An Examination of the Impact of Depth of Anaesthesia on Post-Operative Pain Following Wide Local Excision of Breast Tissue for Breast Cancer

Submitted for the degree of

Doctorate in Clinical Psychology

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1 DECLARATION

I, Peter Beardsworth, declare that the research report is my own work and has not been submitted for any other academic award.

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2 ABSTRACT

Literature Review

Despite Mixed findings previous reviews of the literature have highlighted a predictive relationship between pre-operative psychological variables and post-operative pain (Hinrichs-Rocker, Schulz, Jarvinen & Lefering, 2009). This review examined the research published between 2000 and 2013. Eleven studies were identified and discussed. The review noted evidence that psychological variables specific to aspects of pain, mediated the effect of other psychological variables, which indicate general mood states, on pain. Implications for research and clinical practice were also discussed.

Research report

This paper detailed a feasibility study exploring the issues associated with a full scale project analyzing the link between lightness of anaesthesia and post-operative pain (Law, Sleigh, Barnard & MacColl, 2011). A prospective, longitudinal repeated measures design was employed. To control for pre-operative variables the State Trait Anxiety Inventory, state and trait versions (STAI-Y1 and Y2 respectively), The Magill Pain Questionnaire – Short Form (MPQ-SF), the Pain Locus of Control Questionnaire (PLOCQ) and a non-validated body image screening question were administered pre-operatively. Depth of anaesthesia was measured intra-operatively using a Bispectral Index Monitor (BIS). Follow up was conducted a 1-2 days, 6 weeks and 3 months post-operatively. At follow up the MPQ-SF, STAI-Y1 and body image screening question were administered. Twelve participants were recruited. A statistically significant effect of lightness of anaesthesia on post-operative pain was not detected due to small sample size. It was concluded that a large scale study would be feasible. Implications for the execution of future research projects are discussed, as well as for clinical practice.

Critical Appraisal

The critical appraisal explored personal reflections on the research process. Areas covered included motivations to carry out the research project, the experience of the researcher at various stages of the process and discussion of lessons for future researchers in this area.

3 ACKNOWLEDGEMENTS

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9 LITERATURE REVIEW

THE RELATIONSHIP BETWEEN PRE-OPERATIVE PSYCHOLOGICAL VARIABLES AND POST-OPERATIVE PAIN

10 ABSTRACT

Acute and long term post-operative pain are outcomes of surgery that have a significant impact on many areas of patients' lives (Mei, Seeling, Franck, Radtke, Brantner, Wernecke & Spies., 2010). Previous reviews have been published examining the predictive value of pre-operative psychological variables for long term post-operative pain (e.g. Hinrichs-Rocker, Schulz, Jarvinen & Lefering, 2009). However, such reviews tend to examine the direct effect of general psychological variables, such as anxiety, on long term pain. Additionally, they report mixed findings as regards the relationship between psychological variables and pain (Andersen & Kehlet, 2011). The current review set out to examine the relationships between psychological variables that lead to post-operative pain in the long and short term. It also aimed to examine the impact of more specific variables such as pain catastrophising (Sullivan, Bishop & Pivic,1995). Four electronic databases were scrutinised between August 2012 and January 2013. Eleven unique papers were identified and examined to highlight the methodologies, analyses conducted and findings. Specific psychological variables were shown to be at least as strongly, if not more strongly, associated with post-operative pain than general psychological variables. The review identified evidence indicating a relationship, such that specific psychological variables mediated the effect of general psychological variables, such as anxiety, on post-operative pain. This may help to explain the mixed findings of previous research, whose methodologies have not accounted for such relationships. The implications for future research and clinical practice were discussed, as well as the nature of mediating analyses. Additionally, the need for more high quality research on relationships between psychological variables was highlighted.

11 INTRODUCTION

Post-operative pain has been identified as a serious consequence of surgery, having a long-term impact on ability to work, socialise, and maintain relationships, and mental health and overall quality of life (Mei, Seeling, Franck, Radtke, Brantner, Wernecke & Spies, 2010). Use of opioid analgesia in the treatment of chronic pain has serious side-effects, incurring substantial costs to healthcare systems and patients (Annemans, 2011). In the USA, the cost of managing the side-effects of long-term opioid use is estimated at over US$2,000 per year per patient, with an associated increase in use of healthcare systems (Frank, Schmier, & Kleinman, 2002). Post-operative pain prevalence has been reported to be up to 50% (Nikolajsen & Minella, 2009). Its causes are complex and poorly understood. A significant amount of the variance in indices of post-operative pain is not explained by current research (Lautenbacher, Huber, Schöfer, Kunz, Parthum, Weber, Roman, Griessinger & Sittl, 2010).

Any attempt to understand the causes of post-operative pain should be contextualised within a broader understanding of how pain is experienced. This understanding has long since moved away from the idea of a purely biomedical phenomenon in which pain results from tissue damage, and psychological factors are either a consequence of pain or a cause of psychogenic pain. Current theory now embraces a biopsychosocial model (Engel, 1977). This includes social and psychological factors in health models that once would have been exclusively biomedical. An example of a biopsychosocial model is the Gate Control Theory (Melzack & Wall, 1965; 1982). This hypothesises a pain gate at the spinal cord level, which can be opened to allow signals to the brain, and can be closed to block signals. Factors that open the gate can be biological, such as tissue damage, but

can also be psychological factors, such as affect in the form of anxiety, and depression, and cognitive factors such as the ascribed meaning of the pain (Melzack & Wall, 1965). Appreciation of the multiple factors that contribute to pain experience has stimulated a number of lines of inquiry. This review focuses upon research exploring the psychological factors of causal significance for post-operative pain.

Early work in this area focused on the 'work of worry' (Janis, 1958). This concept entails anticipatory fear of future trauma that facilitates post-operative coping. Optimal levels (neither too high nor too low) lead to the best post-operative outcomes in, for example, analgesia consumption (Sime, 1976). However, the form of curvilinear relationship implied was not consistently supported by subsequent studies (Sime, 1976; Feinmann, Ong, Harvey & Harris, 1987; Johnston & Carpenter, 1980; Wallace, 1986; De Groot, Boeke, Van Den Berge, Duivenvoorden, Bonke & Passchier, 1987; Scott, Clum, & Peoples, 1983). Work that followed on from these studies began to assume a linear relationship between pre-operative anxiety and post-operative pain, searching for positive correlations.

More recent reviews of research assessing links between pre-operative psychological factors and post-operative pain suggest a consensus that there are significant relationships (for example Hinrichs-Rocker, Schulz, Jarvinen & Lefering, 2009). These reviews have approached psychological predictors of post-operative pain using an implicit model from the research literature. The model assumes that the influence of a given psychological variable on post-operative pain is direct and linear. Previous reviews have therefore assessed the evidence supporting such a relationship between particular psychological variables and post-operative pain.

Reviews tend to interrogate literature which relates to psychological variables that are affective and general, such as stress, depression and psychological vulnerability (for example Hinrichs-Rocker *et al.,* 2009). It is less common for more specific and cognitive variables, such as pain catastrophising, to be considered by reviews (for an example of an exception see Nielsen, Rudin & Werner, 2007). Pain catastrophising is theorised to increase focus on pain, thereby heightening pain experience, possibly via a pain gate mechanism (Sullivan, Bishop & Pivic,1995).

The findings of the reviews mentioned above provide a range of important insights. For example, Nielsen et al (2007) found that greater post-operative pain was associated with more invasive surgery, pre-operative pain, younger age and pre-operative pain sensitivity. This review suggested links between female gender and pain, although the reviewers caution that these results may have been influenced by choice of research method. State anxiety was found to be correlated with post-operative pain but pharmacotherapy for anxiety is not proven to reduce post-operative pain. Depression was associated with post-operative pain, except in the case of surgery for breast cancer. It is unclear whether pharmacotherapy for depression reduces post-operative pain.

Additionally, Neilson et al (2007) noted a small number of studies which found associations between neuroticism and post-operative pain. It was not clear whether cognitive interventions or pharmacotherapy for neuroticism were effective in reducing post-operative pain. Links between catastrophising and post-operative were been found, but intervention studies were not available. The reviewers noted that polymorphisms on chromosome 22 may increase response to opioid pain killers, meaning that such patients might require less morphine to manage post-operative pain.

Andersen et al (2011) examined studies of predictors of pain for breast cancer surgery. Pre-operative anxiety and depression were shown to be correlated with pre-operative pain and symptoms in the breast region. Correlations were also found between mental health problems and pain. Pain appeared to be associated with these factors but causality could not be determined due to a lack of suitably designed prospective studies. The reviewers concluded more studies were required to determine the influence on post-operative pain of obesity, ethnicity, pre-operative condition related pain and pain in other locations. Young age was found to be correlated with greater pain. Damage to the intercostal brachial nerve could increase pain, but it was argued more studies were required.

Sentinel node biopsy had less pain associated with it than axillary lymph node biopsy. The evidence for the efficacy of pre-operative analgesia could not be evaluated by the reviewers, due to small sample sizes. Breast conserving surgery is associated with greater levels of arm pain than mastectomy, although this may be due to adjuvant therapies. The effect of adjuvant therapies such as chemotherapy and radiotherapy could not be evaluated due to a lack of quality research. Endocrine therapy, known to cause musculoskeletal pain, may be a confounding variable. Previous breast surgery was noted to be a risk factor.

Hinrichs-Rocker et al (2009) examined psychosocial predictors and correlates of Chronic Post-Surgical Pain (CPSP). Severe depression, psychological vulnerability and stress were all determined to be likely to be associated with post-operative pain. The literature did not clearly support or reject; anxiety, self-control, vitality, self-perception of recovery, higher pain relief expectations, sense of control over health, patients decision making,

psychological aspects of work, social support, marital status, household size, return to work, income, litigation/compensation, low mental healthcare or younger age as correlates or predictors of post-operative pain. The review determined that it was unlikely that neuroticism, female gender, full-time employment, low education, race or surgeon experience were associated with post-operative pain.

Interestingly the reviews discussed above do not attempt to assess the possibility of more complex relationships between pre-operative variables and post-operative pain. There may be interaction effects whereby a moderating variable changes the relationship between the independent and dependent variable. Additionally, causation might rely upon mediating variables, which may enhance understanding of the causal mechanisms involved. This may shed light upon chains of mediating variables where the relationship between independent and dependent variables appears weak.

This form of analysis is based on the assumption that what appears to be a direct relationship (relationship C, Figure 1) between an independent and dependent variable is actually reliant upon an indirect causal mechanism, whereby the independent variable has a causal effect on the mediating variable (relationship A, Figure 1) and the mediating variable has a causal effect on the independent variable (relationship B, Figure 1).

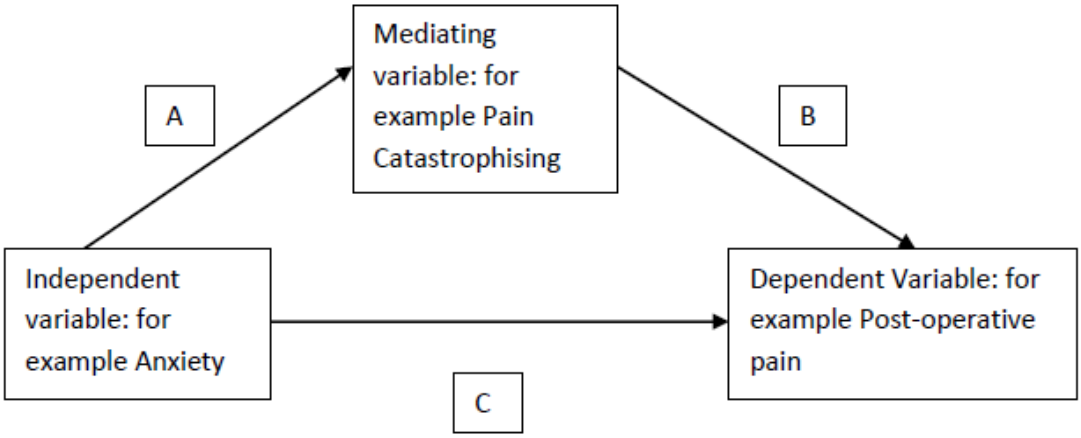

Figure 1 Mediating relationships

This approach offers advantages over multiple regression. Firstly mediation analysis encourages exploration of causal mechanisms linking independent and dependent variables. Secondly, this increases the robustness of claimed causal links. Thirdly, it discourages an empirical approach that searches for associations without elucidating causal mechanisms. Fourthly, understanding these processes facilitates the development of theoretical models of post-operative pain.

Baron & Kenny (1986) recommend a three step approach in order to carry out an effective mediation analysis:

1) Regression of the Mediating Variable on the Independent Variable
2) Regression of the Dependent Variable on the Independent Variable
3) Regression of the Dependent Variable on the Independent and Mediating Variables

For a mediating relationship to be indicated the following must hold true:

- The Independent Variable must be correlated with the Mediating Variable
- The Independent Variable must be correlated with the Dependent Variable
- The Mediating Variable must be correlated with the Dependent Variable

If a mediating relationship is present, when the independent variable is regressed against both the mediating variable and the dependent variable, in step 3, then the strength of C (Figure 1) should be zero in the case of perfect mediation (where only one mediating variable exists) or reduced in the case of partial mediation (when multiple variables mediate). In psychological research, partial mediation is usual, as there are frequently multiple mediating variables.

Studies selected for this review first assessed correlation between predictor variables and post-operative pain. Correlation does not, in itself, prove causation, as, for example, a third variable might be acting on both the predictor variable and the outcome variable. For a variable to be considered predictive a statistical technique, such as multiple regression, is then used to control for other variables. This determine the unique contribution of the predictor variable to the outcome variable (i.e. pain). If the predictor variable is shown to contribute significantly to the outcome variable, when using such a technique, a greater claim to a truly predictive relationship can be made. However, where mediating relationships exist techniques such as multiple regression tend to emphasise the role of the mediating variable and understate the role of the independent variable, leading to its being overlooked.

Therefore, as well as predictive analyses, the current review examines correlations between psychological variables and post-operative pain, since predictive analyses which control for a range of variables may mask these more complex interactions.

Most reviews examine the links between pre-operative variables and chronic pain, which is considered a more serious outcome of surgery than acute pain. However, acute post-

operative pain may play a role in the development of chronic pain (Nikolajsen & Minella, 2009) and so a lack of examination of these possible links may reinforce a simplistic explanatory model of the relationship between pre-operative variables and post-operative pain.

The rationale for this review can therefore be summarised as follows:

1. To examine the relationships between pre-operative psychological variables which might influence post-operative pain, rather than only examining direct relationships as in the existing reviews
2. To examine the influence that specific psychological variables, such as pain catastrophising, have on post-operative pain, in contrast to previous reviews that have mainly focused on general psychological variables such as anxiety
3. To compare the contribution of psychological variables to acute post-operative pain and to longer-term post-operative pain

12 METHOD

A systematic search was conducted of Scopus, Science Direct, Pub Med and PsychINFO for literature published between 2000 and 2012. This period was chosen so as to explore the current direction of research in this area. The search used the following terms and keywords: (Pre-operative psych* variable*) AND (chronic OR acute OR persistent post-operative OR surgical pain), (pre-operative anxiety) AND (post-operative pain), (predict*

OR risk factor* OR vulnerab*) AND (post-operative OR surgery pain), (post-operative OR surgical pain AND psychology).

Reference lists of relevant studies were also examined to find papers that were pertinent to the area studied. Papers published before 2002 were included in the search to aid an understanding of the history of the prediction of post-operative pain from pre-operative psychological variables and 420 unique studies were identified. Titles and abstracts were scrutinised for relevance to the area of the prediction of post operative pain. Papers were excluded from analysis in the review if they were deemed not to be relevant, if they were review papers or if they were conference papers. After being scrutinised, papers from before 2002 were also excluded from the review. Following these exclusions, 366 studies had been set aside, leaving 54 that had relevance to post-operative outcomes. Of these a further 36 were excluded (see table 1) leaving 18 studies.

Table 1 Studies excluded

Reason for exclusion	Number of studies excluded
Examined psychological variables and post-operative pain as outcomes of surgery	12
Examined post-operative outcomes other than pain	5
Examined pre-operative psychological variables' impact on intra-operative requirements	2
Predicted post-operative pain from non-psychological variables only	4
Examined impact of pre-operative psychological interventions on post-operative pain	12
Examined theoretical links between pre-operative psychological variables and post-operative pain	1

Quality assessment was carried out on the remaining 18 studies using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist

(Vandenbroucke, von Elm, Altman, Gøtzsche, Mulrow, Pocock, Poole, Schlesselman & Egger, 2007) and the quality assessment checklist used by Ip, Abrishami, Peng, Wong & Chung, (2009) for studies predicting post-operative pain. Seven were excluded because of methodological flaws, leaving 11 studies in the review. Nevertheless, of the 11 studies included, 2 had significant methodological issues. However, both of these studies analysed the data using noteworthy methods and were therefore included in the review, but findings from these studies were cautiously interpreted.

The use of quality assessment tools highlighted a number of methodological flaws which lead to the exclusion of the seven papers. These shortcomings included a failure to assess the clinical significance of study results. Future studies must therefore define cut off scores for pain and severe pain. Baseline pre-operative pain scores were not consistently measured and future research would need to include these data. Studies largely failed to report any attempts to detect and remedy multicolinearity amongst predictor variables. In future this issue should be addressed explicitly. Studies must also clearly differentiate predictor variables from variables that are simply being controlled for. Studies often did not report prospective validation of psychometric instruments that may have been carried out and researchers should ensure that such validation does occur in the future. Some studies failed to carry out longer-term follow up and such follow up would clearly be valuable. Studies should also report on any procedures for blinding researchers as to measures of pre-operative variables when measuring post-operative pain. Studies did not report any blinding of interviewers to study objectives and training of interviewers in questionnaire administration was not discussed. Both these issues require full reporting in future. In fact, even the studies included in the current review would benefit from closer attention to the above recommendations.

13 RESULTS SECTION

Table 2 sets out the features of the studies in this review. It includes details of authorship, numbers of participants, surgical procedures, measurement points, pre-operative psychological variables measured and post-operative pain measurement.

