen via TwinGuard™ or standard bite block plus nasal cannulae, and during endoscopy were determined. Independent t tests and χ^2 tests were used to compare between groups. Linear regression was used to determine the correlation between falls in oxygen saturation and other variables such as age, weight and respiratory function tests.

Summary – Conclusions

Results:
Demonstrated equivalence in maintaining oxygen saturation levels, with TwinGuard™ providing improved, uninterrupted readings for $ETCO_2$ throughout each stage of the endoscopic procedure.

No significant adverse events reported in either group.

Conclusions:
TwinGuard™ is as safe to use as the standard bite block plus nasal cannulae system, with the superior detection of $ETCO_2$ during endoscopy. Making TwinGuard™ commercially viable as the preferred choice for endoscopy oxygenation and $ETCO_2$ monitoring.

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1. ABBREVIATIONS and DEFINITIONS

AE	Adverse Event
BP	blood pressure
CDD	Centre for Digestive Diseases
CDD HREC	Centre for Digestive Diseases Human Research Ethics Committee
CRF	Case Report Form
$ETCO_2$	end tidal Carbon dioxide
GCP	Good Clinical Practice
HR	heart rate
HREC	Human Research Ethics Committee
ICH	International Conference of Harmonization
NHMRC	National Health and Medical Research Council
O_2 Sat	oxygen saturation
RR	respiratory rate
SAE	Serious Adverse Event
SBB	Standard Bite Block plus Nasal Cannulae
TGA	Therapeutic Goods Administration
TWG	TwinGuard™

2. ETHICS

2.1 Human Research Ethics Committee (HREC)

Prior to study commencement, the study protocol, informed consent document, and any other appropriate documents were submitted to the Centre for Digestive Diseases Human Research Ethics Committee (CDD HREC) Section 12.1.3, with a cover letter listing the documents submitted, their dates of issue, and the site for which approval was sought.

Approval was granted in February 2006. The CDD HREC was constituted in accordance with the *National Statement on Ethical Conduct in Research involving Humans* (June 1999) as issued by the National Health and Medical Research Council (NHMRC), in accordance with the NHMRC Act, 1992 (Cth) and Good Clinical Practice (GCP) guidelines (July 2000), at the time of approval.

2.2 Ethical Conduct of the study

The procedures set out in the study protocol, pertaining to the conduct, evaluation, and documentation of this study, were designed to ensure that the sponsor and investigator abide by the principles of the good clinical practice (GCP) guidelines of the ICH and the ethical principles detailed in the current revision of the Declaration of Helsinki (2000). The study was also carried out in keeping with local legal and regulatory requirements.

2.3 Patient Information and Consent

Before being admitted to the clinical study, informed consent was obtained after the nature, scope, and possible consequences of the trial had been explained in a form understandable to the participant.

An informed consent document that included both study information and participation outline as well as the consent form was prepared. This document complied with all local site and regulatory requirements. The document was written in a language understandable to the subject in layman's terms. The consent form specified who informed the subject. The person who informed the subject and answered queries was either the investigator or research assistant.

The patient was given the Patient Information and Consent Form to read. After reviewing the informed consent document and having queries answered, subjects willing to participate were obliged to give consent in writing. The subjects consent was confirmed at this time by the signature of the subject and the person conducting the informed consent discussions. Subjects were consented post pre-screening and before baseline assessments.

3. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Investigators	Prof Thomas Borody (Principle) Dr Sanjay Ramrakha (Co-Investigator) Dr John Saxon (Co-Investigator)
Study Manager	Kylie Peters, Research Manager
Study Co-ordinators	Margaux Alvaran, Jordana Campbell, and Quincy Cheuk, Responsible for confirmation of patient notes, CRF entry, collation of results, and management of study files.

Please refer to Section 12.1.2 for the curriculum vitae of all study staff.

4. INTRODUCTION

Arterial oxygen desaturation occurs frequently during gastrointestinal endoscopic examination[1,2,3]. This leads to a condition called hypoxia where there is a reduction of oxygen supply to the body tissues despite adequate flow of blood to the tissues [4].

Earlier studies have shown that patients who undergo a panendoscopic evaluation were likely to suffer from oxygen desaturation during intubation of the endoscope[1,2,3]. Treatment of hypoxia usually involves an oxygen face mask or nasal cannulae. The question of whether preferential mouth breathing, nasal breathing or both has not been clearly resolved[5]. There is however, a suggestion that patients change their breathing pattern after intubation from nasal to oral and that this oral breathing continues until the endoscope tube is removed [6,7,8,9].

Post procedure nausea and vomiting are unpleasant for patients and can cause aspiration pneumonia. Supplemental oxygen during the recovery period has shown to reduce the incidence of post operative nausea and vomiting[11].

This study was designed to determine if the new oral-nasal oxygenating device – TwinGuard™ (TWG), which is built as part of a bite block – is similarly effective in oxygen delivery during the procedure, as well as providing ongoing oxygenation post procedure during the recovery period when compared to that of the standard bite block plus nasal cannulae (SBB).

In providing an oral-nasal oxygenating mouth-guard that has a detachable nasal cannula, it is envisaged that costs will be minimised while maintaining safety and efficacy of oxygen delivery. The detachable portion bypasses the need for separate nasal cannulae and can provide comfort for the patient during recovery (post-procedure). Making this novel product commercially competitive, especially in the US market.

It is believed that TWG will not only improve the quality of the procedure and the quality of patient care but also decrease the costs of equipment needed for the procedure. The newly developed TwinGuard™ is aimed at further increasing the level of efficacy and comfort of oxygen delivery during endoscopic procedures and during the recovery period.

The detection of ventilation parameters such as expired end-tidal CO_2 and respiratory rate have been utilised in anaesthetic practice. The fact that there is an open system with conventional bite block oxygenating devices means that the dead space of ventilation is large, unlike that seen in a 'closed' ventilatory circuits associated with general anaesthesia. The TwinGuard™ was designed with sampling ports that are in close proximity to both the nose and the mouth in order to improve detection. Allowing for the problems of dead space, reliable detection of CO_2 and trends from baseline are important factors in assessing adequate ventilation.