Table 2 Studies included

Authors, Year(quality score %)	No of Patients (surgery)	Measurement points	Pre-operative psychological variables	Post-operative pain measurement
Study 1 Pinto, McIntyre, Nogueira-Silva, Almeida, & Araújo-Soares, 2012 (66%)	135 (abdominal hysterectomy) 34 (vaginal hysterectomy) 11 (total laparoscopic hysterectomy) 6 (laparoscopically assisted vaginal hysterectomy)	T1 24 hours pre T2 48 hours post T3 4 months post	Hospital Anxiety and Depression Scale (HADS), The Revised Illness Perception Questionnaire (IPQR), The Surgical Fear Questionnaire (SFQ), The Coping Strategies Questionnaire–Revised Form (CSQ-R)	The Brief Pain Inventory–Short Form (BPI-SF), McGill Pain Questionnaire frequency scale

Table 2 continued

Authors, Year (quality score %)	No of Patients (surgery)	Measurement points	Pre-operative psychological variables	Post-operative pain measurement
Study 2 Poleshuck, Katz, Andrus, Hogan, Jung, Kulick, & Dworkin, 2006 (66%)	95 lumpectomy, lumpectomy with nodes or mastectomy	6 days pre 2 days post 10 days post 1 month post 3 months post	Beck Depression Inventory, Spielberger State-Trait Anxiety Inventory (state), Hamilton Depression and Anxiety Rating Scales, Functional Assessment of Cancer Treatment–Emotional Scale (FACT-E)	Eleven point Numerical Rating Scale for pain (NRS - 11)

Table 2 continued

Authors, Year (quality score %)	No of Patients (surgery)	Measurement points	Pre-operative psychological variables	Post-operative pain measurement
Study 3 Montgomery, Schnur, Erblich, Diefenbach, & Bovbjerg, 2010 (61%)	101 excisional breast biopsy or lumpectomy	T1 At home and Morning of operation T2 One week post	tension-anxiety subscale of the short version of the Profile of Mood States (SV-POMS), Presurgery expectancies for pain, nausea, and fatigue measured with 100-mm visual analog scales (VAS)	pain severity subscale of the Brief Pain Inventory (BPI)

Table 2 continued

Authors, Year (quality score %)	No of Patients (surgery)	Measurement points	Pre-operative psychological variables	Post-operative pain measurement
Study 4 Katz, Poleshuck, Andruse, Hogan, Jung, Kulick & Dworkin, 2005 (65%)	95 Breast cancer surgery: lumpectomy, lumpectomy with nodes or mastectomy	6 days pre 2 days post 10 days post 1 month post 3 months post	Beck Depression Inventory, Spielberger State-Trait Anxiety Inventory (state), Hamilton Depression and Anxiety Rating Scales, Functional Assessment of Cancer Treatment–Emotional Scale (FACT-E) Somatosensory Amplification Scale, Illness Behavior Questionnaire disease conviction scale	Eleven point Numerical Rating Scale for pain (NRS - 11)

Table 2 continued

Authors, Year (quality score %)	No of Patients (surgery)	Measurement points	Pre-operative psychological variables	Post-operative pain measurement
Study 5 Rakel, Blodgett, Zimmerman, Logsden-Sackett, Clark, Noiseux, Callaghan, Herr, Geasland, Yang, & Sluka, 2012 (71%)	215 total knee replacement	1 week pre 2 days post	State-Trait Anxiety Inventory (STAI), Trait Geriatric Depression Scale (GDS), Pain Catastrophizing Scale (PCS)	21 point Numerical Rating Scale (NRS – 21)

Table 2 continued

Authors, Year (quality score %)	No of Patients (surgery)	Measurement points	Pre-operative psychological variables	Post-operative pain measurement
Study 6 Lautenbacher *et al*., 2010 (62%)	84 male Erlangen technique of funnel chest correction	1 day pre 3 months post 6 month post	Dot-probe task; Pain-related words, Social threat words, Positive words, Pain Vigilance and Awareness Questionnaire (PVAQ), Pain Anxiety Symptom Scale (PASS), Pain Catastrophizing Scale (PCS), Screening for Somatoform Symptoms (SOMS), State-Anxiety Inventory (STAI-X1), Center for Epidemiologic Studies Depression Scale (CES-D)	11 point Numerical Rating Scale (NRS – 11)
Study 7 Granot & Ferber, 2005 (48%)	34 hernioplasty, 4 cholecystectomy	1 day pre 1 day post 2 days post	State-Trait Anxiety Inventory (STAI), Pain Catastrophising Scale(PCS)	Visual Analogue Scale (VAS

Table 2 continued

Authors, Year (quality score %)	No of Patients (surgery)	Measurement points	Pre-operative psychological variables	Post-operative pain measurement

Table 2 continued

Authors, Year (quality score %)	No of Patients (surgery)	Measurement points	Pre-operative psychological variables	Post-operative pain measurement
Study 8 Khan, Skapinakis, Ahmed, Stefanou, Ashrafian, Darzi & Athanasiou, 2012 (61%)	64 open heart surgery involving median sternotomy	1 day pre 48 hours post	Pain Catastrophising Scale (PCS), Hospital Anxiety and Depression Scale (HADS)	Verbal Rating Scale (VRS)

Table 2 continued

Authors, Year (quality score %)	No of Patients (surgery)	Measurement points	Pre-operative psychological variables	Post-operative pain measurement
Study 9 Cohen, Fouladib, & Katz, (2005) (55%)	53 elective abdominal hysterectomy	Morning of surgery 1 and 2 hours post average 12, 24 and 48 hour average 1, 2 and 7 days average	State trait anxiety inventory (STAI), Monitor-blunting style scale (MBSS), perceived stress scale (PSS)	Short-Form McGill Pain Questionnaire (MPQ)
Study 10 Pinto, McIntyre, Almeida, & Araújo-Soares, 2012 (74%)	135 abdominal hysterectomy 34 vaginal hysterectomy 11 total laparoscopic hysterectomy 6 laparoscopically assisted vaginal hysterectomy	T1 24 hours pre T2 48 hours post T3 4 months post	Hospital Anxiety and Depression Scale (HADS), Pain Catastrophizing Scale of the Coping Strategies Questionnaire—Revised Form (CSQ-R),	The Brief Pain Inventory–Short Form (BPI-SF), McGill Pain Questionnaire frequency scale

Table 2 continued

Authors, Year (quality score %)	No of Patients (surgery)	Measurement points	Pre-operative psychological variables	Post-operative pain measurement
Study 11* Powell, Johnston, Smith, King, Chambers, Krukowski, McKee & Bruce, 2012 (71%)	135 hernia repair	2 weeks pre 1 week post 4 months post	Hospital Anxiety and Depression Scale (HADS), Tampa Scale for Kinesiophobia (TSK-11), worry about operation Single item measure, Catastrophizing subscale Coping Strategy Questionnaire (CSQ), CSQ Increasing Activity, CSQ Perceived Pain Control, CSQ Ability to Decrease Pain, Expected Pain Control after surgery, Optimism using the Life Orientation Test (LOT), SF-36 Physical Functioning subscale, activity avoidance non validated measure	Single item measure Number of Words Counted (NWC) subscales of the McGill Pain Questionnaire (MPQ and worst pain present)

*Study 11 used a liberal p value of 0.20 as this was the cut-off for inclusion in a further analysis

The structure of the results section is based upon four categories of psychological measure:

- Anxiety
- Depression
- Pain beliefs and coping strategies
- Bodily and illness perceptions and behaviours

Within each section the main findings of correlation and prediction are presented in tabular form, as are the findings in relation to the proportion of measures that are correlated to and predictive of pain in the shorter- and longer-term. All studies in the review performed both correlational and predictive statistical analyses. Unless otherwise stated, all correlations are positive. Additional details which are not tabulated are then described.

13.1 Anxiety

All of the 11 studies examined in this review included some measure of pre-operative anxiety. The anxiety measures included in this section are measures of general anxiety, as opposed to measures of specific anxiety relating to pain, operations or illness. Correlations and predictive relationships are reported in table 3. A relationship is considered to be predictive when the correlation between the predictor variable and the outcome variable is shown to explain the variance in the outcome variable, rather than co-variation between predictor variables.

Table 3 Anxiety Measures and post-operative pain

Study	Measure	Correlation statistically significant	Prediction statistically significant	Shorter-term (average 2.7 days)	Longer-term (average 3.6 months)
1	HADS-A	Yes	No	-	4 Months
2	STAI-Y1	No	No	-	3 Months
2	HDARS-A	No	No	-	3 Months
3	SV-POMS	Yes	Yes	1 Week	-
4	STAI-Y1	Yes	Yes	2 Days	-
4	HDARS-A	Yes	No	2 Days	-
5	STAI-Y2	Yes	No	2 Days	-
6	STAI-Y2	No	No	-	3 & 6 Months
7	STAI-Y1	Yes	Yes	1 & 2 Days	-
7	STA-Y2	No	No	1 & 2 Days	-
8	HADS-A	No	No	2 Days	-
9	STAI-Y1	Yes	Not directly	12 Hours, 1, 2, 3, 4, 9 Days	-
9	STAI-Y2	No	Not directly	12 Hours, 1, 2, 3, 4, 9 Days	-
9	PSS	No	No	12 Hours, 1, 2, 3, 4, 9 Days	-
10	HADS-A	Yes	No	2 Days	-
11	HADS-A	Yes	No	-	4 Months

HADS–A=Hospital Anxiety and Depression Scale (Anxiety), STAI – Y1/Y2=State Trait Anxiety Inventory (state/trait), HDARS-A=Hamilton Depression and Anxiety Rating Scale (Anxiety), SV-POMS=Profile of Mood States-Shortened Version (tension-anxiety), PSS=Perceived Stress Scale

Table 4 Proportion of anxiety measures correlated with and predictive of post-operative pain

Time Period	Correlated measures /Total measures (percentage correlated)	Predictive measures /Total measures (percentage predictive)
Short-term	7/11 (64%)	3/11 (27%)
Longer-term	2/5 (40%)	0/5 (0%)

The proportion of anxiety measures, across studies, correlated with and predictive of post-operative pain in the shorter- and longer-term are reported in table 4. This table

demonstrates that a higher proportion of measures were associated with pain in the short-term than the longer-term and a higher proportion of measures were correlated with pain as opposed to predictive of it.

Study 7 (Granot & Ferber, 2005) found a curvilinear relationship between post-operative pain and pre-operative state anxiety. This study set out to test the concept of the 'work of worry' (Janis, 1958) and found a curvilinear relationship between pre-operative anxiety and post-operative pain, but in the opposite direction to that described by Janis (1958). This finding indicated that patients with moderate anxiety were most at risk of post-operative pain, patients with low pre-operative anxiety were least at risk and those with high anxiety had a slightly reduced risk compared to those with moderate anxiety.

Study 9 (Cohen *et al.,* 2005) conducted a path analysis in which pre-operative trait anxiety was predictive of pre-operative state anxiety. Pre-operative state anxiety was in turn predictive of post-operative state anxiety on the ward and at home. State anxiety on the ward and at home was predictive of post-operative pain on the ward and home respectively. This paper claimed to have found evidence of a causal chain of associations between variables that lead to increased post-operative pain. In this study, ward pain was defined as the average pain score patients reported in the first 2 days post-operatively, whilst on the ward. Pain at home was defined as the average pain score reported during the first 7 days at home.

13.2 Depression

Of the 11 studies included in this review 8 contained measures of depression as pre-operative variables related to post-operative pain. Correlations and predictive relationships are reported in table 5.

Table 5 Depression and post-operative pain

Study	Measure	Correlation statistically significant	Prediction statistically significant	Shorter-term	Longer-term
1	HADS-D	No	No	-	4 Months
2	BDI	No	No	-	3 Months
2	HDARS-D	No	No	-	3 Months
4	BDI	Yes	No	2 Days	-
4	HDARS-D	Yes	No	2 Days	-
5	GDS	Yes	Yes	2 Days	-
6	CES–D	No	No	-	3 & 6 Months
8	HADS-D	No	No	2 Days	-
10	HADS-D	Yes	No	2 Days	-
11	HADS-D	Yes	No	-	4 Months

HADS-D=Hospital Anxiety and Depression Scale (Depression), BDI=Beck Depression Inventory, HDARS-D=Hamiltonian Depression and Anxiety Rating Scale (Depression), GDS=Geriatric Depression Scale, CES-D=Centre for Epidemiologic Studies Depression Scale

Table 6 Proportion of depression measures correlated with and predictive of post-operative pain in the short and longer-term

Time Period	Correlated measures /Total measures (percentage correlated)	Predictive measures/Total measures (percentage predictive)
Short-term	4/5 (80%)	1/5 (20%)
Longer-term	1/5 (20%)	0/5 (0%)

The proportion of depression measures, across studies, correlated with and predictive of post-operative pain in the shorter and longer-term are reported in table 6. This table demonstrates that a higher proportion of measures were associated with pain in the short-

term than the longer-term and a higher proportion of measures were correlated with pain as opposed to predictive of it.

In Study 6 (Lautenbacher *et al*., 2010) the CES-D was correlated with and predictive of post-operative pain disability at 6 months, according to one analysis. Although this review is not specifically examining the related, though separate, concept of pain disability, this may be a noteworthy finding.

Interestingly, Study 11 (Powell *et al*., 2012) found that optimism, measured using the Life Orientation Test (LOT), was negatively correlated with and predictive of post-operative pain. This provides indirect support for the positive correlation between depression scores and post-operative pain, in that optimism might be construed as the antithesis of depression. This measure of optimism has not been included in the above tabulations as its presence may imply, but does not demonstrate, low levels of depression.

13.3 Pain Related Beliefs and Coping Strategies

Of the 11 studies, 8 included measures of pain-related beliefs and coping strategies. These used concepts such as pain catastrophising, pain expectancy and strategies for coping with pain. Correlations and predictive relationships are reported in table 7.

Table 7 Pain Beliefs and post-operative pain

Study	Measure	Correlation statistically significant	Prediction statistically significant	Shorter-term	Longer-term
1	CSQ-R-Pain catastrophising	Yes	Yes	-	4 Months
1	CSQ -R-Ignoring pain	No	No	-	4 Months
1	CSQ -R-Self statements with pain	No	No	-	4 Months
1	CSQ-R-Reinterpreting pain sensations	No	No	-	4 Months
1	CSQ-R-Hoping/praying	No	No	-	4 Months
1	CSQ-R-Distracting/diverting	No	No	-	4 Months
3	VAS-Pain expectancy	Yes	Yes	7 Days	-
5	PCS	No	No	2 Days	-
6	PASS	No	No	-	3 & 6 Months
6	PVAQ	No	No	-	3 & 6 Months
6	PCS	No	No	-	3 & 6 Months
6	DPT-Pain words	No	No	-	3 & 6 Months
6	DPT-Social threat words	No	No	-	3 & 6 Months
6	DPT-Positive words	Yes	Yes	-	3 & 6 Months
7	PCS	Yes	Yes	2 Days	-
8	PCS	Yes	Yes	2 Days	-
10	PCS	Yes	Yes	2 Days	-
11	TSK-11	No	No	-	4 Months
11	SF-36	Yes	No	-	4 Months
11	CSQ-Pain catastrophising	No	No	-	4 Months
11	CSQ-Increasing activity	No	No	-	4 Months
11	CSQ-Perceived pain control	Yes	No	-	4 Months
11	CSQ–Ability to decrease pain	Yes	No	-	4 Months
11	CSQ-Expected pain control	Yes	No	-	4 Months

CSQ-R=Revised Coping Strategies Questionnaire, VAS=Visual Analogue Scale, PCS=Pain Catastrophising Scale, PASS=Pain Anxiety Symptom Scale, PVAQ=Pain Vigilance Awareness Questionnaire, DPT=Dot Probe Task, TSK-11=Tampa Scale for Kinesiophobia, SF-36=Physical Functioning Subscale Version 2, Acute Form, CSQ=Coping Strategies Questionnaire

Table 8 Proportion of pain belief measures correlated with and predictive of post-operative pain in the short- and longer-term

Time Period	Correlated measures /Total measures (percentage correlated)	Predictive measures/Total measures (percentage predictive)
Short-term	4/5 (80%)	4/5 (80%)
Longer-term	6/19 (32%)	2/19 (11%)

The proportion of pain belief measures, across studies, correlated with and predictive of post-operative pain in the shorter- and longer-term are reported in table 8. This table demonstrates that a higher proportion of measures were associated with pain in the short-term than the longer-term and a higher proportion of measures were correlated with pain as opposed to predictive of it.

Study 3 (Montgomery *et al*., 2010) administered a Visual Analogue Scale (VAS) to assess pain expectancy pre-operatively. This took the form of single question: ‘‘after surgery, how much pain do you think you will feel? Please put a slash through this line (shown below on the actual forms) to indicate how much pain you expect to feel.’’ A Sobel test (Sobel, 1982) indicated that pain expectancy partially mediated the effect of distress, measured by the tension-anxiety subscale of the short version of the Profile of Mood States (SV-POMS), on post-operative pain.

Study 6 (Lautenbacher *et al*., 2010) administered a dot probe task to assess avoidance and vigilance for emotional words. Two words at a time were presented to the participant on a computer screen, one emotional and one neutral. The emotional words were split into three categories: pain related words, social threat words and positive words. After 500ms the words disappeared and a dot appeared in the location of one of the words. The participant had to indicate as quickly as possible which word location the dot had appeared in. Response times could indicate either vigilance or avoidance of certain types of emotional words, depending on whether the response was quicker (vigilance) or longer (avoidance) than average.

Study 7 (Granot & Ferber, 2005) conducted a mediation analysis which found that scores on the PCS mediated the effect of anxiety on post-operative pain.

13.4 Bodily and Illness Perceptions and Behaviours

Six of the studies administered measures of participants' perceptions of underlying conditions, beliefs about surgery and attitude to bodily sensations, not directly linked with pain. Correlations and predictions are reported in table 9.

Table 9 Illness perceptions and post-operative pain

Study	Measure	Correlation	Prediction	Shorter-term	Longer-term
1	SFQ	Yes	No	-	4 Months
1	IPQ-R-Timeline acute/chronic	No	No	-	4 Months
1	IPQ-R-Timeline cyclical	Yes	No	-	4 Months
1	IPQ-R-Consequences	Yes	No	-	4 Months
1	IPQ-R-Personal control	No	No	-	4 Months
1	IPQ-R-Treatment control	No	No	-	4 Months
1	IPQ-R-Illness coherence	No	No	-	4 Months
1	IPQ-R-Emotional illness representation	Yes	No	-	4 Months
2	FACT-E	No	No	-	4 Months
4	SAS	Yes	No	2 Days	-
4	IBQ-Disease conviction scale	Yes	No	2 Days	-
4	FACT-E	Yes	No	2 Days	-
6	SOMS	No	No	-	3 & 6 Months
8	MBSS-M	Yes*	Yes*	2 Days	-
8	MBSS-B	No	No	2 Days	-
11	Worry about operation	Yes	No	-	4 Months

SFQ=Surgical Fears Questionnaire, IPQ-R=Revised Illness Perceptions Questionnaire, FACT-E=Functional Assessment of Cancer Treatment Emotion Scale, SAS=Somatosensory Amplification Scale, IBQ=Illness Behaviours Questionnaire, SOMS=Screening for Somatoform Symptoms, MBSS-M/B=Monitor Blunter Style Scale (Monitor/Blunter subscale), Worry about operation was a single item non-validated measure. *Negative correlation.

Table 10 Proportion of illness perception measures correlated with and predictive of post-operative pain in the short- and longer-term

Time Period	Correlated measures /Total measures (percentage)	Predictive measures/Total measures (percentage)
Short-term	4/5 (80%)	1/5 (20%)
Longer-term	5/11 (45%)	0/11 (0%)

The proportion of illness perception measures, across studies, correlated with and predictive of post-operative pain in the shorter- and longer-term are reported in table 10. This table demonstrates that a higher proportion of measures were associated with pain in the short-term than the longer-term and a higher proportion of measures were correlated with pain as opposed to predictive of it.

Study 1 (Pinto, McIntyre, Nogueira-Silva, Almeida & Araujo-Soares, 2012) administered the Surgical Fear Questionnaire (SFQ) which assessed fears associated with the long term and short term consequences of surgery. In addition the following subscales of the Revised Illness Perceptions Questionnaire (IPQ–R) were used:

- ‘‘Timeline acute/chronic’’ (for example, ‘‘My illness will last for a long time’’)
- ‘‘Timeline cyclical’’ (for example, ‘‘My symptoms come and go in cycles’’)
- ‘‘Consequences’’ (for example, ‘‘The disease underlying surgery has major consequences on my life’’)
- ‘‘Personal control’’ (for example, ‘‘I have the power to influence my illness’’)
- ‘‘Treatment control’’ (for example, ‘‘Surgery can control my illness’’)
- ‘‘Illness coherence’’ (for example, ‘‘My illness is a mystery for me’’)
- ‘‘Emotional illness representation’’ (for example, ‘‘When I think about my illness I get upset’’)

Study 2 (Poleshuck *et al*., 2006) administered the Functional Assessment of Cancer Treatment – Emotion Scale (FACT – E), a measure designed to assess mood and anxiety in cancer patients. Study 4 (Katz *et al.,* 2005) used the Somatosensory Amplification Scale, a measure of sensitivity to and amplification of unpleasant bodily sensations that may also reflect somatic anxiety. In addition, the Illness Behaviour Questionnaire (IBQ) disease conviction scale, a measure of symptom preoccupation, rejection of physician reassurance, and affirmation of physical disease, was used.