5. STUDY OBJECTIVES

Primary objectives

1. To determine the efficacy of the TwinGuard™ in oxygen delivery during and post procedure.
2. To determine if the TwinGuard™ achieves and/or surpasses the level of quality of the standard nasal prong oxygenation with bite block during the procedure.

Secondary objectives

1. To determine cardiorespiratory perimeters of safety of the TwinGuard™, including the addition of the CO_2 accessory.
2. To assess the comfort of the TwinGuard™ device.

6. INVESTIGATIONAL PLAN

6.1 Overall Study Design and Plan-Description

Design Open labelled

Population The per protocol (PP) population, which completed the study, comprised of 150 consecutive consenting eligible patients scheduled for endoscopic evaluation.

A total of 151 patients underwent to efficacy and safety assessment, of those, 1 patient withdrew consent for use of their data.

Please see Attachment 1 for study protocol and Attachment 2 for sample Case Report Form.

6.2 Discussion of Study Design

This was a single centre, randomised parallel study designed to determine the safety and efficacy of the TWG™ compared to the SBB. The patient population was drawn from subjects scheduled for endoscopic evaluation.

6.3 Selection of Study Population

6.3.1 Inclusion Criteria

The population base consisted of patients who presented to the Centre for Digestive Diseases with a endoscopic procedure scheduled. Patients deemed eligible to enter the trial were approached by the investigator and invited to participate. A total of 200 patients who fully completed participation were to be recruited.

All eligible patients who were willing to participate in the study were given the opportunity to ask questions, and were thoroughly informed about the study before signing consent.

Patients who failed the inclusion/exclusion criteria were informed that they were not eligible for the study and would continue under the care of the investigator as per standard clinical practice. Those who were successfully recruited began treatment once baseline examinations were conducted and eligibility confirmed. All patients who were screened for eligibility were documented regardless of successful recruitment or otherwise.

The patient had to meet all of the following criteria to be eligible for inclusion in the trial:

1. Males and females aged 18 to 75 years.

2. Medically assessed preoperatively to either ASA (American Society of Anesthesiology) grade I or II.

3. Scheduled to undergo a panendoscopy.

4. Have provided written fully informed consent as shown per protocol.

5. No clinical evidence of any other disease which might interfere with the patient's ability to enter the trial.

6. Fasted for 4-6 hours prior to enrolment as per standard clinical practice for panendoscopy.

6.3.2 Exclusion Criteria

Patients were excluded for any of the following reasons:

1. Patients refusing to consent to participate.

2. Patients considered high risk, or patients suffering from cardio respiratory disease that may hinder their breathing during the procedure (eg. moderate to severe asthma, lung and heart disease, lung infections, emphysema).

3. Patients who have not fasted for 4-6 hours prior to enrolment, as per standard clinical practice.

4. Unable to communicate well with the Investigators and to comply with the requirements of the entire study.

5. Patients with clinical evidence of any other disease which might interfere with the patient's ability to enter the trial.

6. Patients who are currently or have a history of drug or alcohol abuse.

7. Patients who have been involved in an experimental drug protocol within the past four weeks.

6.3.3 Removal of patients from assessment

No patients was completely withdrawn from the assessment, only withdrawn from assessment if data was missing for a particular data set analysed. No patients were withdrawn due to a serious adverse event.

6.4 Measurements

Pre-endoscopy – Peak flow expiratory rate predicted with patients height, cardiorespiratory parameters, heart rate, respiratory rate, $ETCO_2$, blood pressure.
Post sedation administration - $ETCO_2$, O_2 saturation, blood pressure, heart rate, respiratory rate, level of sedation (mild moderate, and deep). During sedation, during endoscopy, and in recovery.
Comfort assessment – Four scale assessment, as determined by the patient prior to discharge.

6.5 Assessment Variables

6.5.1 Assessment Measurements

The following measurements were collected at the visit:

- Peak Flow Expiratory Rate (PFER)
- End-tidal CO_2 ($ETCO_2$)
- O_2 Saturation (O_2)
- Respiratory Rate (RR)
- Heart Rate (HR)
- Blood pressure (BP)
- Patient Comfort

Each if these readings, except comfort, can be affected by patient weight, height, physical fitness levels. By randomising patients to one of two oxygenating devices, it was hoped that the two groups would be evenly matched in these variables to provide the analysis with meaning.

Section 8.4.5 outlines the adverse events recorded over the period of the study. Section 12.8 contains a complete list of all adverse events broken down per patient. There were no serious adverse events reported in the duration of the study.

6.5.2 Appropriateness of measurements

The measuring device, Capnocheck^{TM}, was used to measure O_2 Sat, RR and $ETCO_2$ levels throughout the procedure. As a predicted decrease in oxygen saturation was anticipated with increasing sedation. The rate of rise of oxygen was measured after it reached 90%.

Additionally, a decrease in respiratory rate and the rise in $ETCO_2$ was anticipated with increasing levels of sedation.

The significance of changes, rather than absolute values, in $ETCO_2$ is relative to the baseline values in predicting ventilatory embarrassment.

6.5.3 Data Quality Assurance

Data quality assurance methods implemented for this study include:

1) Data verification through the use of source documentation,
2) Use of a single laboratory for all standard laboratory testing, and
3) Monitoring of site files using internal Standard Operating Procedures.

6.6 Statistical Methods Planned in the Protocol and Determination of Sample Size

6.6.1 Statistical and analytical plans

A total of 151 patients were screened for study eligibility. Of these 151 patients were found eligible for study participation and were enrolled into the study. A total of 150 patients completed the study and data was included in the assessments.

The two groups of patients (75 per group) were anticipated to be reasonably matched in terms of age, weight and baseline oxygen saturation. The mean oxygen saturation at baseline, following sedation and administration of supplemental oxygen via TWG™ or SBB, and during endoscopy were determined. Independent t tests and χ^2 tests were used to compare the two groups. Linear regression was used to determine the correlation between falls in oxygen saturation and other variables such as age, weight and respiratory function tests.