Study 6 (Lautenbacher *et al*., 2010) administered the Screening for Somatoform Symptoms (SOMS), a self-rating scale of somatization, which assesses 53 organically unexplained physical symptoms. Study 9 (Cohen *et al*., 2005) administered the Monitor Blunting Style Scale (MBSS) which assessed two responses to coping with surgery. The monitor subscale assessed active seeking of information and the blunting subscales assessed avoidance of information. High scores on the monitor subscale were correlated with and predictive of lower pain scores on the ward in the two days post-operatively. A path analysis was conducted that indicated that pain on the ward, in turn, was predictive of pain at home during the first 7 days post-discharge.

14 DISCUSSION

Previous reviews have sought to assess the strength of the direct associations between particular psychological variables and post-operative pain, and then given a likelihood of the causal link being relevant (Hinrichs-Rocker *et al*., 2009; Nielsena *et al.,* 2007). This is also the pattern followed by reviews which include demographic and clinical variables. However, the problem with this approach is that it may mask more complex interactions

between variables. This review has focused on complex interactions between pre-operative psychological status and post-operative pain, so that recommendations can be made regarding the prediction and treatment of post-operative pain and for future research.

The findings of the review can be summarised as follows:

14.1 Specific Verses General Psychological Variables

This review is the first to examine the difference in the predictive power of general pre-operative psychological variables and more specific psychological variables. This distinction is made in a number of papers included in the review (for example study 1, Pinto *et al*., 2012).

General psychological measures aim to assess global psychological states that do not reference any particular situation or concern. A specific measure is one that directly relates to particular aspects of the situation. For example the Pain Catastrophising Scale asks questions about the subject's attitude to and beliefs about pain.

In the studies reviewed, measures of depression (general), pain beliefs (specific) and illness perceptions (specific) were most likely to be correlated with shorter-term pain (80% of measures correlated). Measures of pain beliefs (specific) were most likely to be predictive of shorter-term pain, with 80% being found to be predictive.

Illness perceptions (specific) were most likely to be correlated with longer-term pain (45% of measures correlated). Pain beliefs (specific) were most likely to be predictive of longer-term pain (11% of measures being predictive). However, this second finding does not provide robust statistical evidence of a predictive relationship. This may be an artefact of

the statistical techniques used, such as multiple regression analysis, which may mask more complex relationships.

In this limited analysis, more specific measures seem at least comparable to measures of general affect, when predicting post-operative pain. This should not be interpreted as indicating that specific measures are necessarily preferable predictors to general measures, as this may only be a broad tendency. It might be more useful to examine the relationships between these two variable types, relationships which cannot be detected by many of the statistical techniques used, for example multiple regression.

14.2 Contribution of Pre-Operative Psychological Factors to Post-Operative Pain in the Shorter-Term as Compared to the Longer-Term

The review examined the relationship between categories of psychological variables and post-operative pain in the shorter-term compared to the longer-term. It noted that 64-80% of measures of pre-operative psychological status were correlated with shorter-term post-operative pain, and 20-80% of measures were predictive in the same period.
Between 20% and 45% of measures were correlated with longer-term post-operative pain (average 3.6 months) and 0-11% of measures were predictive in the same time period. This indicates a reduction in the correlation with, and ability to predict, post-operative pain, with increasing time following the operation. The standard interpretation of this would be that pre-operative psychological factors are not effective predictors of longer-term post-operative pain. Alternatively, this could also be indicative of a relationship between pre-operative and post-operative psychological factors and post-operative pain that is not assessed by standard statistical analyses. It might indicate that techniques assessing only

direct relationships between pre-operative psychological variables and pain do not have the power to detect longer-term relationships.

14.3 The Nature of More Complex Relationships Between Pre-Operative Psychological Variables and Post-Operative Pain

Four studies examined the nature of relationships between pre-operative psychological status and post-operative pain. Three studies carried out mediation analyses that indicated that measures of pain beliefs mediated the effect of anxiety. Study 3 (Montgomery *et al*., 2010) found that pain expectancy mediated the effect of distress. Studies 7 and 10 (Granot & Ferber, 2005; Pinto *et al*., 2012, respectively) found that pain catastrophising mediated the impact of anxiety. This indicated a mediating relationship between pain beliefs (specific) and anxiety (general).

Study 3 (Montgomery *et al*., 2010) uses a Sobel test (Sobel, 1982) that provides an approximation of the significance of the mediating relationship. However, it does not take into account measurement error of the Mediating Variable and so is open to the problem of underestimating the strength of the mediation effect and overestimating the strength of the direct relationship (Baron & Kenny, 1986).

Study 7 (Granot & Ferber, 2005) found evidence of a curvilinear relationship between anxiety and post-operative pain in the opposite direction to that suggested by Janis (1958). However, due to methodological limitations, such as small sample size and a failure to assess pre-operative pain, the findings of this study need to be replicated before serious consideration is given to them.

Study 10 (Pinto *et al.*, 2012) highlighted the low statistical power in Baron & Kenny's approach noted by MacKinnon, Lockwood, Hoffman, West & Sheets (2002) and instead used Preacher & Hayes' (2008) bootstrapping methods to estimate indirect effects. It is claimed that this approach increases power and reduces Type I error rates, compared to other techniques, for estimating indirect effects in small samples that are unlikely to be normally distributed (Preacher & Hayes, 2008). The approach they describe consists of taking K small samples from the data set (where K should be at least 1000) and testing the strength of the indirect effect in each sample. This allows for the estimation of bootstrap confidence intervals for the strength of the indirect effect.

More psychological variables were correlated with post-operative pain than were found to be predictive. This arises because more stringent statistical criteria are applied to the demonstration of prediction. The standard interpretation is that independent variables that correlate with dependent variables, but do not predict them, are co-varying with truly predictive independent variables. However, mediating variables can reduce the apparent strength of the relationships between independent and dependent variables when the mediating variables are controlled for. Therefore, a multiple regression style of analysis may mask causal relationships that involve mediation.

One other study examined the nature of more complex relationships between pre-operative psychological variables and post-operative pain (Cohen *et al*., 2005, study 9). Using a path analysis it demonstrated links between pre-operative trait and state anxiety, post-operative anxiety and post-operative pain, in the recovery room, on the ward and in the week following discharge.

This finding suggests that the analysis of causal chains of predictor variables can provide insight into processes underlying development of post-operative pain. This study also claimed that trait anxiety was predictive of pre-operative state anxiety. This may point to a mechanism whereby trait anxiety induces state anxiety. Alternatively, it may be the result of a third underlying variable that influences both. State anxiety directly influenced participants' pain experience when the two were measured at similar points in the study. Nevertheless, pre-operative state anxiety indirectly influenced post-operative pain on the ward and at home. This indicates the possibility of a chain of mediating pre-operative and post-operative psychological variables that link pre-operative trait anxiety and post-operative pain, which would otherwise appear to be unconnected without this form of analysis.

However, the study has a number of methodological limitations, such as small sample size and a failure to measure pre-operative pain. Therefore, its results need to be replicated. However, it does serve as an example of an approach that explores causal pathways between psychological variables and pain, taking into account indirect effects. The study suggests post-operative psychological factors may be important in the maintenance of longer-term post-operative pain.

14.4 Research Recommendations

This review has highlighted a number of areas for future research. Increased awareness of the importance of specific psychological variables, such as pain beliefs and illness perceptions, is required, as well as continued research on general measures, such as anxiety and depression. Although this review did not specifically examine the relationship

between different personality variables and post-operative pain, the lack of focus on personality in the literature was noted. Personality variables could act as underlying variables for both pain and anxiety, for example and, as such, could be incorporated into future research designs.

Broadly, the studies reviewed examine concepts such as pain intensity and pain quality, on the assumption that these provide indications of pain impact. However, there is not necessarily a clear relationship between these variables. For example, one of the reviewed studies (Lautenbacher *et al*., 2010) examined both pain intensity and pain disability and found that different psychological variables were predictive of these related but distinct phenomena. Therefore, more research into pain disability, and its links with depression, is required as it may have a different relationship with pre-operative psychological variables, compared to pain intensity.

More research is required into mediating relationships between psychological variables that might influence post-operative pain. This review found tentative evidence that measures of specific psychological variables, pain catastrophising and pain expectancy, mediated the effect of anxiety on post-operative pain from studies 3, 7 and 10 (Montgomery *et al*., 2010; Granot & Ferber, 2005; Pinto *et al.*, 2012, respectively). Future research needs to aim to confirm these findings. Additional mediating relationships must also be examined:

- Between anxiety and other specific psychological variables such as illness perceptions
- Between other general psychological variables (such as depression) and specific variables such as pain beliefs and illness perceptions

Relationships between pre-operative and post-operative psychological variables also require further scrutiny, as this research could elucidate how pain is triggered and maintained post-operatively. For example, pre-operative anxiety might lead to post-operative anxiety which in turn might increase pain.

The fact that pain beliefs seem to have an important role in the development of post-operative pain, suggests that the meaning that patients ascribe to a particular pain experience could be an important area for future research.

As well as vulnerabilities to post-operative pain, more research is required on protective factors. This review identified the possible role of optimism, as measured by the Life Orientation Test (LOT), in reducing the risk of post-operative pain. Similarly, information seeking, as measured by the Monitor subscale of the MBSS was related to lower levels of post-operative pain. This, and other potential protective factors, might prove to be fruitful lines of future research.

The work reviewed has also highlighted the importance of mediating variables as avenues for future research. However, as well as mediating variables, moderating relationships and underlying variables must also play a central role in further explorations.

The use of statistical techniques, such as mediating, moderating and path analysis, might prove more powerful than standard logistic regression, as they can highlight indirect relationships where direct relationships are not statistically significant. This increase in power may come at the risk of more frequent Type I errors and so any findings would have to be reliably replicable.

Despite the fact that an impressive amount of quantitative work has been carried out, the large number of possible interactions between variables means that, as yet, there is no coherent theoretical foundation for the systematic understanding of the relationships uncovered. Therefore, a qualitative approach could be used in order to explore the complexities entailed in these interactions, and to provide the foundation for more refined quantitative analyses.

14.5 Practice Recommendations

If research confirms there is a mediating relationship between a particular specific and a particular general measure of psychological status, then screening for vulnerability to post-operative pain could be enhanced by administering both to patients pre-operatively. Patients scoring highly on both measures would be most urgently targeted by pre- and post-operative interventions. These might include psychopharmacological, psycho-education and health psychology interventions. Interventions might target general anxiety, for example through the use of anti-anxiety medication and relaxation techniques.

This review has noted that more specific variables are also associated with pain. Therefore, interventions focused on these specific variables may also play an important role in managing and mitigating post-operative pain. For example, Cognitive Behaviour Therapy for pain catastrophising might prove useful in reducing pain experience.

Increased monitoring of post-operative pain for those identified to be most at risk would also be important. Interestingly, study 1 did highlight links between pre-operative and

post-operative psychological variables and their influence on pain (Pinto *et al*., 2012). This implies that intervening, post-operatively, could prevent the development of chronic pain from acute pain.

What is more, one of the studies reviewed (Lautenbacher *et al*., 2010) found a link between depression and pain disability which, if confirmed, suggests a range of targeted screening measures and interventions.

More broadly, the research reviewed suggests that patients must be viewed holistically. Clinicians need to appreciate differing pain sensitivities, general affect, pain beliefs, illness perceptions, meanings of pain and operation type, amongst a host of other factors, to help improve prevention and treatment of post-operative pain.

14.6 Limitations of Review

This review was necessarily limited by the relatively short research period and amount of time available to a single researcher with a range of competing work commitments. These limitations, along with the variability in operations studied and statistical techniques employed, meant that a full-scale meta-analysis, although desirable, was not feasible.

In the studies identified by the literature search, personality variables did not emerge as a focus of research. This absence may be due to the fact that such variables have not figured prominently in work carried out in the ten year period covered by the review. Future reviews might usefully continue to monitor the research literature for any developments in the field of personality variables as predictive of post-operative pain.

The relationship between post-operative psychological variables and pain was beyond the remit of this review. However, a number of studies did contain such variables and their inclusion may benefit future reviews. The literature search did not uncover any studies which featured a qualitative component. Qualitative methodologies may prove to be relevant to the detailed understanding of the psychological processes relating to post-operative pain. Therefore, future reviewers should be alert to this possibility.

The review focused on post-operative pain, which was operationalised by the studies examined as pain intensity and pain quality. Only one study in the review (Lautenbacher *et al*., 2010) examined the impact of pain by also measuring patients' pain disability. A worthwhile dimension of future reviews would be an explicit focus on the various aspects of pain disability.

Finally, an important limitation of the review is that it excluded any examination of the literature on interventions relating to psychological variables. Clearly, future reviews need to encompass such research in order to develop understanding of the efficacy of the various forms of intervention.

14.7 Conclusion

A significant proportion of the studies reviewed carry out statistical analyses that assess direct relationships whilst attempting to control for the inter-correlations of predictor variables. Although this line of research has given information about which variables may or may not be predictive of post-operative pain, it has produced inconsistent results as to

which predictors are useful. Some of this inconsistency is, no doubt, due to random error. However, as this review highlights, it may also be because these analyses are masking more complex relationships between predictor variables and post-operative pain.

For example, the influence of general measures of psychological distress, such as anxiety, on post-operative pain, might be mediated by more specific psychological constructs. Additionally, post-operative psychological factors may play a role in the process through which acute pain may develop into chronic pain.

If these relationships are replicated reliably by future research, they may have significant implications for the use of interventions to change psychological variables that may influence acute and chronic post-operative pain.

The understanding of the phenomenon of post-operative pain is important for the promotion of the well-being of surgical patients. Over the preceding 10 years the studies reviewed have built upon the foundations of an earlier tradition of research in this area, and have considerably extended knowledge in this field. This, in turn, has provided several promising lines of future research. What is more, an understanding of the limitations and strengths of these studies, which this review has sought to provide, is essential for the posing of fruitful research questions and the selection of appropriate methodologies in the future.

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16 RESEARCH REPORT

An Examination of the Impact of Depth of Anaesthesia on Post-Operative Pain Following Wide Local Excision of Breast Tissue for Breast Cancer

17 ABSTRACT

Post-operative pain has a significant impact on patients (Mei, Seeling, Franck, Radtke, Brantner, Wernecke, & Spies, 2010). The causes of this complex phenomenon are poorly understood (Lautenbacher, Huber, Schöfer, Kunz, Parthum, Weber, Roman, Griessinger & Sittl, 2010). The prevention of post-operative pain requires the identification of the factors that predict it. This study hypothesised that intra-operative wakefulness without explicit recall, which may be caused by lightness of anaesthesia (Russell, 1989), could be predictive of post-operative pain. A number of studies noted a link between lightness of anaesthesia and post-operative pain (e.g. Law, Sleigh, Barnard & MacColl, 2011). None of these studies controlled for pre-operative variables, or examined longer term post-operative pain. This research took the form of a feasibility study that examined the issues involved in executing a large scale research project examining the impact of lightness of anaesthesia on post-operative pain, whilst assessing and controlling for pre-operative variables. The Magill Pain Questionnaire - Short Form (MPQ-SF), the State Trait Anxiety Inventory state and trait versions (STAI-Y1 and Y2), Pain Locus of Control Questionnaire (PLOCQ) and a non-validated body image concern question were administered pre-operatively. Follow-up was conducted at 1-2 days post-operatively and at 6 weeks and 3 months by telephone and involved administration of the MPQ-SF, STAI-Y1 and body image question. Twelve participants were recruited to the study at pre-operative clinics and consented on the morning of the operation. Depth of anaesthesia was monitored using the Bispectral Index (BIS). The study did not find a significant difference between high and low anaesthesia groups due to low power and small sample size. The study found a large scale project would be feasible and discussed implications for recruitment, pain measurement, monitoring of anaesthesia, blinding of anaesthetist, future research and clinical practice. Limitations of the study were also discussed.

18 INTRODUCTION

Post-operative pain has been identified as a serious consequence of surgery and can have a long-term impact on people's ability to work, socialise, and maintain relationships, as well as on mental health and overall quality of life (Mei, Seeling, Franck, Radtke, Brantner, Wernecke, & Spies, 2010). This inadequately understood phenomenon may have far reaching implications for affected patients. Indeed it has been argued that:

"Poorly managed pain can slow recovery, create burdens for patients and their families, and increase costs to the healthcare system." (Chang, Mehta, & Langford, 2009, page 2)

The use of opioid pain killers in the treatment of chronic pain has serious side effects that incur substantial costs to healthcare systems and to patients (Annemans, 2011). To improve treatments and prevent post-operative pain, it is important to determine the factors that predict it. Multiple variables have been linked to post-operative pain, although this complex phenomenon is still poorly understood. Indeed, there is considerable variation in presentations of post-operative pain for which research has so far been unable to account completely (Lautenbacher, Huber, Schöfer, Kunz, Parthum, Weber, Roman, Griessinger & Sittl, 2010).

During procedures involving general anaesthetic, intra-operative wakefulness without explicit recall may occur due to lightness of anaesthesia (Russell, 1989). In these instances the patient will have no post-operative conscious awareness of such episodes. However, despite the lack of post-operative recall the patient may have experienced pain, paralysis, distress and heard comments made by surgical staff.

The possibility of a link between chronic post-operative pain and intra-operative wakefulness without explicit recall, as a consequence of lightness of anaesthesia, has not been fully researched. A previous study examining the relationship between depth of anaesthesia and post-operative pain found a modest link between intra-operative brain activity, as measured by an electroencephalogram, and pain in the immediate post-operative period (Law, Sleigh, Barnard & MacColl, 2011). Another study found that light anaesthesia increased use of analgesics in the immediate post-operative period (Henneberg, Rosenborg, Jensen, Ahn, Burgdorff, & Thomsen 2006). These studies show that inadequate anaesthesia may increase pain in the immediate post-operative period. However, this may be due to inadequate use of analgesics during the operation, leaving patients in greater pain post-operatively. These studies were not longitudinal and did not demonstrate whether this effect increased chronic pain after the immediate post-operative period. Additionally they did not control for pre-operative demographic or psychological variables.

Quiet clearly, a longitudinal research design is required for an effective analysis of this phenomenon, which also controls for pre-operative variables and examines links between acute and longer-term pain. However, such an approach raises a range of crucial methodological and ethical issues. What is more, it has far reaching implications both for the amount of resources required and the lengthy timescales involved in data collection. Prior to the launch of a full scale project a feasibility study is essential in order to explore the viability of the design and the logistical issues involved. Therefore, this study takes the form of just such an exploration.

A specific example of post-operative pain is chronic pain following breast surgery for cancer, which occurs in a sufficiently high proportion of women undergoing these

procedures to make it a worthwhile focus for research. The following discussion of the theoretical and empirical foundations of this study contains four elements:

- Factors related to post-operative pain
- The Gate Control Theory of Pain
- The nature of general anaesthesia
- The impact of light anaesthesia with and without explicit recall.

A discussion of the methods of measuring depth of anaesthesia will follow these four elements, along with an exposition of the relevance of the research as well as the study's aims and objectives.

18.1 Factors Related to Post-Operative Pain

As noted above, the risk factors for post-operative pain are complex and poorly understood. Several factors have already been shown to be associated with higher levels of post-operative pain. These include young age, female gender, obesity, use of nitrous oxide anaesthetic, and duration and location of surgery, which can increase surgical stimulation (Mei *et al.,* 2010). Some of these factors may hint at a role for depth of anaesthesia in post-operative pain, particularly the use of nitrous oxide and the level of surgical stimulation. Indeed, nitrous oxide may allow patients to form explicit and implicit memories of intra-operative events (Ghoneim, Block, Dhanaraj, Todd, Choi, & Brown, 2000; Utting, 1987). Using the isolated forearm technique (see *methods of measuring depth of anaesthesia* below) it was demonstrated that approximately half of patients

indicated wakefulness (without explicit recall) during surgery when nitrous oxide and an opioid intravenous bolus was used as anaesthetic (Russell, 1989). There is also abundant evidence that surgical stimulation can increase the level of awareness of patients (for example, Bethune, Ghosh, & Gray, 1992).