Primary

The mean percentage oxygen saturation at baseline and the changes in percentage oxygen saturation following sedation and administration of supplemental oxygen and during endoscopy will be analysed. These variables were compared to determine the efficacy of TWG and SBB for administration of supplemental oxygen. The unit of measure is oxygen in litres/min or volume. The change from baseline is expressed as percentage of oxygen saturation.

Secondary

Changes in respiratory rate, heart rate and arterial CO_2 tension occurring after sedation and during endoscopy were analysed. These variables including age, weight, initial measurements of lung function (ventilatory function) and oxygen saturation will be analysed to determine whether they relate to falls in oxygen saturation and to the administration of supplemental oxygen using TWG™ as compared to SBB.

Significance

A p value <0.05 will be considered significant.

6.6.2 Determination of sample size

The sample size for this study was originally limited to 100 in each group. The smallest difference that can be detected between means is approximately 11 with the desired power of 80% and the significance level α or type error I probability of 0.05.

The change in the sample size to 150 patients with 75 in each group, was determined to be of sufficient power for the study.

6.7 Changes in Conduct of the Study or Planned Analyses

The only change to the study was the sample size, as discussed in Section 6.6.2.

7. STUDY PATIENTS

7.1 Disposition of Patients

All enrolled patients are listed in Section 12.2. This table outlines the details of consent, completion status and reasons for this status. For this study, a total of 151 patients were screened. Zero were excluded at screening and 1 patient withdrew consent after completing study participation.

7.2 Protocol Deviations

This study was conducted in compliance with the protocol agreed to by the sponsor and the investigator.

Four patients deviated from the guidelines of the protocol. Three patients (patient #'s 1001 TWG, 1008 SBB, 1009 TWG) were over the maximum 75 years old as specified in the first Inclusion criterion. One patient (patient # 1113 SBB) reported emphysema, which is also an exclusion as per second exclusion criterion. Waivers were granted by the Sponsor, as these patients were deemed to be of a physical fitness level which would not be of risk by participating.

8. EFFICACY EVALUATION

8.1 Data Sets Analysed

The 150 patients, 75 per group, that completed the study were included in the efficacy analyses. Patients withdrawn from the study were not included in the efficacy analysis. The data sets analysed include $ETCO_2$, O_2 Sat, HR, and RR at each stage of sedation, endoscopy, and recovery, and compared between the two test groups.

Other data sets analysed were attained from entries in the patient history notes and from data collated from the patient case report forms. These included concomitant medications, current symptoms and physical examination, and level of patient comfort.

8.2 Demographic and Other Baseline Characteristics

Full patient population

One hundred and thirty eight (137) patients were Caucasian, 11 Asian, 1 Hispanic, and 1 unknown, with their place of birth being 95 from Australia, 17 Italy, 6 United Kingdom, 4 Lebanon, Pacific Islands, 3 Poland, 3 Korea, 2 South Africa, 2 Argentina, 1 unknown, and 1 from each of Jordan, Belgium, Denmark, Egypt, Germany, Greece, Hungry, Malaysia, New Zealand, Sri Lanka, Sudan, Turkey, Philippines and 1 United States of America.

The age range of eligible patients was from 20 to 80 years of age, with the mean age being 53 years. The eligible population was divided between 78 males and 73 females. The majority (90/150, 60%) of the study population were non-smokers, with 16/150 (10.6%) patients who smoked an average of 10 cigarettes daily, 5/150 (3.3%) occasional smokers, and 39/150 (26%) were ex-smokers, with an average of 14.5 years since quitting. Fifty one (51/150, 34%) patients consumed alcohol on a daily basis, with 73/150 (48.8%) occasionally consuming alcohol, 22/150 (14.6%) never consuming alcohol, and 3 unknown.

TwinGuard™ Group

Sixty seven (67) patients were Caucasian, 7 Asian, and 1 unknown, with their place of birth being 51 from Australia, 8 Italy, 3 United Kingdom, 3 Pacific Islands , 2 Korea, 1 unknown, and 1 from each of Lebanon, Poland, Denmark, Egypt, Hungry, Malaysia, Philippines.

The age range of eligible patients was from 24 to 80 years of age, with the mean age being 54 years. The eligible population was divided between 41 males and 34 females. The majority (46/75, 61.3%) of the study population were non-smokers, with 6 (8%) patients who smoked an average of 12

cigarettes daily, 4/75 (5.3%) occasional smokers, and 19/75 (25.3%) were ex-smokers, with an average of 11 years since quitting. Twenty three (23/75, 30.6%) patients consumed alcohol on a daily basis, with 38/75 (50.6%) occasionally consuming alcohol, 11/75 (14.6%) never consuming alcohol, and 2 unknown. (Section 12.6A).

All patient medical history was recorded at baseline (see Section 12.7A). Of the 75 patients, 7 (9.3%) reported mild asthma.

Standard Bite Block plus Nasal Cannulae
Seventy (70) patients were Caucasian, 4 Asian, 1 Hispanic, with their place of birth being 44 from Australia, 9 Italy, 3 United Kingdom, 3 Lebanon, 2 Poland, 2 South Africa, 2 Argentina, 1 unknown, and 1 from each of Jordan, Belgium, Germany, Greece, New Zealand, Sri Lanka, Sudan, Turkey, Philippines and 1 United States of America.

The age range of eligible patients was from 20 to 78 years of age, with the mean age being 51 years. The eligible population was divided between 37 males and 38 females. The majority (44/75, 58.6%) of the study population were non-smokers, with 10/75 (13.3%) patients who smoked an average of 7 cigarettes daily, 1/75 (1.3%) occasional smokers, and 20/75 (26.6%) were ex-smokers, with an average of 17 years since quitting. Twenty nine (29/75, 38.6%) patients consumed alcohol on a daily basis, with 34/75 (45.3%) occasionally consuming alcohol, 11/75 (14.6%) never consuming alcohol, and 1 unknown. (Section 12.6B).

All patient medical history was recorded at baseline (see Section 12.7B). Of the 75 patients, 9 (12%) reported mild asthma, 1 reported past exposure to asbestos, all breath sounds deemed normal on physical examination prior to endoscopy.

8.3 Measurements of Compliance

Not applicable.

8.4 Efficacy Results

8.4.1 Analysis of efficacy

8.4.1.1 Stages of Sedation (See Section 12.3.2 and 12.4.2)

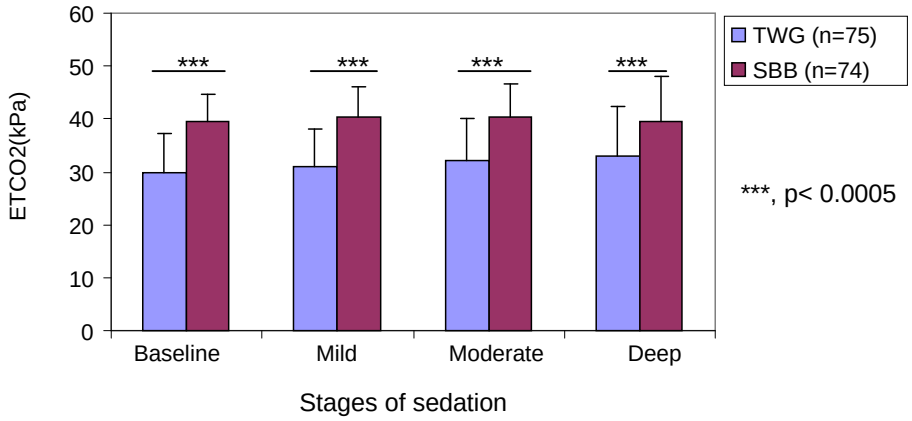
Baseline
There was no significant difference in the levels of O_2 Sat, HR and RR between TWG and SBB. Higher absolute $ETCO_2$ levels were observed with SBB (m=39.52, n=75) than with TWG (m=29.72, n=74) (*P*=0.0005).

Mild sedation
No significant difference in O_2 Sat, RR and HR levels between TWG and SBB was observed. A significantly higher absolute $ETCO_2$ was observed with SBB (m=40.51; n=75) than with TWG (m=30.92; n=74) (*P*=0.0005).

Moderate sedation
No difference in O_2 Sat, HR and RR between TWG and SBB was observed. Absolute $ETCO_2$ levels were significantly higher (m=40.36, n=75 with SBB versus m=32.18, n=74 with TWG; *P*=0.0005).

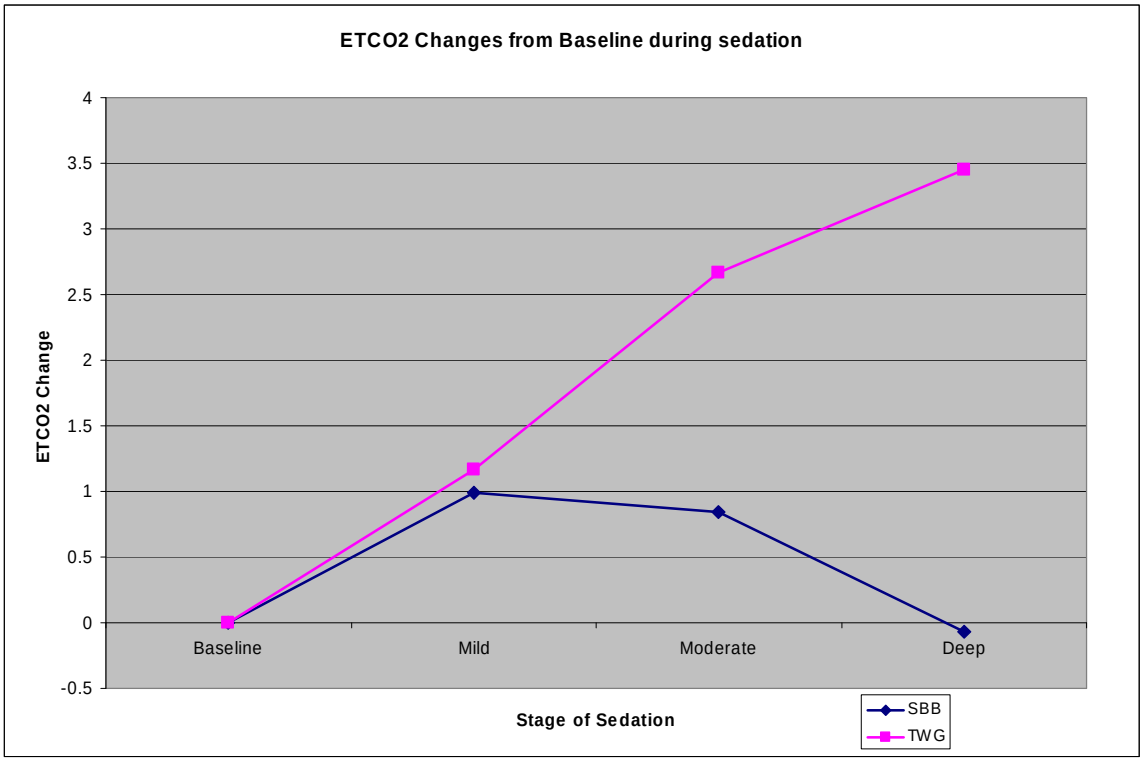
Deep sedation
No significant difference in O_2 Sat, HR and RR levels between TWG and SBB was detected. Higher absolute $ETCO_2$ levels were detected with SBB (m= 39.45, n=75) than with TWG (m=33.1, n=74, *P*=0.0001).

Comparison between TWG and SBB for monitoring absolute $ETCO_2$ during sedation



Overall

A difference in the change of $ETCO_2$ levels within each group was noted. SBB measured mean $ETCO_2$ levels which did not significantly deviate from baseline during the different levels of sedation. However, TWG noted a mean increase of $ETCO_2$ levels from baseline progressively as sedation deepened, difference between TWG and SBB during sedation demonstrated statistical significance, p<0.0001.