18.1.1 Pre-operative anxiety

Pre-operative anxiety is an important factor to consider as there is a possibility that it could increase the level of anaesthetic required to render the patient adequately unconscious during the operation (Wilson, 2005). Therefore, there is a possible causal chain, in that high pre-operative anxiety may lead to difficulty in inducing adequate anaesthesia. This, in turn, may lead to light anaesthesia, which may lead to increased post-operative pain. Pre-operative anxiety could also increase post-operative pain with adequate anaesthesia (see discussion of Gate Control Theory below). It is also possible that light anaesthesia could influence post-operative pain by increasing post-operative anxiety (see discussion of Gate Control Theory below).

18.1.2 Post-operative pain following surgery for breast cancer

The prevalence of chronic pain following breast cancer surgery ranges from 25 – 60% (Gartner, Jensen, Nielsen, Ewertz, Kroman & Kehlet, 2009).

Breast conserving surgery (a procedure known as wide local excision of breast tissue for breast cancer) is now becoming more common. Chronic pain following breast conserving

surgery may be as high as 60%, but this maybe due to adjuvant treatments such as auxiliary lymph node dissection and radiation therapy (Gartner *et al*., 2009)

Katz, Poleshuck, Andrus, Hogan, Jung, Kulick, & Dworkin (2005) also noted a number of factors associated with higher levels of post-operative pain following such procedures. These included: younger age, single marital status, more invasive surgery and higher levels of pre-operative anxiety.

18.1.3 Body Image

Another factor to take into account is the impact that surgery for breast cancer has on body image and sexual issues. Research indicates that over the course of a 3-year follow-up only a minority of women have ongoing sexual or body image issues (Hopwood, Lee, Shenton, Baildam, Brain, Lalloo, Evans & Howell, 2000). The minority of women with these ongoing problems tend to have ongoing post-operative complications such as chronic post-operative pain (Hopwood *et al*., 2000). In the months immediately following the operation (the period over which data were collected in the present study) body image and sexual problems are more prevalent (Fobair, Stewart, Chang, D'onofrio, Banks & Bloom, 2006). The relationship between these problems and chronic pain is not so clear in this period (Fobair *et al*., 2006). Therefore, there may be a relationship between pre-operative concerns about body image and pre-operative anxiety, and post-operative concerns about body image may increase post-operative anxiety and increase pain experience.

18.2 Gate Control Theory of Pain

There is an extensive body of theory related to the experience of pain. One specific theory that is of particular relevance this study is the Gate Control Theory proposed by Melzack and Wall (1965; 1982) and Melzack (1979). This theory was an attempt to introduce psychological factors into the biomedical model of pain, which assumes that pain is a direct result of damage to tissue (Goldschneider, 1920). The theory suggests that a pain gate, which moderates signals from the site of the injury, exists at the spinal cord level. The output of the gate is influenced not only by signals from the injury site but also from descending signals from the brain. The pain gate can be opened by various factors, allowing more signals to pass to the brain. These factors can be physiological, such as signals from the injury site; emotional, such as pain-related anxiety; and behavioural such as responses to pain (see Figure 2). It is also relatively well established that an experience of pain can lead to sensitisation to pain (Woolf & Salter, 2000).

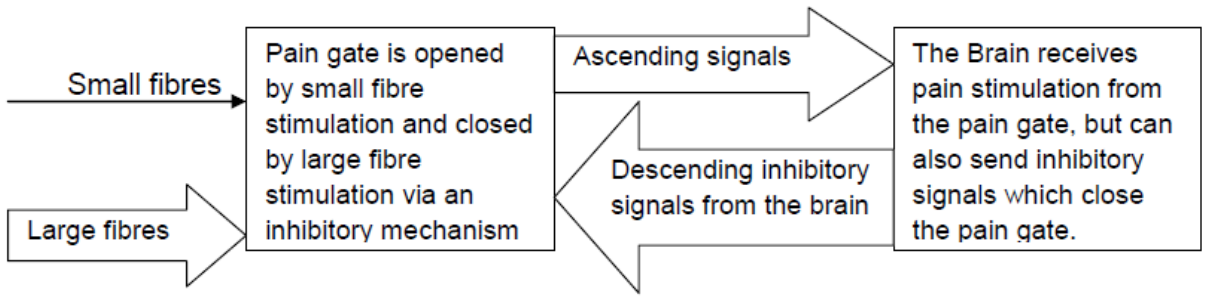

Figure 2 Gate control theory of pain

18.2.1 Causal Mechanisms

Light anaesthesia could lead to an experience of pain intra –operatively (Russell, 1993). It is possible that this experience could in turn lead to sensitisation of the pain system thereby increasing post-operative pain. This sensitisation conceivably could occur with subsequent explicit amnesia. Even if an individual does not experience pain during light anaesthesia, (see discussion of general anaesthesia below) the distress caused (see discussion of consequences of inadequate anaesthetic depth with and without explicit recall below) could also increase the patient's level of post-operative pain, as distress and negative affect can still open the pain gate in the absence of a pain sensitisation experience.

18.3 The Nature of General Anaesthesia

Before discussing the nature and consequences of inadequate anaesthesia, it will be useful to discuss some of the key characteristics of anaesthesia. Modern general anaesthesia includes a number of different drugs designed to affect the patient in three different ways. The first component is a hypnotic that renders the patient unconscious. This is to prevent undue distress in the patient that might be caused by awareness during surgery, (although some sedation procedures require the patient to be conscious and so do not contain this component). The second is an analgesic that reduces the patient's sensitivity to physical stimulation. This is to prevent the patient from going into physiological shock and to contribute to post operative analgesia. The final component is a muscle relaxant. This is to prevent reflex movement during surgery and, in the case of abdominal and thoracic surgery, to improve surgical access. Failure of one or more of

these independent components can lead to inadequate anaesthesia. For example, the hypnotic component of the anaesthetic can fail, leading to an experience where the patient is conscious and aware during the operation but may not experience any pain. This occurrence could be distressing for the patient as they may experience paralysis whilst conscious and may be aware of pain during surgery. The crucial issue here is that if the hypnotic component fails, then it will not be immediately obvious to anyone in the operating theatre, as the muscle relaxant will prevent any movement or communication by the patient of her or his level of consciousness. If the muscle relaxant were also to fail, then this would become apparent as the patient would move in response to surgical stimulation. A number of factors can lead to inadequate anaesthesia, for example: selection of inadequate anaesthetic dose, patient resistance to anaesthetics, human error and mechanical failure or misuse of the anaesthetic machine (Ghoneim, 2001). However, explicit recall of intra-operative events is unusual, at approximately 1 in 600 (Wang, 2001). What may be more common is for patients to receive inadequate anaesthesia but without explicit recall. This is due to the fact that the dose of hypnotic required to prevent recall is less than the dose required to cause unconsciousness (Ghoneim, 2001).

18.4 The Consequences of Inadequate Anaesthesia with and Without Explicit Recall

Anaesthetic awareness with explicit recall during surgery has the potential to cause significant trauma symptoms in the patient. Some patients will go on to develop post-traumatic stress disorder including nightmares about the operation, anxiety, sleep problems, and irritability. They may also experience an unwillingness to discuss their symptoms and harbour a fear of future episodes of anaesthetic awareness (Ghoneim, 2001). These problems can present when a patient has explicit recall of intra-operative

events. For example, they may recall sounds, voices, paralysis, pain, distress and their own cognitions. However, this explicit trauma is not the only cause of post-operative distress.

Evidence has also been found that patients with no explicit recall of events during anaesthesia can later recall information presented during surgery whilst under hypnosis (Levinson, 1965). Evidence has been found of implicit learning during surgery amongst patients with no explicit recall of intra-operative events. For example, Bethune *et al*. (1992) played a taped message to patients under anaesthetic and undergoing cardiac surgery, and again in the post-operative period where the patient was still under anaesthetic, but not undergoing surgery. A second group had the tape played to them whilst under anaesthetic in the post-operative period only. Only patients who had the tape played to them during surgery showed signs of implicit recall. This not only shows that patients can learn whilst under the influence of anaesthetic, but raises the possibility that increasing levels of surgical stimulation may increase implicit learning during surgery. The explanation for these observations is that it is possible for patients to receive a dose of anaesthetic high enough to prevent explicit recall but less than that required for unconsciousness. A series of studies (Andrade, 2001) also indicated that learning under anaesthesia was increased by the presence of surgical stimulation. The author suggested one possible explanation might be that the production of stress hormones such as cortisol, epinephrine and norepinephrine increased learning whilst under sedation. However, it was not clear if stress hormones lightened anaesthesia, or if they contributed to learning despite depth of anaesthesia (Andrade, 2001).

The fact that implicit learning of incidentally presented stimuli, can take place under anaesthetic, implies that it may be possible for patients to suffer an implicit psychological trauma if they experience inadequate anaesthesia without explicit recall. The evidence for implicit psychological trauma is mainly anecdotal, although it is certainly enough to warrant further investigation. Wang (2001) described a study where various measures of depth of anaesthesia, including hemodynamic variables, vapour concentrations and the isolated forearm technique (see below), were used to assess the likelihood of light anaesthesia in hysterectomy patients during surgery. Measures of post-operative anxiety were significantly higher in the 'likely to have experienced wakefulness' group. These differences in anxiety were not apparent pre-operatively. Other measures of psychopathology were also higher in the 'likely to have experienced wakefulness' group, although these latter differences did not reach statistical significance at the $p = 0.05$ level. None of the patients recalled any intra-operative events or knew to which group they had been allocated. This provides compelling evidence that the impact of inadequate anaesthesia without explicit recall merits further investigation.

18.5 Measuring Depth of Anaesthesia

To be effective, this investigation requires an accurate and meaningful measure of depth of anaesthesia. Such a measure will need to fulfil the following criteria:

- *It must show a dose effect of decreasing levels of consciousness with higher doses of anaesthetic*
- *It must not be affected by a neuromuscular blocking drug*
- *It must be independent of anaesthetic technique*

- *It must show responses to surgical stimulation*
- *It must reflect the level of consciousness*
- *The monitoring must be able to take place during the operation*
- *It must be non-invasive and cost-effective*

(Jones & Agarwal, 2001)

18.5.1 Methods for Measuring Depth of Anaesthesia

The following is a selection of techniques used to assess depth of anaesthesia; each is discussed along with some of its advantages and disadvantages:

18.5.1.2 *Isolated Forearm Technique*

In this technique, the forearm is isolated from the circulation, and therefore from the neuromuscular blocking drug, by the use of a pneumatic tourniquet. Patients who appear to be in a deep state of unconsciousness due to anaesthesia, but are actually only paralysed, are able to respond to commands with the forearm (Tunstall, 1977). This can take the form of answers to yes or no questions. The main problem with the isolated forearm technique is that it provides a binary, (yes or no) response to the question of whether anaesthesia is adequate or not. This would potentially limit the ability of this study to describe the depth of anaesthesia numerically and then relate this to the levels of post-operative pain.

18.5.1.3 *Clinical Signs*

Blood pressure, heart rate, sweating and tear production can be used to assess depth of anaesthesia (Evans & Davies, 1984). However, all these signs can be affected by drugs administered in the operation and by disease processes (Jones & Agarwal, 2001). When compared to the isolated forearm technique, clinical signs are not reliably able to detect patients who respond as being wakeful (Russell, 1989).

18.5.1.4 *Frontalis Electro-myogram*

An electro-myogram of the frontalis muscle is very sensitive to depth of anaesthesia. However this technique cannot be used in conjunction with neuromuscular blockade, i.e. when the patient is paralysed. (Jones & Agarwal, 2001)

18.5.1.5 *Electroencephalogram (EEG) Methods*

The effect of anaesthesia on the EEG is the most common way to measure the depth of anaesthesia. In the relaxed and alert individual, EEG produces alpha waves of about 10 Hz. Upon arousal, the alpha wave gives way to low amplitude random fluctuations in the EEG of no particular frequency. With anaesthesia, there is an increase in low-frequency high amplitude waves on the EEG and a reduction in low amplitude high-frequency waves. At deeper levels of anaesthesia, periods of ‘burst suppression’ occur where EEG activity is minimal. Some EEG changes are specific to particular drugs and the EEG at recovery can be different to that before anaesthesia (Jones & Agarwal, 2001). Therefore, signal processing of the EEG is important to extract features that can be used to classify depth of

anaesthesia. The most common signal processing technique is Bispectral Analysis (BIS), (Jones & Agarwal, 2001). The National Institute for Health and Clinical Excellence (NICE) concluded that the BIS monitor was clinically effective and cost effective for use in patients undergoing general anaesthesia (National Institute for Health and Clinical Excellence , 2012). It considered a Cochrane Review of the BIS monitor and an External Assessment Group, which identified studies published subsequent to the Cochrane Review. Areas considered included; awareness during surgery, patients at high risk of awareness, anaesthetic consumption, time to extubation, time to discharge, post-operative nausea and vomiting and long term cognitive dysfunction. Although the findings were heterogeneous between studies the NICE review recommended the use of the BIS monitor, adding that there was more evidence for the clinical effectiveness of the BIS than the E-Entropy or Narcotrend-Compact M devices, although it also recommended both these devices as alternatives to the BIS (NICE, 2012). However, some studies have shown that the BIS index is not a reliable indicator of intraoperative consciousness. Although it has been validated against post-operative recall, it has not been validated against intra-operative wakefulness. In one study involving anaesthetist volunteers receiving muscle relaxant without anaesthetic, a BIS index of 30 was misleading in a fully conscious but paralysed participant (Messner, Beese, Romsto, Dinkel, & Tschaikowsky, 2003). This is because the BIS algorithm uses the frontalis EMG as one its components. Moreover, the BIS index is a probabilistic measure such that, for example, a BIS index of 50 might indicate that 95% of people will be unconscious, but the individual patient might be in the 5% tail of individuals who are resistant to anaesthetic drugs, and actually be wakeful (Iselin-Chaves, Flaishon & Sebel, 1998).

18.6 Relevance of Research

The psychological consequences of implicit memory of intra-operative events have begun to be investigated, but only limited attempts have been made to examine the consequences for pain experience. Factors associated with increased post-operative pain have also been investigated. Some of these factors allow for the possibility that the implicit memory of pain, formed intra-operatively, could impact on levels of post-operative pain. The establishment of a link between post-operative pain and intra-operative wakefulness without explicit recall, as indicated by lightness of anaesthesia, would give rise to the following significant developments:

- The finding of a positive relationship would have implications for the treatment and prevention of post-operative pain, as it could be considered a symptom of implicit psychological trauma.
- Such a finding may facilitate the refinement of anaesthetic techniques to the benefit of future patients undergoing surgery.
- In addition, if a link between lightness of anaesthesia and post-operative pain were found, this would require modifications to anaesthetic practice, as anaesthetists are currently trained that a lack of recall of intra-operative events indicates successful anaesthesia.
- There is a debate about the value of light versus deep anaesthesia. Light anaesthesia is seen as having some advantages over deep as it is felt there is less chance of side-effects for the patient. There is also a debate over whether the function of anaesthesia should be to cause unconsciousness or simply

amnesia. A positive finding here might discourage an emphasis on light anaesthesia and amnesia.

18.7 Aims and Objectives

The objectives of a large scale study would be:

- To determine if there is a positive relationship between lightness of anaesthesia and levels of post-operative pain;
- To determine if the relationship between lightness of anaesthesia and levels of post-operative pain extends to longer term post-operative pain levels (3 months);
- To determine if there is a relationship between pre-operative anxiety and lightness of anaesthesia.

The objectives of this feasibility study are:

- To determine the feasibility of a large scale project;
- To make recommendations regarding changes in design and implementation;
- To report any preliminary findings relating to immediate post-operative pain.

19 METHOD

19.1 Design

This study is a prospective, longitudinal repeated measures design. The dependent variable is pain as measured by the McGill Pain Questionnaire (Short Form) (MPQ-SF). The independent measures are state and trait anxiety as measured by the State Trait Anxiety Inventory (STAI), depth of anaesthesia as measured by the BIS, age as gathered by clinical interview, pain locus of control as measured by the Pain Locus of Control Questionnaire (PLOCQ) and expected impact of operation on body image as measured by a non-validated single item measure. Although depression has been noted to be associated with post-operative pain (Neilson et al, 2007) it has not been included as a measure in this study as these same reviewers also cite a number of studies which found that depression was not a factor in post-operative pain in the specific case of surgery for breast cancer.

19.2 Participants

19.2.1 Operation choice

To investigate the impact of light anaesthesia on post-operative pain, a suitable operation had to be selected. Of central importance in the selection were the expected levels of post-operative pain. In effect, the study compared participants who experienced higher levels of post operative pain with those who experienced lower levels. To maximise the power of the study, the operation chosen had to be associated with a range of post-

operative pain presentations. In other words, the high pain group and the low pain group had to be of roughly equal proportion. A procedure such as hernia operations, with about 10% levels of chronic post-operative pain (Nikolajsen & Minella, 2009), could have produced too few participants with high levels of post operative pain. An operation such as amputation, which can have levels of chronic post operative pain as high as 70% (Nikolajsen & Minella, 2009), could have reduced the power of the study by limiting the number of participants with low levels of post-operative pain. An operation with levels of chronic post-operative pain of around 50% would give the best spread of pain presentations and increase the power of the study. The research on post-operative pain following orthopaedic surgery is not yet of sufficient quality to predict accurately its prevalence (Nikolajsen & Minella, 2009). As a result, this surgery was not considered for use in this study.

19.2.2 Wide local excision of breast tissue for breast cancer

Post-operative pain following surgery for breast cancer occurs in between 25%-60% of patients (Gartner *et al.*, 2009). There are two types of surgery for breast cancer: mastectomy (removal of the breast) and wide local excision of breast tissue for breast cancer, which conserves the breast. Some studies have found that pain following surgery is greater for wide local excision of breast tissue for breast cancer (Gartner *et al.*, 2009), although this may be due to adjuvant therapies such as chemotherapy and radiation therapy that are more common with wide local excision of breast tissue for breast cancer (Tasmuth, Kataja, Blomqvist, von Smitten & Kalso, 1997). Wide local excision of breast tissue for breast cancer is increasingly common as surgeons favour breast conserving surgery. This means that there is a larger pool of potential participants undergoing wide

local excision of breast tissue for breast cancer. Radiotherapy and chemotherapy may increase post-operative pain (Tasmuth *et al.*, 1997) and, as these therapies were more likely in wide local excision of breast tissue for breast cancer, it was necessary to study only one operation to increase homogeneity. If both wide local excision of breast tissue for breast cancer and mastectomy were studied, then the difference in adjuvant therapies may have introduced a confounding variable into the study. Therefore, for the purpose of this study, participants were selected from patients undergoing wide local excision of breast tissue for breast cancer (with and without therapies such as chemotherapy/radiotherapy) in the Leicestershire area.

19.2.3 Exclusion Criteria

Participants were excluded on the basis of psychiatric diagnosis of major mental illness, use of psychotropic drugs, narcotics or alcohol dependence, diagnosis of a pre-existing chronic pain condition, and profound cognitive impairment. In addition, patients undergoing surgical procedures other than wide local excision of breast tissue for breast cancer, requiring anaesthesia, were excluded, as this could have introduced a significant number of confounding variables. Although some males undergo breast surgery for cancer this study included only female participants. Finally, patients who could not read or speak English were excluded from the study as the questionnaires had not been validated in other languages.

19.3 Demographic information

The participants in this study represent an opportunity sample rather than a random sample and, as a result, may have systematic biases in their demographic characteristics that could affect the results of the study. Also, the study participants are all undergoing the same procedure and are all female, both factors that can influence post operative pain (Nikolajsen & Minella, 2009; Mei *et al.,* 2010). Depth of anaesthesia has been found to have a modest impact on immediate post-operative pain in a variety of operations (Law *et al*., 2011; Henneberg *et al.* 2005; Gurman, Popescu, Weksler, Steiner, Avinoah & Porath, 2003). However, the findings of the present study may not be generalisable to other post-operative pain populations. Rather, the results of this study may be indicative that it is worthwhile carrying out similar research with other populations.