8.4.1.2 Stages of Endoscopy (See Section 12.3.3, and 12.4.3)

Oxygen saturation (O_2 Sat)

Oxygen saturation (%) was measured at baseline, intubation, nadir, 15sec, 30sec, 1min, midpoint and endpoint following sedation. No statistically significant difference in O_2 Sat levels between TWG (n=72) or SBB (n=73) at all stages of endoscopy were found, indicating that TWG is equivalent to SBB for administration of oxygen during endoscopy.

Heart Rate (HR)

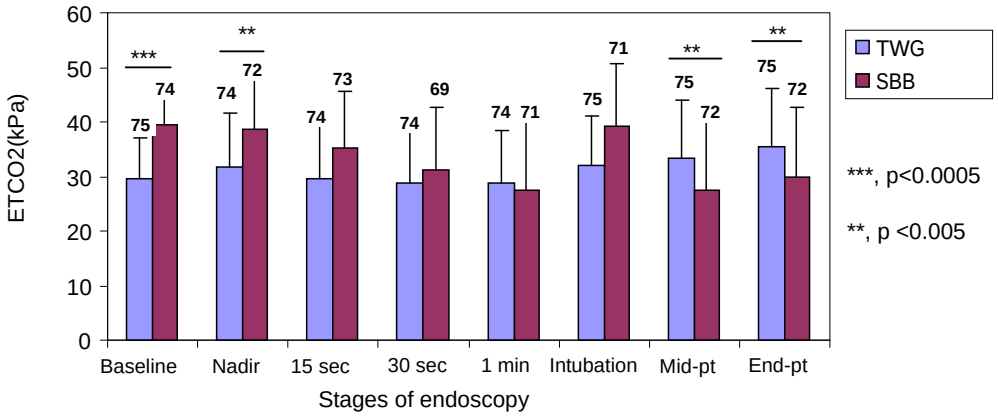
HR was measured at baseline, intubation, nadir, 15sec, 30sec, 1min, midpoint and endpoint following sedation. No significant difference was observed between TWG and SBB groups.

End tidal CO_2 ($ETCO_2$)

Adequate monitoring of $ETCO_2$ throughout the entire procedure was observed for 72/75 (96%) patients with TWG, compared to 58/75 (77.3%) patients in the SBB group demonstrating inadequate $ETCO_2$ monitoring for 22.7% of these patients, where switching to oral measurements was required (*P*= 0.0005). This switching meant time in which the patient is inadequately monitored.

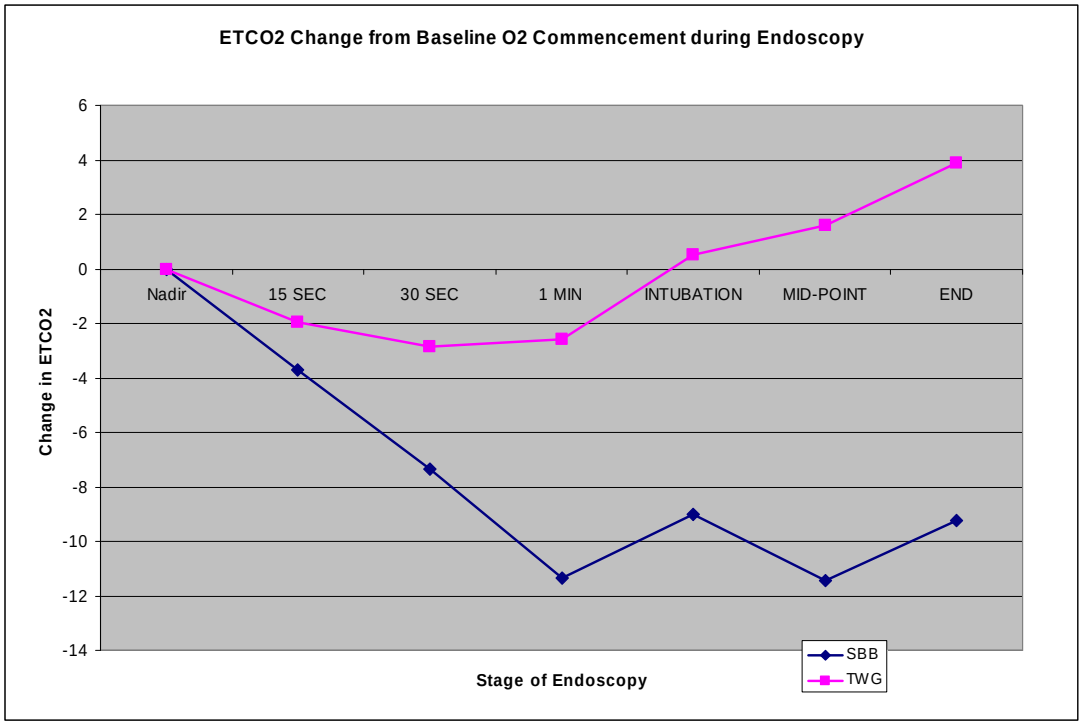
Of note higher mean absolute $ETCO_2$ levels were recorded with SBB (59/75, 78.6%) at Nadir and at 15 sec after supplemental O_2 than with TWG (72/75) (39.2±9.9 vs 31.4±9.3) and 29.5±9.9 vs 35.7±10.4), *P*=0.0005, respectively).

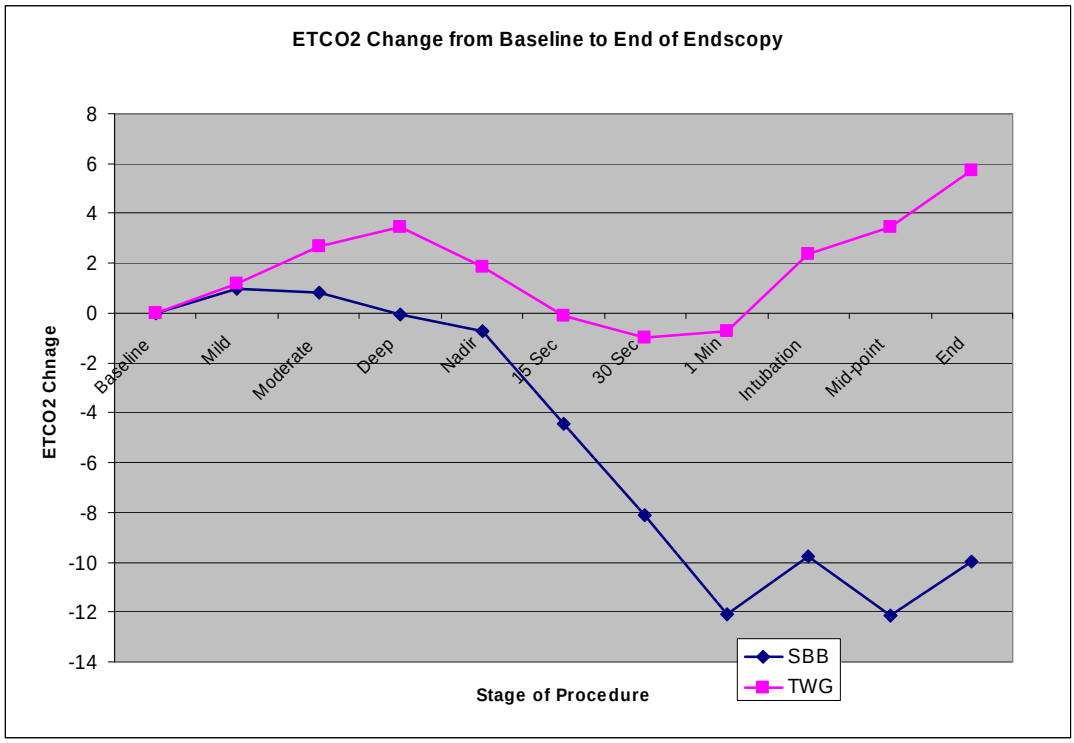
Comparison between TWG and SBB for monitoring absolute $ETCO_2$ during endoscopy



The change in $ETCO_2$ from baseline however, demonstrates a 'wash out' period between nadir and 1 min in the SBB group. This 'wash out' is likely due to the commencement of supplemental oxygen which is likely interfering with the $ETCO_2$ detection.

The change in $ETCO_2$ in the TWG group is representative of the predictive $ETCO_2$ changes during endoscopy. The difference between TWG and SBB at the nadir, midpoint and end of procedure did reach statistical significance, p<0.001.





Respiratory Rate (RR)
No significant difference was observed between TWG and SBB during the procedure.

8.4.1.3 Stages of Recovery (See Section 12.3.4 and 12.4.4)

Pre- and post-recovery phases showed no statistically significant difference in O_2 Sat and HR between TWG (n=74) and SBB (n=73) compared with arrival.

8.4.2 Relationship between Oxygen Saturation and HR, RR and $ETCO_2$

No correlation was found between O_2 Sat and HR, RR or $ETCO_2$ in any stage of endoscopy or sedation for TWG. In contrast, a significant correlation between the variables was obtained for SBB in the following groups at the 0.05 level (2-tailed). There was a negative correlation between O_2 saturation and RR at intubation (r=-0.243) and during mild sedation (r=-0.286). In contrast, there was a positive correlation between O_2 saturation and $ETCO_2$ during mild (r=0.374) and moderate sedation (r=0.299). The results suggest that there is a weak relationship between O_2 saturation and RR during intubation at mild sedation and a moderate relationship between O_2 saturation and $ETCO_2$ during mild to moderate sedation.

O_2 Sat and RR at intubation – Pearson Correlation r = -0.243, *P* = 0.039
O_2 Sat and $ETCO_2$ for mild sedation – r = 0.374, *P* = 0.001
O_2 Sat and RR for mild sedation – r = -0.286, *P* = 0.013
O_2 Sat and $ETCO_2$ for moderate sedation – r = 0.299, *P* = 0.009

No correlation was observed between O_2 Sat and HR , RR, or $ETCO_2$ at any stage of endoscopy or sedation in the TWG group indicating that whilst these parameters are interlinked and can be used individually to predict or determine the trend of the others, they are to a certain extent partly independent, and as such small changes or deviations within each individual set of parameters will not significantly alter or influence the processes of the other parameters.

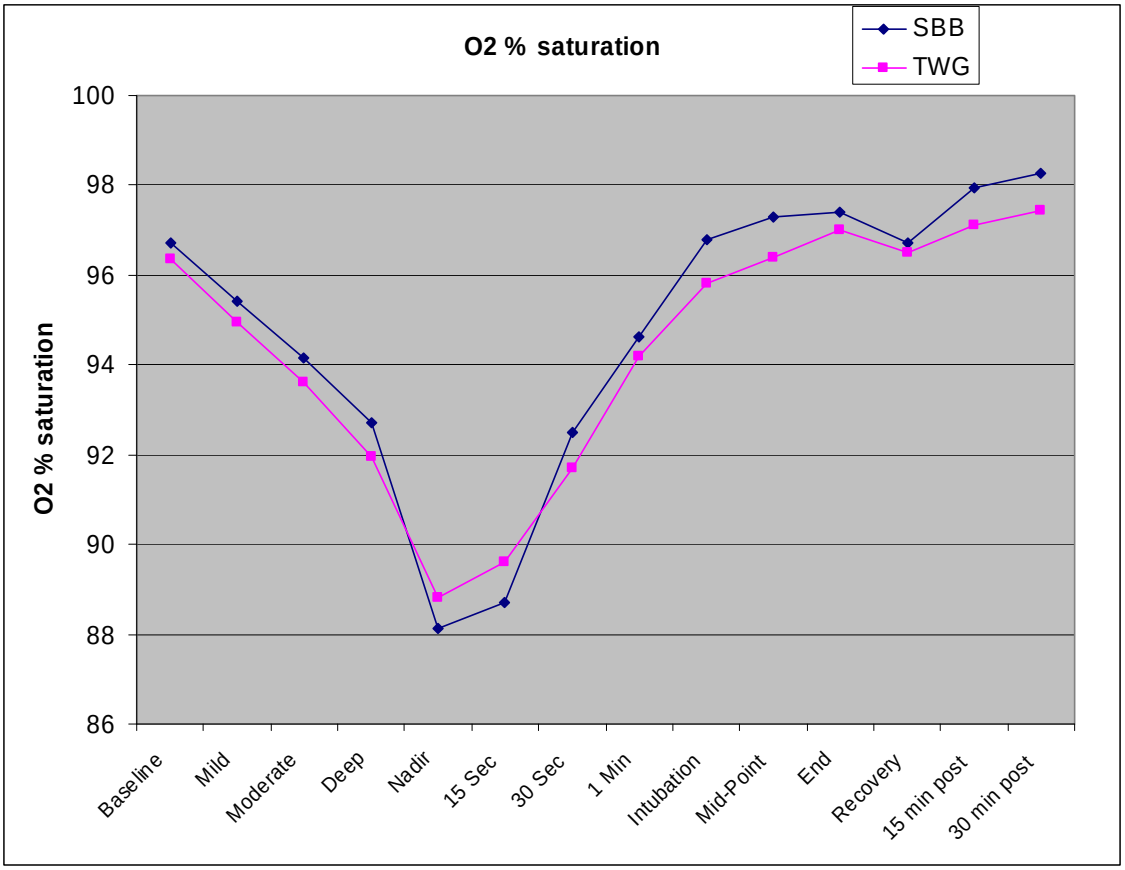
This may infer that minor respiratory problems, mouth/oral breathing and slight changes in the respiratory rates while under sedation may not increase the risk of hypoxia when TWG is used with supplemental oxygen.