19.4 Measures

19.4.1 Bispectral Analysis

A BIS monitor was used to measure depth of anaesthesia. This method of monitoring was favoured as it offered a graded measure of depth of anaesthesia.

Bispectral analysis uses statistical components of the EEG and produces a score between zero (minimal consciousness) and 100 (awake). At different points on this scale the BIS gives weight to different aspects of the EEG to monitor depth of anaesthesia (Jones & Agarwal, 2001). The complex time varying signal of the EEG can be broken down into simple component waves referred to as sine waves, characterised by:

- Amplitude, measured in μV (half peak to peak voltage)
- Frequency measured in hertz or cycles per second
- Phase angle in degrees, which reflects the position of the wave at time zero.

The relationship between these different component sine waves can be used to characterise depth of anaesthesia. For example, low frequency high amplitude waves predominate in deeper anaesthesia. The relationship between the phases of different sine waves can also be used to characterise depth of anaesthesia. The BIS also uses periods of burst suppression to characterise very deep anaesthesia. High frequency EEG activity indicates light levels of sedation. These different factors are combined using non-linear iterative data modelling techniques to produce scores between 0 and 100 (Sigl & Chamoun, 1994). A proportion of the BIS score is calculated using the Frontalis Electromyogram (EMG) and so it is not entirely independent of neuromuscular blockade.

The range of BIS scores considered safe for surgery is between 40 and 60 (Struys, Versichelen, Byttebier, Mortier, Moerman & Rolly, 1998). However, some studies have found evidence of implicit learning for BIS scores between 40 and 60 (Lubke, Kerssens, Phaf & Sebel,1999). A score higher than 70 is normally considered indicative of wakefulness. BIS is not entirely independent of the anaesthetic agent employed. For example, nitrous oxide does not affect the BIS score even when the patient loses consciousness (Barr, Jakobsson, Öwall & Anderson,1999).

19.4.2 Measures of Pain

A number of different pain measures were considered. Verbal rating scales, where the pain is rated, by the patient, as not present, mild, moderate or severe, by the patient were not used as there is concern that the difference between mild and moderate pain may not be the same as the difference between moderate and severe pain, and so the data cannot be considered interval. Visual Analogue Scales (VAS) were considered, where the patient rates pain on a 10cm line, with 0 cm indicating no pain and 10 cm indicating extremely severe pain. However, there was concern that a VAS could be difficult to administer over the telephone. Numeric Rating Scales (NRS) were also considered. An advantage is that these can be considered as interval/ratio, and are easily administered over the phone. NRS have good reliability and validity (Jensen, Karoly & Braver, 1986). Using the NRS 101, which asks patients to rate pain from 0 to 100, may make the rating sensitive to changes in pain. Pain-related measures such as the Pain Self-Efficacy Questionnaire (PSEQ) (Nicholas, 2007) and the Roland-Morris Disability Questionnaire (RMDQ) (Roland & Morris, 1983) were considered as measures of the impact of pain. The Pain Discomfort Scale (PDS) (Jensen, Karoly & Harris, 1991) was considered, as it measures pain affect. However, the McGill Pain Questionnaire (MPQ - Melzack, 1987) allows assessment of pain quality, asking the patient to assess different qualities of pain such as ‘shooting’, ‘stabbing’ and ‘burning’ pain. Although it might have been advantageous to administer a battery of pain questionnaires, this was beyond the scope of the present study. In addition, it was felt it was important to avoid overloading participants with large numbers of questionnaires due to ethical and practical reasons. To this end, the short form of the MPQ was used which included the Present Pain Index (PPI) (Melzack, 1987). The VAS of the MPQ short form was replaced with the NRS 101 for ease of administration over the

telephone. The McGill Pain Questionnaire (MPQ) was used to measure pain pre-operatively, in the acute post-operative phase (1-2 days following surgery) and then in a longer term post-operative follow up (at 6 weeks and 3 months). The MPQ short form has acceptable levels of reliability and validity, with Cronbach's alpha 0.705 for test and 0.713 for retest. Reliability was demonstrated with intraclass correlation coefficients from 0.716 to 0.891 (Yakut, Yakut, Bayar, & Uygur, 2007). Correlations with Numeric Rating Scales ranged from 0.637 and 0.700 (Yakut *et al.*, 2007). The MPQ short form has been demonstrated to be an acceptable substitute for the Long Form MPQ when time constraints do not allow its administration (Melzack, 1987). The pain questionnaire was administered pre-operatively and at post-operative follow-up.

19.4.3 Anxiety

The State Trait Anxiety Inventory (STAI) has been specifically designed for assessing anxiety at any given time (state anxiety) and levels of long term stable anxiety (trait anxiety) (Spielburger, Gorsuch, Lushene, Vagg & Jacobs,1983). It has acceptable levels of reliability and validity, with Cronbach's alpha calculated to be 0.86 and high intraclass correlation coefficients of 0.39 to 0.89 (Quek, Low, Razack, Loh, & Chua, 2004) and good construct validity (Metzger, 1976). Depression and anxiety have been linked with chronic pain and implicit trauma from light anaesthesia (Howard, 1987; Goldmann, 1988). The State and Trait versions of the questionnaire were administered pre-operatively. At post-operative follow-up only the State version was re-administered as trait anxiety is seen to be a more stable construct.

19.4.4 Pain Locus of Control Questionnaire

The Pain Locus of Control Questionnaire (PLOQ) (Penzien, Mosley, Knowlton, Slipman, Holm & Curtis, 1989) was also administered. It is a pain-specific version of the Health Locus of Control Questionnaire. Pain locus of control is a factor that may influence post-operative pain as it influences health-related behaviours (Coughlin, Badura, Fleischer & Guck, 2000). The Health Locus of Control questionnaire has been shown to have acceptable levels of reliability with Cronbach's alpha greater than 0.7 for all subscales and Pearson's correlation coefficients for test – retest reliability ranging from 0.60 to 0.93 (Araújo, Lima, Sampaio, & Pereira, 2010). Construct validity has been demonstrated by findings of a positive correlation between external subscales on the Health Locus of Control Questionnaire and disability ($r = 0.58$ $p < 0.05$), (Oliveira, Furiati, Sakamoto, Ferreira, Ferreira, & Maher, 2008). The Pain Locus of control questionnaire was only administered once, pre-operatively.

19.4.5 Body Image Screening Question

Participants were asked to rate the following question on a scale of 0 (not at all) to 10 (could not be worse):

How much do you feel having breast surgery will impact on how you see yourself as a woman?

After the operation the following question was asked:

How much do you feel having had breast surgery impacts on how you see yourself as a woman?

This was used to assess if body image was related to anxiety and pain experience.

19.5 Procedure

Potential participants who met the exclusion/inclusion criteria were identified by an anaesthetist involved with the study. The anaesthetist and/or researcher approached suitable patients at the pre-operative assessment, with the consent of the surgical team, and discussed the project with them. Suitable patients were given copies of a Patient Information Sheet (see Appendix D), designed in line with National Research Ethics Service (NRES) guidelines. If they were interested in being involved in the study, then the researcher and the anaesthetist met with the patient upon her admission to hospital. Initially, the patient was given the opportunity to decline any further involvement. If the patient agreed, the aims of the study were explained, along with what participation would involve. The patient had the opportunity to ask any questions of the researcher and the anaesthetist. The researcher reassured the patient that if she chose not to participate in the study her care would not be affected. If, after this reassurance, the patient agreed to participate the researcher consented the patient and administered the pre-operative questionnaires.

The BIS electrode was fitted in the anaesthetic room by a member of the surgical team, as the patient was being prepared for surgery. This allowed time to verify that the monitor was functioning within parameters. Once it was ascertained that the BIS monitor was producing a score, it was detached from the electrode and the patient moved from the anaesthetic room to the operating theatre. Inside the operating theatre the monitor was re-attached to the electrode and a BIS score obtained continuously throughout the surgical procedure. The researcher was positioned on the far side of the anaesthetic equipment from the anaesthetist, so as to facilitate the blinding procedure. This meant there was no visual contact between the researcher and the anaesthetist and the anaesthetist could not view the BIS screen or index. If the score on the BIS monitor exceeded 55, or dropped below 30, the researcher would inform the anaesthetist by saying: “the score is below/above 30/55”. If the score only momentarily went above 55 or below 30 the researcher informed the anaesthetist by saying “the score went below/above 30/55 but is back within the safe limits now”. On those occasions when the anaesthetist asked the researcher whether the BIS score was satisfactory, the researcher would reply “the score is within acceptable limits”. This response was designed to reassure the anaesthetist, while at the same time avoiding giving cues relating to the depth of anaesthesia, which might influence anaesthetic practice. The researcher recorded the BIS score every sixty seconds on the minute, using a standard Anaesthetic Record Form, from the point at which the patient was being prepared for surgery in theatre. A note was made of the minute interval during which the first incision was made. Procedures lasted typically 90 minutes, giving approximately 90 data points per participant. In addition, the researcher recorded all those one minute intervals during which the BIS score fell outside the range 30 to 55.

One to two days post-operatively, at a time agreed with the participant, the researcher administered the follow-up questionnaires by telephone. Six week follow-up was achieved by re-administration of the questionnaires, by the researcher, at the patients' follow-up clinic or via post or telephone. For longer term follow-up at three months, questionnaires were posted to participants and telephone calls used to increase response rates. Data were anonymised by the researcher, once they were linked to the three-month follow-up data, and unique identifying numbers were then used to identify participants. Collected data were stored securely at the University of Leicester. All members of the surgical teams who were involved in the study, including anaesthetists and surgeons, were informed as to the nature of the study and the whole procedure, including how consent was taken, administration of questionnaires, and use of the BIS monitor in operations. This was achieved by meeting with the surgical teams before the commencement of the research. The researcher only worked with surgical teams who agreed to collaborate. The teams were encouraged to discuss any concerns they had about any part of the procedure described.

19.6 Data Analysis

In a full-scale study, the primary statistical analysis would be repeated measures ANOVA, which would be used to determine the extent that lightness of anaesthesia contributes to post operative pain over the course of the 3 measurement points. The present feasibility study did not aim to gather the follow-up data to perform this analysis, in the timescales allowed. In addition to the primary analysis, the full-scale study would perform an ANCOVA to examine the co-variance between pain and other key variables, to partition out the unique relationship between pain and lightness of anaesthesia. The present study

used an ANCOVA to analyse the data for immediate post-operative pain only. Variables that could be used in a full-scale study are age, anxiety and pre-operative pain. The feasibility study controlled for pre-operative pain only, and used a regression matrix to determine links between lightness of anaesthesia, anxiety, age, body image concerns and differences between pre- and post-operative pain scores. This allowed an exploration of any possible confounding variables.

The lighter and deeper anaesthesia groups were generated by recording the amount of time that patients' BIS scores are over a threshold of 50. Patients were then ranked in order of time spent over 50 during the operation. A median split was used to divide participants into 'deeper' and 'lighter' levels of anaesthesia. These two groupings were used in the ANCOVA analysis in the present study. A full-scale study would use both ANOVA and ANCOVA analyses.

20 RESULTS

The results section contains the following elements:

- a discussion of the process of gathering data for future studies
- a discussion of the descriptive statistics of the variables measured (including details of transformations performed)
- plots of the means of the three measures of post-operative pain scores split by depth of anaesthesia
- Scatter plots of pre-operative pain against post-operative pain for all participants
- T-tests performed on each of the three pain scores to detect differences between Lighter and Deeper anaesthesia groups

- an ANCOVA examining the difference in means of post-operative pain in lighter and deeper anaesthesia groups whilst controlling for pre-operative pain
- a narrative account of the follow-up data collected at the 6 week and 3 month points

20.1 Data collection and participant recruitment

Recruitment of participants commenced on 18th February 2013. The first eligible participants were approached on 18th March 2013 and consented on 21st March 2013. The final participant was approached on 8th July 2013 and consented on 11th July 2013. In this 21 week period, 18 patients who were undergoing the target operation were identified and given information, face-to-face, about involvement in the project. Of those approached, 14 agreed to be involved in the project and 12 were recruited into the study. Eleven of the participants either had complete sets of data or were awaiting follow up at the 6 week and/or 3 month intervals.

Four patients did not agree or were deemed ineligible for the study. One had recently had significant health complications and so declined involvement; another declined after discussing involvement with family members; the third, during discussion with the researcher, disclosed a history of panic attacks and was deemed ineligible. The fourth declined involvement but, in any case, had been deemed ineligible due to disclosure of active mental illness. Two patients agreed to participate but were not consented, both due to rescheduling of surgery. One participant was recruited, but became ineligible for the study at the six week interval following an additional surgical procedure, so no further data were collected.

Thus, of the 18 patients identified, 16 were eligible and of these 14 agreed to involvement, 12 were consented and complete follow up data were obtained for 11. Therefore of the

original 18, complete data were collected for 61%. All participants that remained eligible engaged in the follow-up post-operatively, at six weeks and three months. The main difficulty with recruitment came from a lack of eligible participants that the study was able to access, given the very limited number of patients of the collaborating anaesthetists, who were undergoing the target operation in the relatively short study period.

20.2 Descriptive statistics

This section contains a discussion of the main variables considered in this study and reports descriptive statistics (see table 11). The results of the Body Image Screening questionnaire and the Pain Locus of Control Questionnaire are included in Appendix L.

Table 11 Descriptive statistics

Descriptive Statistics									
	N	Minimum	Maximum	Mean	Std. Deviation	Skewness		Kurtosis	
	Statistic	Statistic	Statistic	Statistic	Statistic	Statistic	Std. Error	Statistic	Std. Error
Age	12	30	85	60.08	17.952	-.460	.637	-.502	1.232
Pre operative MPQ scores (0-45)	12	0	11	2.42	3.450	1.744	.637	2.702	1.232
Pre-operative Pain Intensity scores (0-100)	12	0	55	12.75	19.721	1.412	.637	.598	1.232
Pre-operative Present Pain Index scores (0-5)	12	0	2	.50	.674	1.068	.637	.352	1.232
Post-operative MPQ scores (0-45)	12	0	15	6.92	5.125	-.015	.637	-1.091	1.232
Post-operative Pain Intensity scores (0-100)	12	0	80	24.42	23.971	1.180	.637	1.171	1.232
Post-operative Present Pain Index scores (0-5)	12	0	2	1.17	.937	-.383	.637	-1.931	1.232
Pre-operative state anxiety (STAIY1) (20-60)	12	21	59	38.75	12.285	-.016	.637	-1.105	1.232
Pre-operative trait anxiety (STAIY2) (20-60)	12	20	41	29.33	6.243	.364	.637	-.532	1.232
Mean BIS score	12	33.02	45.36	40.96	3.82	-.994	.637	.307	1.23

The data were examined to identify any significant deviations from normality. This was to ensure that the assumptions of the ANCOVA were not violated. The skewness and kurtosis scores of each of the sets of data were calculated. If the scores exceeded twice the standard error of the statistic then the data were considered to be significantly skewed and a transformation was performed. Pre-operative MPQ-SF scores were considered to be significantly positively skewed and to have significant leptokurtosis (an overly pointed distribution). To manage the positive skew a log base 10 transformation was carried out. Before this could be done, one was added to all the scores so that zero values were removed. Both skewness and kurtosis were brought within acceptable limits by these transformations (skewness 0.628 and kurtosis -0.895).

Pre-operative pain intensity scores were also significantly positively skewed (skewness=1.412), therefore a log base 10 transformation was also performed (after adding one to remove all non-zero scores). This brought skewness to within twice the standard error (skewness = 0.657). The other variables were within the limits of 2 standard errors of the skewness and kurtosis characteristics.

When z-scores were calculated, one case exceeded the 1.96 cut-off on a number of the measures administered. On average, 5% of scores might be expected to exceed this limit due to random variation. Thus, the fact that one score in twelve (approximately 8%) exceeded this limit does not appear unusual.

BIS scores were sampled every minute. A score was taken as indicative of lighter anaesthesia if it exceeded 50. The number of scores exceeding 50 was noted and a median split performed with the highest 50% of scores being in the lighter anaesthesia

group and the lowest 50% in the deeper anaesthesia group. The number of scores above 50 is noted in table 12 along with placement in deeper or lighter anaesthesia group.

Table 12 BIS scores above 50

Participant Number	Scores exceeding 50	Lighter or deeper anaesthesia group
1	4	DEEPER
2	2	DEEPER
3	7	LIGHTER
4	5	LIGHTER
5	17	LIGHTER
6	2	DEEPER
7	0	DEEPER
8	9	LIGHTER
9	1	DEEPER
10	10	LIGHTER
11	7	LIGHTER
12	1	DEEPER

20.3 Post-operative pain scores

Post-operative pain scores were measured using the MPQ-SF, which included Pain intensity measured by Visual Analogue Scale (VAS) and Present Pain Intensity (PPI). Mean post-operative pain scores in lighter and deeper anaesthesia groups are presented in table 13 and figures 3-5.

Table 13 Post-operative pain scores

	Level of anaesthesia	Mean	Std. Deviation	Standard Error
MPQ-SF	DEEPER	7.00	5.367	2.191
	LIGHTER	6.83	5.382	2.197
Pain Intensity	DEEPER	31.33	30.690	12.530
	LIGHTER	17.50	14.405	5.881
PPI	DEEPER	1.50	.837	0.342
	LIGHTER	.83	0.98	0.400