Significant correlations were observed when the same parameters were compared in the SBB group. A negative correlation between O_2Sat and RR both at intubation and during mild sedation suggests a weak relationship between these two parameters and that changes in the respiratory rate may influence or alter oxygen saturation levels during intubation and mild sedation. This could indicate that closer monitoring at these two stages is required.

A positive correlation was also identified between O_2Sat and $ETCO_2$ at mild and moderate sedation. This suggests a stronger relationship between these two parameters and as such changes in the $ETCO_2$ will definitively influence oxygen saturation levels. This may indicate that the supplemental oxygen delivery is at its most importance during mild and moderate sedation.

8.4.3 Reliability of Oxygen Supplementation

When comparing the reliability of measurements during endoscopy between the two groups (see 8.4.1 Stages of Sedation), it becomes apparent that the TWG design and process of oxygen supplementation results in a more reliable device with which $ETCO_2$ can be monitored, thus allowing for improved safety for patient monitoring during this type of procedure.



8.4.4 Patient Comfort (12.3.5, and 12.4.5)

Patient comfort was determined by asking the patient to rate their comfort prior to discharge. All patients regardless of group rated comfort between Unaware (32.43 v 28.77%), Unaware/Aware but comfortable (24.3 v 27.37%), and Aware but Comfortable (43.24 v 41.10%), TWG (n=74) and SBB (n=73) respectively. However, in the SBB group 2.74% noted discomfort.

8.4.5 Adverse Events

In total 23 Adverse Events were reported by 17 patients. 20 of these were deemed to be Unrelated to the study. Three (3) were deemed to be probably related to the biteblocks used,

each from a different patient. two (2) were reported in the SBB group (swollen lips, lip ulcer), and one from TWG (swollen lip).

8.4.6 Handling of Drop-outs and Missing Data

All data for the single patient who withdrew consent was not used in any analysis.

Single data points missing were not included in the analysis. Any patient with missing the majority of a data set was not included in the analysis for the entire data set.

9. DISCUSSION AND OVERALL CONCLUSIONS

The hypothesis was that the TWG would be able to provide at least equivalent oxygen supplementation to that of a SBB, improve quality of patient care during and post procedure, and provide at least equivalent comfort to patients.

No significant difference in oxygen saturation between TWG and SBB was observed during endoscopy. TWG provides adequate $ETCO_2$ monitoring for all patients throughout the procedure than SBB. Comparative to baseline $ETCO_2$ levels in each group did show improved detection using TWG. The location of the nasal sampling of the TWG appears to provide more sensitive $ETCO_2$ readings for the deeper levels of sedation. As it is expected that $ETCO_2$ levels will rise during increasing depths of sedation, the SBB showed no significant change, on average, whilst the TWG, on average, did demonstrate the expected increasing levels of $ETCO_2$. No significant difference in HR or RR between TWG and SBB was found.

It has therefore been demonstrated that the TWG provides equivalent oxygen supplementation to that of the SBB during an endoscopic procedure. In addition, the TWG provides for greater reliability of detection of $ETCO_2$, during endoscopy – a current requirement in the US - thereby improving the quality and accuracy of care that can be provided to the patient. There is a suggestion that early in sedation, when oxygen wash out is not a factor, and that TWG is a more reliable measure than SBB. This continues after the commencement of oxygen.

No significant difference in reported patient comfort was noted, with the exception of 2 reports of discomfort in the SBB group. No significant adverse events were reported during this study. Only 4 possibly/probably related adverse events were recorded, 3 with SBB and 1 with TWG. These were mild in nature and transient.

Conclusions

Based on the current data, the study demonstrated that TWG and SBB are equivalent in terms of oxygenating during endoscopic procedures, with the TWG improving patient safety by providing superior $ETCO_2$ detection. There appears to be more predictive changes in $ETCO_2$ when comparing values from baseline. This may prove to improve monitoring of ventilation in patients undergoing endoscopy.

Overall, from a commercial viewpoint, the TwinGuard™ would be the device of choice for endoscopy oxygenation and CO_2 monitoring.