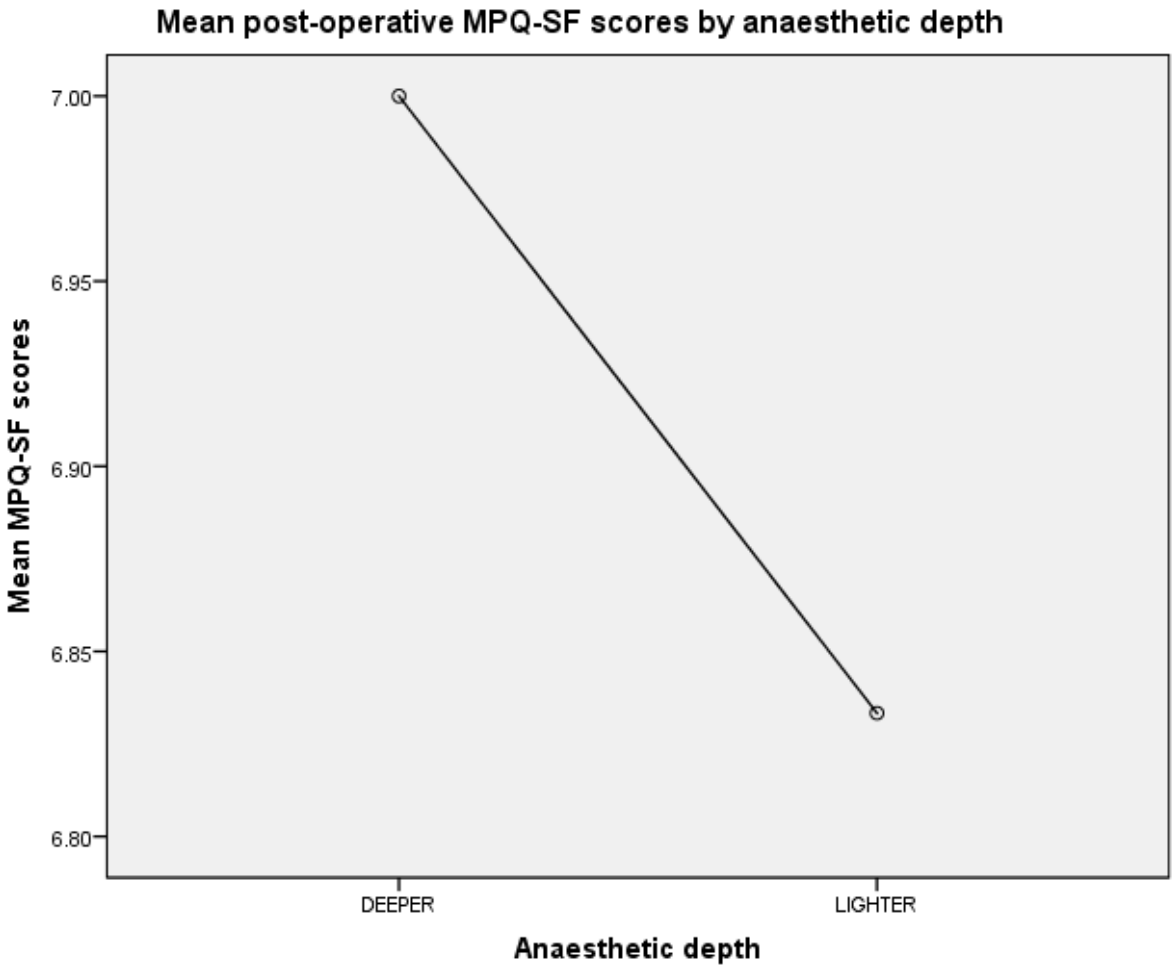

Figure 3 Mean post-operative MPQ-SF scores by anaesthetic depth

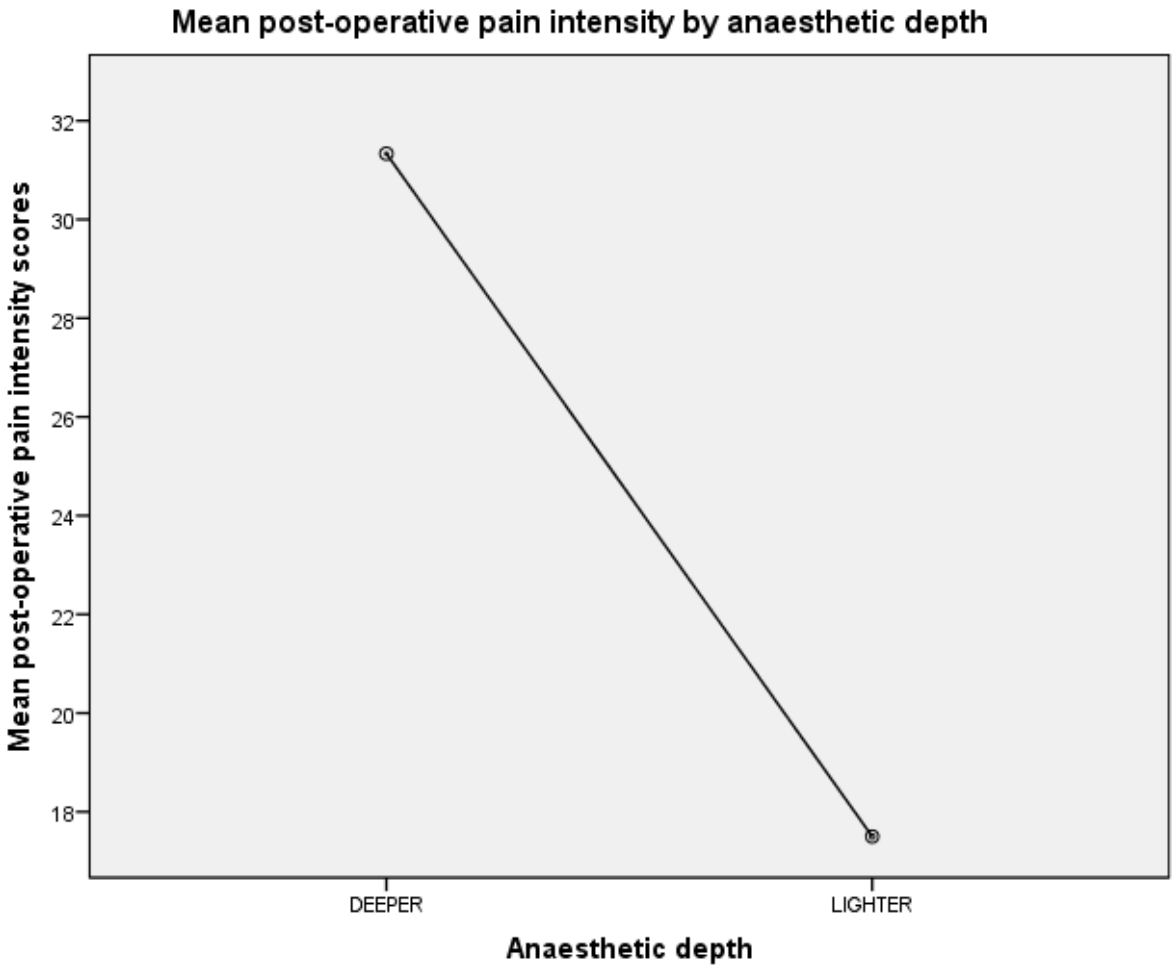

Figure 4 Mean post-operative Pain Intensity scores by anaesthetic depth

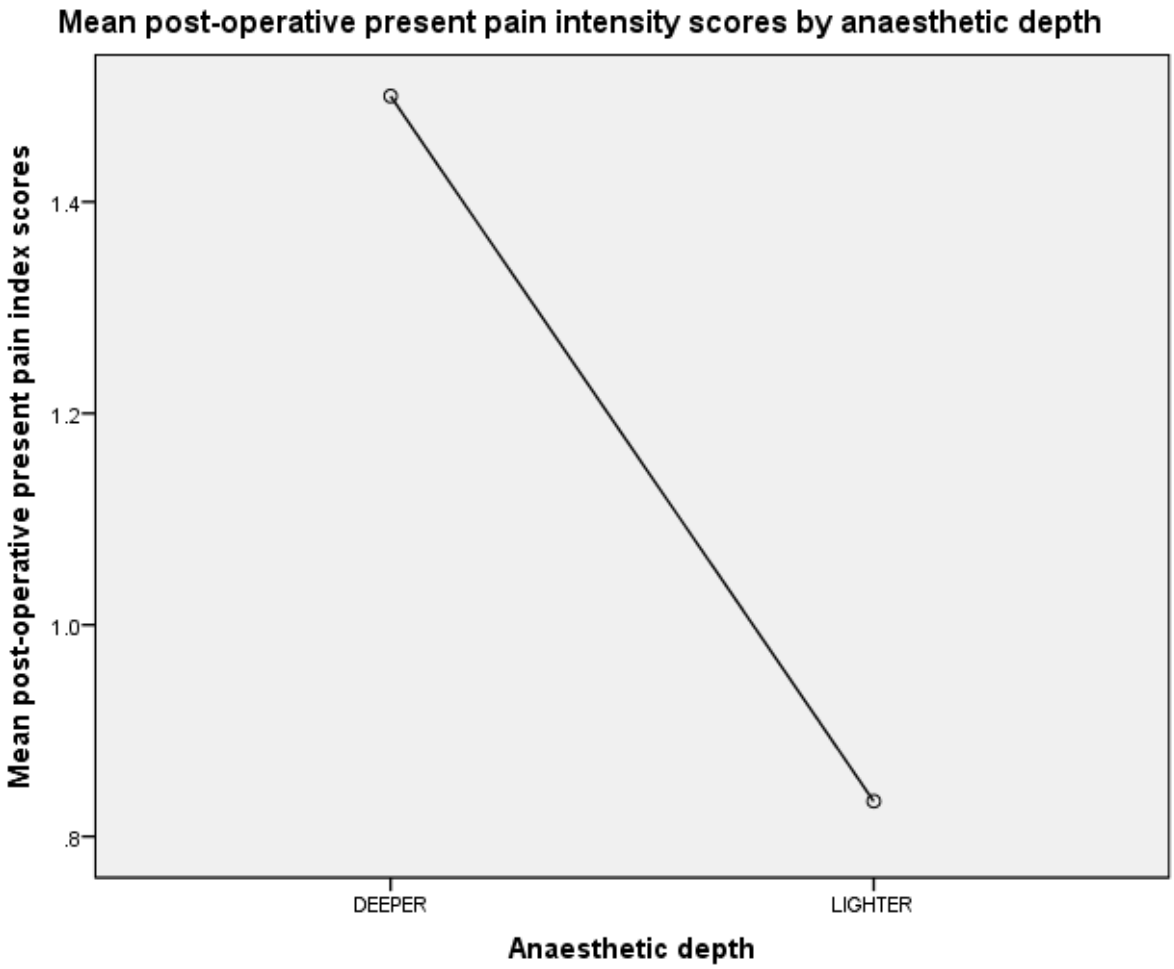

Figure 5 Mean post-operative PPI scores by anaesthetic depth

20.4 SCATTER PLOTS

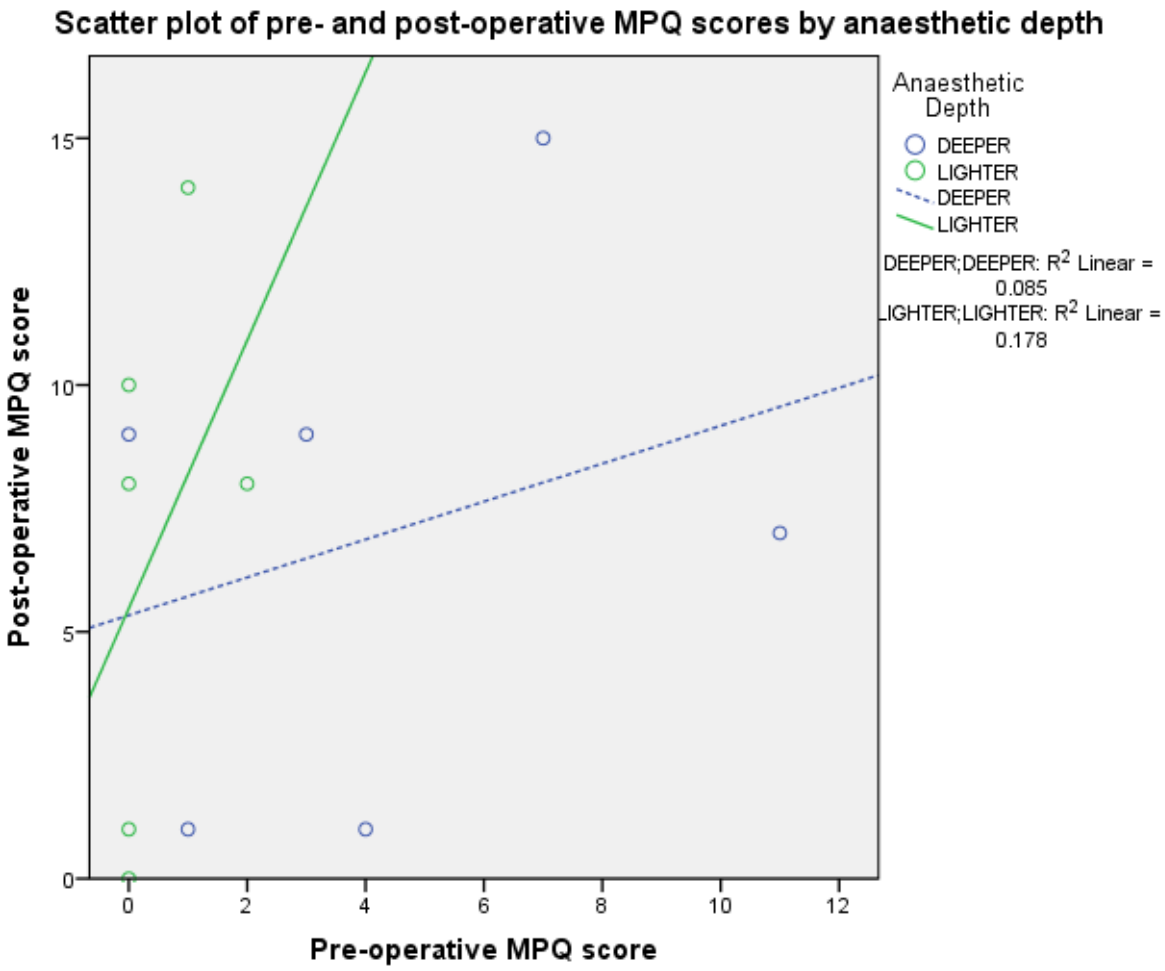

Figure 6 Scatter plot of pre- and post-operative MPQ scores by anaesthetic depth

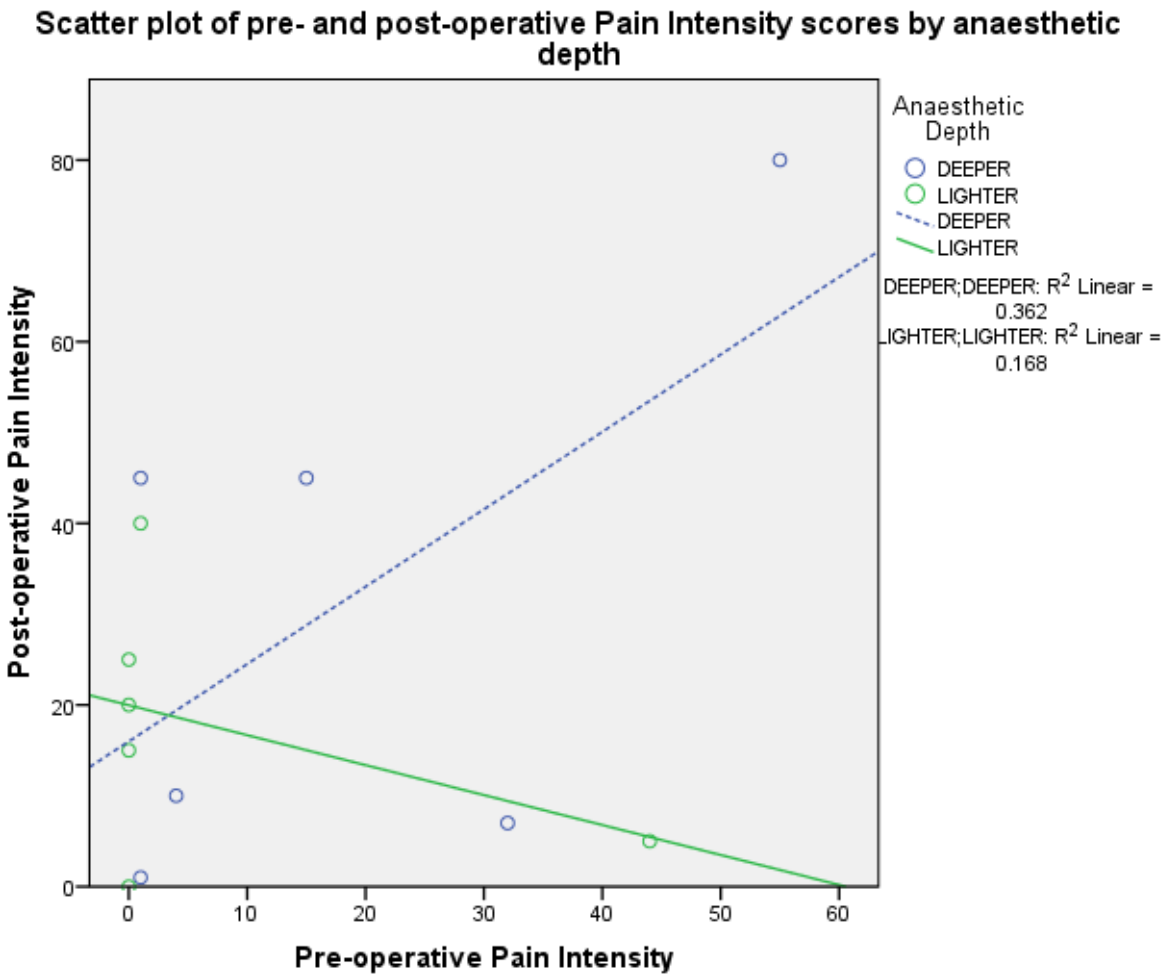

Figure 7 Scatter plot of pre- and post-operative Pain Intensity scores by anaesthetic depth

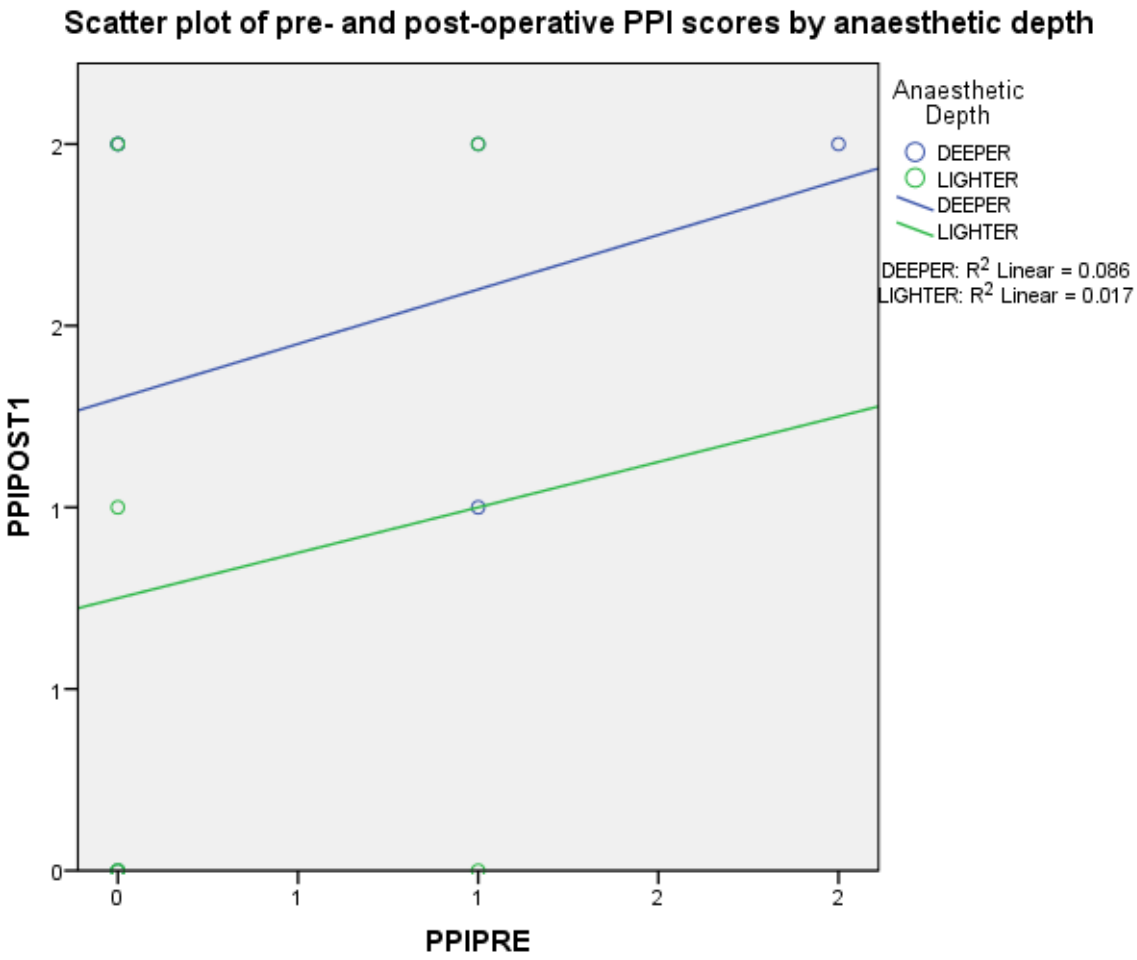

Figure 8 Scatter plot of pre- and post-operative PPI scores by anaesthetic depth

Figure 5 shows 2 possible outliers, in the deep anaesthesia group and Figure 6 shows 1 possible outlier, in the deep anaesthesia group. Figure 7 does not appear to show any possible outliers. The outliers identified may be responsible for the skewness in the MPQ-SF scores and Pain Intensity scores. As noted above, appropriate transformations for skewness were carried out prior to data analysis.

20.5 T-TEST

A series of 2-tailed independent measures t-tests was performed to determine if there were significant differences in post-operative pain between the lighter and deeper anaesthesia groups. Levene's test was used to determine whether data violated the assumption of homogeneity of variance. Levene's test for was non-significant for all t-tests performed indicating that the assumption of homogeneity of variance had not been violated.

20.5.1 MPQ-SF scores

There was no significant effect of anaesthesia group on post-operative MPQ scores ($t_{(10)}$ = 0.189, p = 0.854)

20.5.2 Pain Intensity scores

There was no significant effect of anaesthesia group on post-operative Pain Intensity scores ($t_{(10)}$ = 0.555, p = 0.591)

20.5.2 PPI scores

There was no significant effect of anaesthesia group on post-operative PPI scores ($t_{(10)}$ = 1.265, p = 0.235)

20.6 ANCOVA

An ANCOVA was performed to determine if post-operative pain was significantly different between lighter and deeper anaesthesia groups, whilst controlling for pre-operative pain. Before the ANCOVA was completed the data were checked to ensure that they did not violate the assumption of homogeneity of regression slopes. Additionally the relationship between covariate (pre-operative pain) and dependent variable (post-operative pain) was examined to determine whether or not the assumption of a linear relationship in both groups had been violated.

20.6.1 MPQ-SF results

Regression slopes were determined to be homogeneous, as assumed by the ANCOVA analysis. Although a plot of the pre-operative against post-operative pain scores, measured on the MPQ-SF, indicated a linear relationship in the lighter anaesthesia group (R^2=0.229) the relationship was weak in the deeper anaesthesia group (R^2=0.039). The ANCOVA was still performed as an indicator of any possible relationships. After adjusting for pre-operative pain, there was no significant effect of anaesthesia group ($F_{(1,9)}$=0.172, p=0.668). Table 14 and Figure 6 indicate that pain scores increased by a greater degree post-operatively in the lighter anaesthesia group than in the deeper anaesthesia group, and that pain scores were higher pre-operatively in the deeper anaesthesia group. Estimated marginal means of post-operative MPQ-SF scores (controlling for the effect of pre-operative pain) suggest that post-operative pain for the lighter anaesthesia group would have been slightly higher (log base 10 of MPQ-SF scores = 0.829) than in the deeper anaesthesia group (log base 10 of scores = 0.694).

Table 14 Mean MPQ-SF scores

Pain	Anaesthesia	Mean (SD)	Log base 10 MPQ-SF score (SD)
Pre-operative MPQ-SF score	Low	4.33 (4.082)	0.60 (0.40)
	Lighter	0.50 (0.837)	0.13 (0.21)
Post operative MPQ-SF score	Low	7.00 (5.367	0.78 (0.39)
	Lighter	6.83 (5.382)	0.74 (0.47)

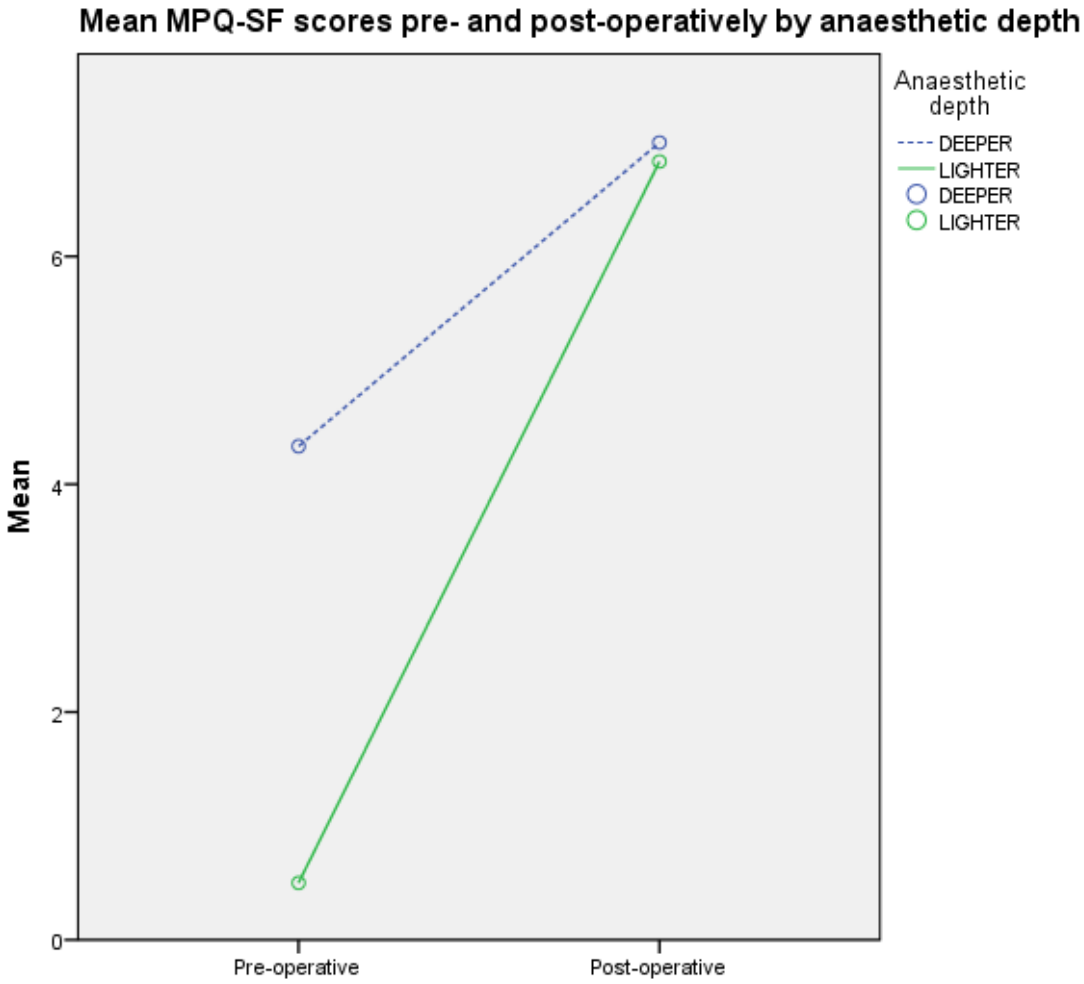

Figure 9 Mean MPQ-SF scores pre- and post-operatively by anaesthetic depth

20.4.2 Pain Intensity

Homogeneity of regression slopes was confirmed. Although a plot of the pre-operative against post-operative pain intensity scores, measured on the VAS, indicated a linear relationship in the deeper anaesthesia group (R^2=0.196) the relationship was weak in the lighter anaesthesia group (R^2=0.022). The ANCOVA was still performed as an indicator of any possible relationships. After adjusting for pre-operative pain the main effect of anaesthesia was not significant ($F_{(1,9)}$=0.069, p=0.799). Table 15 and Figure 7 demonstrate that pain scores increased by a greater degree post-operatively in the deeper anaesthesia group than in the lighter anaesthesia group, and that pain scores were higher pre-operatively in the deeper anaesthesia group. Estimated marginal means, controlling for pre-operative pain intensity, indicated higher scores in the deeper anaesthesia group, i.e. the same direction of trend when not controlling for pre-operative pain intensity. However, scores were reduced in the deeper anaesthesia group (log base 10 pain intensity = 1.21) and raised in the lighter anaesthesia group (log base 10 pain intensity = 1.10)

Table 15 Mean Pain Intensity

Pain	Anaesthesia	Pain Intensity (SD)	Log base 10 pain intensity (SD)
Pre-operative pain intensity	Deeper	18 (21.67)	0.96 (0.62)
	lighter	7.5 (17.88)	0.33 (0.66)
Post-operative pain intensity	Deeper	31.333 (30.68)	1.25 (0.61)
	lighter	17.5 (14.40)	1.05 (0.59)

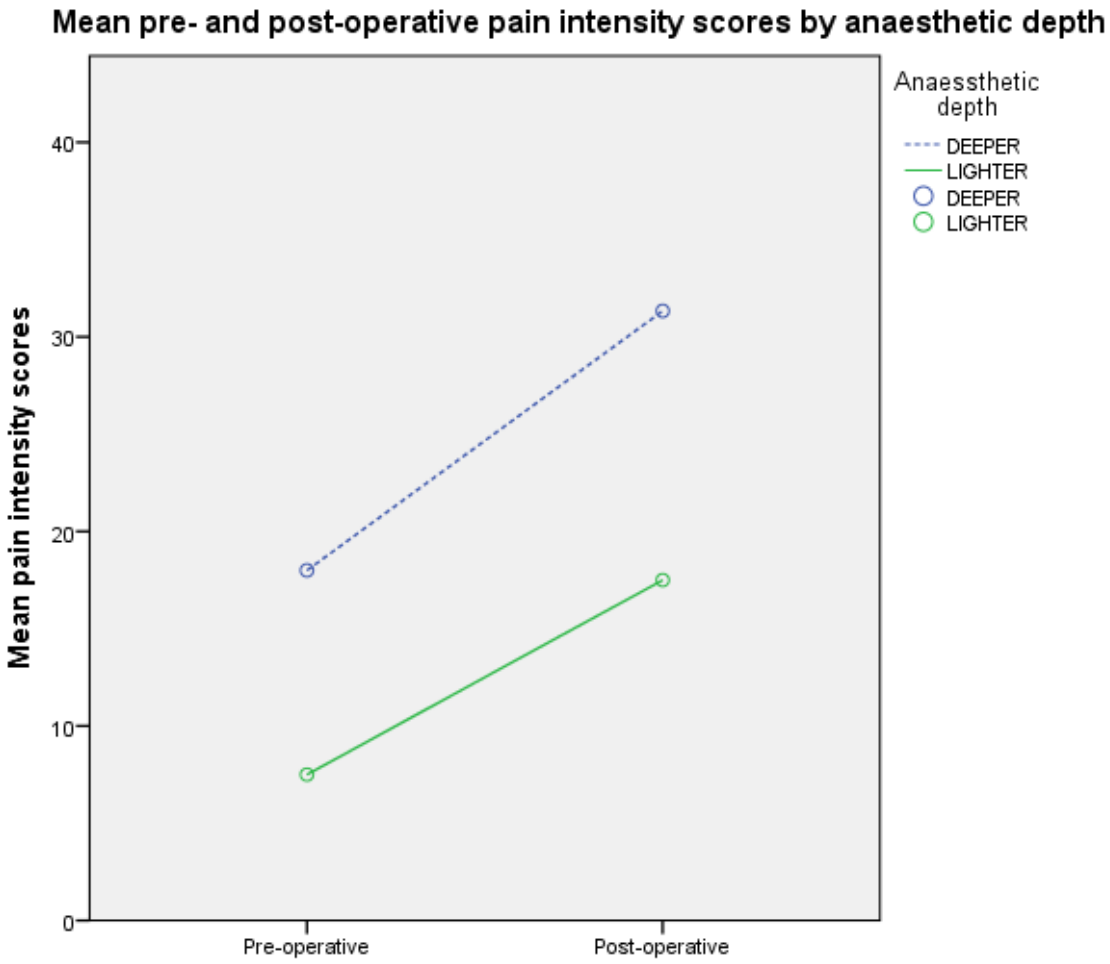

Figure 10 Mean pain intensity scores pre- and post-operatively by anaesthetic depth

20.4.3 Present pain intensity

Homogeneity of regression slopes was confirmed. Plots of the relationship between dependent variable (post-operative PPI) and the covariate (pre-operative PPI) indicated weak linear relationships in both the lighter and deeper anaesthesia groups (R^2=0.017 and R^2=0.089 respectively). The ANCOVA was still performed as an indicator of any possible interactions. After controlling for pre-operative pain the main effect of anaesthesia was not significant ($F_{(1,9)}$=1.035, p=0.336). Table 16 and Figure 8 indicate that pain scores

increased by a greater degree post-operatively in the deeper anaesthesia group than in the lighter anaesthesia group, and that pain scores were higher pre-operatively in the deeper anaesthesia group. The estimated marginal means of post-operative PPI indicated that scores were higher in the deeper anaesthesia group than the lighter anaesthesia group after controlling for pre-operative pain. However, pain in the deeper anaesthesia group was slightly reduced (1.45) and slightly raised in the lighter anaesthesia group (0.88)

Table 16 Mean PPI scores

Pain	Anaesthesia	Mean (SD)
Pre-operative PPI	deeper	0.66 (0.81)
	lighter	0.3333 (0.51)
Post-oprerative PPI	deeper	1.5 (0.83)
	lighter	0.83 (0.98)

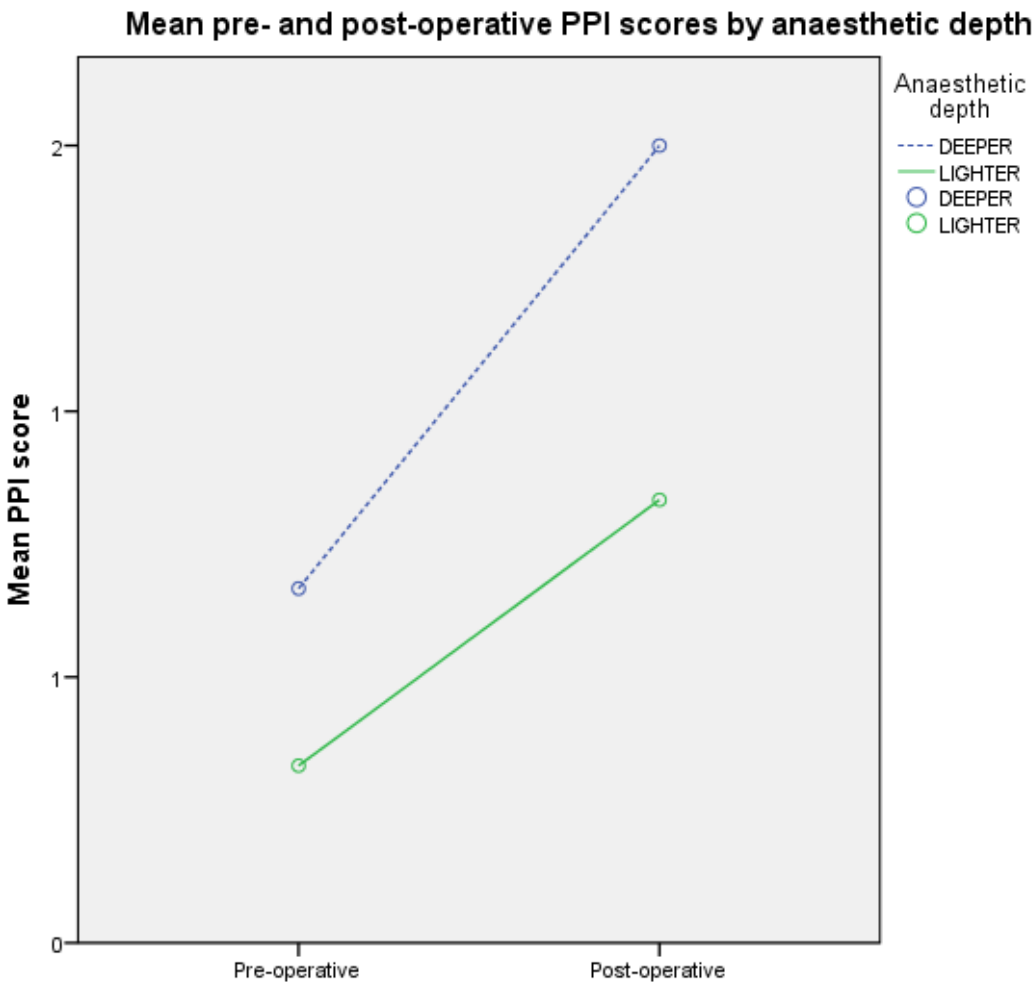

Figure 11 Mean PPI scores pre- and post-operatively by anaesthetic depth

20.5 Correlation Matrix

The main variables measured in the study were correlated against one another using Pearson's r. This exploratory analysis was performed to examine any possible relationships in the data. The differences between pre- and post-operative pain scores were used for each of the pain measures to control for the effect of pre-operative pain. Correlation coefficients and two-tailed significance scores are reported in table 17.

Table 17 Pearson's r correlations

		Pre-operative state anxiety	Post-operative state anxiety	Trait Anxiety	Pre-operative Body Image score	Post-operative body image score	BIS scores exceeding 50	MPQ-SF scores difference	Pain intensity difference	Present Pain Intensity difference
Age	r	-.110	-.065	-.592*	-.660*	-0.662*	-.019	-.259	-.493	-.163
	P	.734	.840	.042	.020	.019	.953	.416	.103	.613
Pre-operative state anxiety	r		.409	.154	.398	-.013	-.411	-.088	.065	-.060
	P		.187	.633	.200	.968	.184	.785	.840	.853
Post-operative state anxiety	r			.501	0.33	.578*	.353	.215	.330	-.103
	P			.097	.289	.049	.261	.503	.295	.751
Trait Anxiety	r				.563	.656*	-.017	.216	.370	.330
	P				.057	.020	.959	.501	.237	.294
Pre-operative Body Image score	r					.524	.094	-.026	.286	.065
	P					.081	.771	.936	.367	.840
Post-operative body image score	r						.378	.178	.356	-.143
	P						.225	.581	.256	.658
BIS scores exceeding 50	r							.273	.382	-.044
	P							.390	.220	.893
MPQ-SF scores difference	r								.751*	.552
	P								.005	.062
Pain intensity difference	r									.566
	P									.055

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

r=Pearson's r

p=p value

Age was significantly negatively correlated with trait anxiety and pre- and post-operative body image scores. Post-operative state anxiety and trait anxiety were significantly positively correlated with post-operative body image scores. Differences in MPQ-SF scores were significantly correlated with differences in pain intensity scores. Relationships that showed trend levels of significance ($p<0.10$) included positive correlations between:

- Trait anxiety and post-operative state anxiety
- Trait anxiety and pre-operative body image score
- Pre-operative body image score and post-operative body image score
- MPQ-SF difference and PPI difference
- Pain intensity difference and PPI difference

There was also a positive correlation between MPQ-SF difference and BIS scores exceeding 50 as well as pain intensity differences and BIS scores exceeding 50, although these correlations were not significant.

20.6 Outcomes at 6 Weeks and 3 Months

Of the 12 participants, data were collected for 8 at the 6 week follow-up and for 6 at the 3 month follow up. The incomplete set of follow-up data arose from the fact that, at the cut-off point at which data could be incorporated into this study, only 8 participants had reached the 6 week interval, and only 6 had reached the 3 month interval. Due to the incomplete data set a statistical analysis was not attempted but the means and standard deviations were examined (see table 18) and any tentative patterns noted.

Table 18 Mean pain scores at 6 weeks and 3 months follow-up

Anaesthesia	Weeks (Deeper n=4, Lighter n=4)			3 months (Deeper n=3, Lighter n=3)		
	MPQ-SF (SD)	Pain intensity (SD)	PPI (SD)	MPQ-SF (SD)	Pain intensity (SD)	PPI (SD)
Deeper	4.00 (4.89)	7.50 (15.00)	0.25 (0.50)	1.66 (2.88)	6.00 (10.39)	0.33 (0.57)
Lighter	4.50 (6.60)	2.00 (4.00)	0.25 (0.50)	0 (0)	0 (0)	0 (0)

At the 6 week follow up, the direction of the relationship between lighter and deeper anaesthesia groups on MPQ-SF scores was reversed, with higher scores for the lighter anaesthesia group. However, pain intensity, measured with the VAS, was still higher in the deeper anaesthesia group. There was no difference between the groups on PPI scores. At three months all the relationships were in the same direction as the one day follow-up with pain higher in the deeper anaesthesia group according to all measures. Some of the differences may be due to random variation but it appears that the direction of the relationships have been preserved at the 3 month point.

21 DISCUSSION

Any conclusions that might be drawn from the empirical findings of this study must be treated as highly tentative. The main aim of was to determine the feasibility and methodology of a larger scale project examining this phenomenon. Thus, much of this discussion will be focused on recommendations for future studies and research directions.

21.1 Empirical Findings

One of the main empirical findings was that differences in the mean scores on the pain measures used, between lighter and deeper anaesthesia groups, were in the *opposite*

direction to that predicted (i.e. the pain scores were higher in the deeper anaesthesia group). However, none of these finding was statistically significant. Pre-operative pain was also higher in the deeper anaesthesia group on all pain measures.