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12. APPENDICES

12.1 Study Information

12.1.1 HREC involved in the Approval of the Study

Centre for Digestive Diseases Human Research Ethics Committee
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12.1.2 List of Investigators and other Study Staff (CV's included on following pages)

Principle Investigator - Curriculum Vitae

Name	Thomas Julius Borody
Present Appointment	Director
Address	Centre for Digestive Diseases Level 1, 229 Great North Rd, Five Dock NSW 2046
Qualifications	**1971**: BSc(Med) (Hons) University of New South Wales, Australia **1974**: MB BS (Hons) University of New South Wales, Australia **1982**: FRACP Royal Australasian College of Physicians **1984**: MD University of New South Wales, Australia **1993**: FACG American College of Gastroenterology
Previous Appointments/Experience	***Professional training*** **1974**: Internship -St Vincent's Hospital, Sydney, Australia **1975-1977**: Residency - St Vincent's Hospital, Sydney, Australia **1981-1983**: Fellowship (Registrar) - St Vincent's Hospital, Sydney, Australia ***Research Training*** **1971**: Research fellow - Pathology Dept, University of NSW, Australia **1979-1980**: NH&MRC postgraduate scholar – Garvan Institute of Medical Research, Australia **1983-1984**: Fellow in Gastroenterology – NH&MRC Scholar, Mayo Clinic, Rochester, MN, USA ***Appointments*** **1978**: Medical Officer (Tropical Gastroenterology Training) – Atoifi Adventist Hospital, Malaita, Solomon Islands **1981**: Medical Registrar – St Vincent's Hospital, Sydney, Australia **1982**: Senior Medical Rregistrar – St Vincent's Hospital, Sydney, Australia **Current**: Director and practicing Gastroenterologist - Centre for Digestive Diseases, Sydney, Australia **Current**: Consultant Gastroenterologist – St Vincent's Hospital, Sydney, Australia **Current**: Consultant Gastroenterologist – Sydney Adventist Hospital, Australia
Publications	175 publications including original papers, reviews, case reports and abstracts (over 130 in peer-reviewed journals) 8 book chapters 1 book
Date of Issue	February 2006

Co-Investigator 1 Curriculum Vitae

Name	Sanjay Ramrakha
Qualifications	**1986** MBBS, University of NSW, Sydney
Present appointment	Sedationist
Address	Centre for Digestive Diseases, Level 1, 229 Great North Road Five Dock NSW 2046
Previous appointments/experience	***Appointments***
	1999- current Staff Specialist, Emergency Department, Royal Prince Alfred Hospital, Sydney
	Medical Consultant, Sydney Turf Club
	General Practitioner, Drummoyne
	1999 Locum Staff Specialist, Emergency Department, Liverpool Hospital
	Medical Educator, South West Area Health Service, Sydney
	1997 Intensive Care/Resuscitation Registrar, Liverpool Hospital
	1996-1998 Emergency Registrar, Liverpool Hospital
	Medical Officer, Emergency Department, NSW Private Hospital, Ashfield
	1995-1996 Medical Officer, Emergency Medical Systems, Sydney
	Professional Training
	1993- 1994 Emergency Registrar Trainee, Liverpool Hospital
	1993 Emergency Registrar Trainee, Royal Alexandra Hospital for Children, Camperdown
	Anaesthetic Registrar, Liverpool Hopsital
	1990-1992 General Practitioner, Drummoyne NSW, and Rosebury TAS
	1988-1989 Resident Medical Officer, St Vincent's Hospital
	1987 Internship, St Vincent's Hospital
Publications	4 Publications
Date of issue	February 2006

Co-Investigator 2 Curriculum Vitae

Name	John Saxon	
Qualifications	**1985**	MBBS, University of New South Wales, Sydney
Present appointment	**1995- current**	VMO (Sedationist)
Address	Centre for Digestive Diseases, Level 1, 229 Great North Road Five Dock NSW 2046	
Previous appointments	**2000- current**	VMO (Sedationist), Rosemont Endoscopy Centre, Wollongong
	2000- current	Injury Management Consultant, Quality Occupational Health, Merrylands
	1999- current	Chief Medical Officer, Sydney Turf Club
	1999- current	VMO, Quality Occupational Health, Merrylands
	1998-2000	Senior Emergency Registrar, Royal prince Alferd Hospital, Camperdown
	1997-2000	Director, Emergency Department, NSW Private Hospital
	1996	Emergency Registrar, St George Hospital, Kogarah
	1995-1997	Emergency Medical Officer, Relieving Director, Masonic Hospital, Ashfield
	1994	Emergency Supervisor, Emergency Department, Shellharbour Hospital, Illarwarra.
	1989-1993	Registrar, Intensive Care, St Vincent's Private Hospital, Darlinghurst
	Professional Training	
	1985	Intern, St Vincent's Hospital, Darlinghurst
	1986	Resident Medical Officer, St Vincent's Hospital, Darlinghurst
	1987-1988	Senior Resident Medical Officer, St Vincent's Hospital, Darlinghurst
Publications	5 presentations on Emergency medicine 7 presentations on various topics	
Date of issue	February 2006	

Study Manager Curriculum Vitae

Name	Kylie Peters
Qualifications	**1997–2000**: Bachelor of Science (Biological Science) University of Western Sydney, Nepean
Present appointment	**2005- current** Research Manager
Address	Centre for Digestive Diseases Level 1, 229 Great North Road, Five Dock NSW 2046
Previous appointments/experience	**2000–2005**: Clinical Research Officer and Study Coordinator
Publications	7 Abstracts and 1 paper in the field of Gastroenterology. 1 Paper on the influence of salinity on biomass production by Australia *Pisolithus* species (ectomycorrhizal fungi) isolates.
Date of issue	February 2006

Study Co-ordinator 1 Curriculum Vitae

Name	Margaux Alvaran
Qualifications	**2000 - 2003** Bachelor of Science (Biochemistry) University of Western Sydney, Nepean
Present appointment	**2006- current** Clinical Research Officer
Address	Centre for Digestive Diseases Level 1, 229 Great North Road, Five Dock NSW 2046
Previous appointments/experience	**2004 - 2006** Clinical Research Assistant and Study Coordinator
Publications	3 Abstracts in the field of Gastroenterology
Date of issue	February 2006

Study Co-ordinator 2 Curriculum Vitae

Name	Jordana Campbell
Qualifications	**2003-2005** Bachelor of Science University of Western Sydney, Nepean
Present appointment	**2006 – current** Clinical Research Assistant
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Publications	N/A
Date of issue	March 2006

Study Co-ordinator 3 Curriculum Vitae

Name	Quincy Cheuk
Qualifications	**2004-2006** Bachelor of Medical Science University of Sydney
Present appointment	**2006-current** Clinical Research Assistant
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Publications	N/A
Date of issue	November 2006