Interestingly, although the lighter anaesthesia group had much lower pain scores on the MPQ-SF scale pre-operatively, post-operatively this group's scores increased to a much greater degree than the deeper anaesthesia group's, almost to the point of convergence. On the pain intensity and PPI scales, the increase in pain scores was greater in the deeper anaesthesia group. The estimated marginal means (predicted means controlling for pre-operative pain) indicated higher post-operative pain scores on the MPQ-SF in the lighter anaesthesia group. Estimated marginal means for pain intensity and PPI predicted higher pain scores in the deeper anaesthesia group.

When the six week follow-up data were examined the results were mixed. At the three month follow-up, pain scores were all higher in the deeper anaesthesia group.
Two-tailed tests of significance were carried out when performing correlations on variables. Age was negatively correlated with body image and anxiety scores. Pre-operative anxiety scores positively correlated with body image issues. Differences on some of the pain measures were positively correlated and a non-significant positive correlation between BIS scores above 50 and pain increase was noted. A non-significant negative relationship between pre-operative state anxiety and BIS scores above 50 was also noted.

21.2 Relating Findings to Initial Hypotheses

The hypotheses that this study design set out to explore were:

1) Lightness of anaesthesia increases post-operative pain.
2) This relationship will influence pain at the 3 month point
3) Pre-operative anxiety will be positively correlated with lightness of anaesthesia.

The tentative findings of this study indicate that the evidence related to the first hypothesis is mixed. Most measures indicated higher post-operative pain in the deeper anaesthesia group, in the opposite direction to that predicted. On one measure (MPQ-SF), pain scores appear to have increased by a greater degree in the lighter anaesthesia group. These findings must be treated with caution due to insufficient power, related to a small sample size.

The follow-up data provide mixed support for the second hypothesis, with relationships between pain scores differing depending on the measure used at the six week follow-up point, but all pain scores being lighter in the deeper anaesthesia group at three months. A small sample size precluded statistical analysis of the follow-up data.

Finally, a negative correlation was noted between pre-operative state anxiety and scores exceeding 50 on the BIS, which was in the opposite direction to the one predicted. It was noted in a doctoral thesis study (Wilson, 2005) that extroversion combined with anxiety made patients more susceptible to anaesthetic, while introversion combined with anxiety made patients more resistant to anaesthetic. The small sample size might mean that a significant proportion of patients were extrovert, which may account for this result.

Unfortunately a lack of power, due to a small sample size, means a direct comparison with current literature is difficult and the empirical findings of this study cannot be added to this area of knowledge.

21.3 Comparison with the Literature

Three previous papers have examined the relationship between depth of anaesthesia, as assessed by EEG methods, and immediate post-operative pain. Law *et al.* (2011) examined three specific characteristics of the EEG: state entropy, spindle-like activity and delta band power. The authors also examined other intra-operative variables including operation type, depth of volatile anaesthesia and estimated effect site morphine concentration. They found that lower state entropy and higher spindle-like activity (indicating deeper anaesthesia) were linked to lower pain in the immediate post-operative period. This study design allowed examination of which aspects of the EEG might specifically relate to post-operative pain, rather than using a composite measure like the BIS. However, they did not examine, or control for, pre-operative or demographic variables, which could have led to bias in the results. Neither did they examine whether this relationship extended to longer-term post-operative pain. This study was able to recruit 94 participants and so had the statistical power to find an effect of anaesthetic depth on post-operative pain.

Henneberg *et al.* (2005) used Mid Latency Auditory Evoked Potentials (MLAEPs) as an EEG measure of depth of anaesthesia. Differences in use of Patient Controlled Analgesia (PCA) were statistically significant between light and deep anaesthesia groups, in the 24 hours following surgery, with the lighter anaesthesia group using more analgesia.

Statistically significant differences were not detected in the following 2 days, or on pain measures. This indicates that there could be an interaction between pain and analgesia consumption, such that higher levels of pain are masked by the higher consumption of analgesics, when they are patient controlled. This study again did not examine pre-operative or demographic variables and did not examine the longer-term impact on pain. Anaesthetists involved in the study were blinded as to the EEG status of the patient, and so depth of anaesthesia as measured by the MLAEP did not influence anaesthetic practice, unlike in the present study, where anaesthetists were alerted to BIS scores outside of agreed limits.

Gurman *et al.* (2003) used Spectral Edge Frequency (SEF) as an EEG measure of depth of anaesthesia, in a population of morbidly obese patients undergoing laparoscopic gastric banding, whose obesity put them at risk of inadequate anaesthesia. They found that immediate post-operative pain was greater in the lightly anaesthetised group. Anaesthetists were blinded as to the SEF and used standard indicators to control depth of anaesthesia.

All of these studies found greater immediate post-operative pain in the lightly anaesthetised group (as measured by a variety of EEG methods), in contrast to the present study. This finding may have emerged as all three studies used a sample size that provided sufficient level of statistical power to test their hypotheses. However, unlike the present study, none of them attempted to control for pre-operative or demographic factors, introducing possible bias into the findings. Additionally, they did not examine whether these differences in pain experiences, between light and deep anaesthesia groups,

extended to longer-term post-operative pain. This feasibility study established the practicality of incorporating these additional aspects in this type of design.

21.4 Limitations of the Study

One of the main limitations of the study was restricted resources. One researcher collaborated with one anaesthetist (for most of the study) at one site. This slowed the rate of data collection, especially due to constraints on the availability of the researcher and anaesthetist relating to competing commitments. The small sample size and power thus achieved is a second major limitation.

Additionally, a number of limitations can be discussed linked to the measurement of variables. As a preliminary examination of this area of research, the STAI was employed, a general measure of anxiety. A more specific measure, for example the surgical fear questionnaire (Peters, Sommer, Rijke, Kessels, Heineman, Patijn, Marcus, Vlaeyen & van Kleef, 2007), might be more closely linked to intra-operative and post-operative outcomes. The MPQ-SF does not distinguish between different sources of pain. Participants reported pre-operative pain due to the condition for which surgery was being received, pre-operative investigations/treatments, or for reasons unrelated to the condition. These different types of pain are not necessarily captured by the MPQ-SF and may have different relationships with post-operative pain.

Finally, the scores on the BIS monitor were relatively low, with a mean score of 40.96, close to the lower limit which the manufacturer recommends for operations (40). This raises the question of what constitutes a significantly light enough level of anaesthesia,

intra-operatively, to influence post-operative pain (assuming a relationship exists). The mean score was also close to the mid-point (42.5) of the lighter (55) and deeper (30) thresholds of BIS scores at which the anaesthetist was informed the BIS was either lighter or low. Therefore, it is possible that informing the anaesthetist of lighter and deeper scores may have reduced the variability of the BIS scores and reduced the power of the study.

21.5 Recommendations for a Full-Scale Study

A full-scale study would require 100 or more participants to achieve power. At the rate of data collection achieved in this feasibility study (11 participants in 21 weeks) it could take 3-4 years to recruit the necessary number of participants. The first recommendation of this feasibility study is, therefore, that multiple researchers work with multiple anaesthetists, possibly at multiple sites to collect the data at a more expedient rate. Multiple researchers would also be able to generate multiple hypotheses about, and examine different relationships in, the collective data set. These could include pain locus of control, body image, anxiety and pain relationships.

An important factor in the success of any future research project is the role of local collaborators. Anaesthetists who are prepared to work closely with researchers, and who are motivated, supportive, able to identify potential participants and facilitate recruitment, are essential. Without such contacts the collection of data would not be practical. Therefore, the second recommendation is that data collection only proceeds when motivated local collaborators, who feel they have the capacity to perform this crucial role, have been identified.

The measurement of pain produced a number of important issues which must be considered in any future study. Patients would often ask *what kind of pain* they should report when filling out the pain questionnaires. It became apparent that participants experienced pain in a number of different categories. Participants reported pain that was:

- Pre-operative and related to the condition (breast cancer)
- Pre- or post-operative and related to non-surgical treatments or exploration (for example chemo therapy)
- Pre- or post-operative and unrelated to treatment or condition (for example arthritis)
- Post-operative and related to surgery

Pre-operative pain may be an important predictor of post-operative pain and the source of the pain may change any relationship that exists. It may also be important to note post-operative pain from sources other than the operation. A number of interesting relationships between different types of pain could be hypothesised and explored by measuring each source of pain separately. Indeed, this could encourage future researchers to be involved in the project to explore these relationships. This feasibility study has shown that administering the pre-operative questionnaires needs to be done efficiently to ensure that all questionnaires are completed before the participant's operation. Therefore, it would be unlikely that the MPQ-SF could be administered 3 times pre-operatively. A more feasible recommendation would be to complete a VAS for each type of pain pre-operatively, and a NRS for each type of pain post-operatively by telephone interview.

Another important recommendation of this feasibility study is related to the monitoring of BIS scores and its relationship to the variability of the data. For this study to have power there must be adequate variability in the BIS scores, without putting participants at risk.

Once the BIS monitor is connected to a participant, there is an ethical imperative to inform the anaesthetist if the score moves out of the agreed boundaries. This will inevitably have the effect of reducing the variability in the data.

One way to manage this balance is by modifying the boundaries that are used as thresholds for informing the anaesthetist. The scores that are considered safe by the manufacturer are between 40 and 60 (midpoint of 50). At the study site, BIS monitor alarms are routinely set at 35 and 60 (midpoint 47.5). In this feasibility study the thresholds were set at 30-55 (midpoint of 42.5) in agreement with the anaesthetist and the ethics committee. The mean BIS score recorded for participants was just under 41, which is close to the midpoint between the threshold scores and, importantly, close to the lower boundary of what is considered safe by the manufacturer. This may indicate that the boundaries are affecting the variability in the data. We might, therefore, assume that by raising the lower boundary, we would increase the midpoint of the threshold scores and potentially increase the average BIS score.

There are two important questions to ask at this point:

1) Within the boundaries set by the manufacturer, what constitutes a depth of anaesthesia that might increase post-operative pain?
2) Is it ethical to allow the BIS scores to vary within the boundaries given the unconfirmed hypothesis of increased post-operative pain?

In this study, it was estimated that BIS scores exceeding 50 were more likely to put participants at risk of post-operative pain that scores of 50 or less. Due to the deeper BIS scores recorded in this study it might be that participants did not experience scores that, although within the manufacturer's guidelines, might have increased the risk of post-

operative pain. We also have to consider whether it is ethical to expose participants to BIS scores exceeding 50, given this hypothesis.

It is important to note that it is unclear whether or not BIS scores of 51-60 do constitute an increased risk of post-operative pain and, additionally, it is not clear what risks BIS scores of 30-40 might pose. By increasing the lower boundary from 30 to 40 participants could experience more scores on the BIS monitor from 51-60, due to increased anaesthetist intervention. The risks this poses are uncertain, but at the same time the risk of allowing participants' BIS scores to be between 30 and 39 is also uncertain. Therefore, increasing the lower boundary from 30 to 40 could be argued as exchanging one set of uncertain risks (that of having a BIS score between 30 and 39) for another set of uncertain risks (that of having a BIS score between 51 and 60). Therefore, it is possible to make an argument for increasing the lower threshold from 30 to 40. Importantly, the ethics committee was only concerned with applying an upper threshold of 55. The lower threshold was developed in agreement with the collaborating anaesthetist. Increasing the upper threshold from 55 to 60 would also increase the variability in the data. However, this would constitute an unacceptable risk to participants. Therefore, the recommendations for a future study would be to increase the lower threshold to 40 whilst maintaining the upper threshold of 55. This would give a midpoint of 47.5 and might increase the power of the study to detect a difference between lighter and deeper levels of anaesthesia.

The final recommendation is to modify the process by which the researcher informs the anaesthetist that the BIS score has passed a threshold. In the study this was achieved by informing the anaesthetist verbally. Setting the alarms on the BIS monitor at the 40 and 55 points would represent a more standardised way of informing the anaesthetist. The

researcher could inform the anaesthetist by simply saying “high” or “low” depending on which boundary was passed when the alarm sounded.

21.6 Research recommendations

This study did not have the power to examine the relationships between the variables measured. However, future directions of research could examine moderating or mediating relationships between independent variables, covariates and dependent variables. This would help increase understanding of not only which factors contribute to post-operative pain, but also how they interact to influence post-operative pain. For example, the relationship between pre-operative anxiety and post-operative pain could be examined, whilst using depth of anaesthesia as a moderating or mediating variable. The impact of pre-operative body image concern and pre-operative anxiety on post-operative anxiety or post-operative pain could also be explored. Essentially, this feasibility study recommends that future research should explore the relationships between variables to improve understanding of the processes which create and maintain post-operative pain, rather than simply controlling for covariates to determine the impact of the independent on the dependent variable.

21.7 Clinical Implications

This feasibility study did not produce any statistically significant findings related to differences in post-operative pain between lighter and deeper levels of anaesthesia. Despite the lack of statistical significance, it was noted that post-operative pain was higher in the deeper anaesthesia group according to most analyses. A minority of findings

supported greater risk of post-operative pain in the lighter anaesthesia group. For example, the increase in pain pre- and post-operatively was greater in the lighter anaesthesia group on the MPQ-SF. These results may have been complicated by higher levels of pre-operative pain in the deeper anaesthesia group than in the lighter anaesthesia group.

Due to the mixed findings of the study, as well as small sample size, low power and possible anomalies in the data, it would be unethical to make any recommendations for clinical practice. Before any meaningful insights can be gained, further studies need to collect more data, whilst attending to the recommendations of this study.

21.8 Conclusion

This study has demonstrated the feasibility of a large scale investigation of the relationship between depth of anaesthesia and post-operative pain.

Although it did not achieve statistical significance and results may have been influenced by a small sample size, it was able to make important recommendations for the future. These included:

- Gathering data with multiple researchers and collaborating anaesthetists, possibly at multiple sites
- Involving motivated and supportive collaborating anaesthetists
- Measuring pain from multiple sources, i.e. condition-related, treatment-related, pain-related to surgery and unrelated pain, both pre- and post-operatively using VAS/NRS

- Changing the threshold BIS scores for informing the anaesthetist to 40 and 55
- Using alarms on the BIS monitor to help inform the anaesthetist of when threshold scores have been passed
- Exploring the relationships between variables that contribute to post-operative pain, to improve understanding of triggering and maintaining mechanisms

These recommendations could facilitate and direct further investigations, thereby enhancing the scientific understanding of post-operative pain and the wellbeing of surgical patients in the future.

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23 CRITICAL APPRAISAL OF THE RESEARCH PROCESS

Prior to commencing the DClinPsych I had worked in health psychology and pain management. During my work in this service I first encountered the phenomenon of post-operative pain. Soon after starting the course I decided that my preference was to design and implement my own research idea, rather than taking up an existing protocol or contributing to an ongoing programme. At this early stage in the process of developing my ideas, I was not fully aware of the advantages and disadvantages of these two approaches to research selection and design. Had my awareness of these issues been higher this might have informed my decision.

Initially my ideas revolved around how patients accounted for therapeutic change over the course of therapy. However, during teaching in the first year, I was introduced to the concept of intra-operative wakefulness, without explicit recall, by Professor Mike Wang. The insights that Professor Wang's teaching provided led me to consider the possibility of a link between this phenomenon and unexplained post-operative pain, which I had encountered a number of times whilst running pain management groups. I inquired if there had been any research regarding links between depth of anaesthesia and post-operative pain. Professor Wang informed me that it had been an idea that some of his colleagues had previously discussed with him. Subsequently, an investigation of this formed one of my proposed research topics.

My second proposed topic was linked to my idea about therapeutic change and was developed in discussion with Dr Jon Crossly. This was related to a homeless hostel that had a reputation of being successful with clients who had experienced a number of

unsuccessful placements, and who had complex needs. The theme of this type of research was the development of theories of therapeutic aspects of the environment that had facilitated change.

Unfortunately, there was not the opportunity to meet with Professor Wang to discuss a topic for a literature review, related to the post-operative pain topic, in time to meet the deadline for the submission. As a result, I chose to carry out a literature review related to my second proposed topic of therapeutic change. Therefore, my initial literature review was in the area of complex post-traumatic stress disorder (CPTSD). On reflection, I feel it would have been helpful if the first year literature review had formed an integral part of the background research for the eventual project proposal. The literature review I carried out in the third year, on post-operative pain, could only be completed after the project had been designed and implemented, due to time constraints inherent in the organisation of the course. Therefore, key insights this review provided could not be used to inform the process of design and implementation.

When it was confirmed that I had been allocated my first project topic, on post-operative pain, I was part way through completing my first year literature review on CPTSD. At this point it became clear that the considerable amount of effort I had invested in the first year literature review would not be relevant to the thesis I would eventually be required to complete. In order for me to make a success of the first year literature review, it was necessary for me to adjust to this eventually and maintain my motivation. Although I initially considered the possibility of changing the review topic, I had to acknowledge that this was not feasible within the time period available. Given these circumstances, I decided to focus my attention on CPTSD, since it was an intrinsically interesting area from

which I derived important insights that were valuable for my development as a trainee clinical psychologist.

I met with Professor Wang and our initial discussions were related to operation selection. Amongst early possibilities discussed were hernia operations. However, research for my proposal indicated low levels of post-operative pain for this procedure. This made them less suitable candidates for research, despite the fact they were relatively common.

In this period Professor Wang contacted his colleagues who had been interested in this area of research. One had retired and the other, although interested and willing to provide advice, was unable to commit to direct involvement in the study, due to time pressures. However, she did suggest mastectomy as a possible research focus. She felt that mastectomy patients were usually happy to be involved in research that could help others. Importantly, the level of pain for mastectomy patients would be likely to contain enough variance to increase the power of the study to find any effect. We therefore agreed to focus on this procedure.

It was now that I began to appreciate more fully some of the challenges that this research would involve. Not least of my concerns was the prospect of monitoring patient's depth of anaesthesia during operations. I had never witnessed an operation first hand before and was not sure how I would cope. However, we did not have the opportunity to discuss this in our research meetings in any detail. I felt that I needed to prepare myself and therefore I watched a number of televised procedures.

We also discussed what method would be used for the measurement of depth of

anaesthesia. We decided on the Bispectral Index (BIS) monitor as this would give a reading from 0 (completely unconscious) to 100 (completely awake) that could be correlated with post-operative pain. This was felt to be more effective than the isolated forearm technique which could only provide dichotomous 'consciousness/unconscious' data. Additionally, Professor Wang had been loaned a BIS monitor by the manufacturer, which was being used in another project. He was confident that our application to the manufacturer, for its use in this project, would be successful.

A number of concerns were highlighted when the proposal was peer reviewed in the University department. One was that participants could be exposed to distressing ideas (such as intra-operative wakefulness). The project proposal was refined to address this point explicitly. A second was the possible confounding variable of body image. A screening question was included to detect pre- and post-operative concern about body image issues. Another issue that was highlighted was the need for this research to proceed to a tight schedule due to the volume of work required.

The next step was to make a local contact with an anaesthetist who would be willing to be involved. Professor Wang and I discussed which of us would be better placed to make this contact. My view was that as course director, Professor Wang would carry more weight in this area and so we agreed that he would make initial contact. The G. Hospital was identified as the centre for all breast surgery in Leicestershire and Dr. E.J. was contacted as a consultant anaesthetist working in this department.

Dr. E.J. was extremely helpful and supportive, and was interested in being directly involved in the research. She arranged a meeting with the surgeons, which, unfortunately, I was

unable to attend. Professor Wang attended this meeting in order to explain the nature and aims of this research. None of the surgeons objected to being involved in the study. The surgeon that Dr. E. J. most commonly worked with (Mr J. K.) met with us and suggested that the research should study lumpectomy rather than mastectomy, as breast conserving surgery was becoming increasingly common and mastectomy relatively unusual. This was agreed, but, as the application to NHS ethics was being completed in parallel with this process, it was not possible to alter the project proposal that had already been sent by this point.

Dr. E. J. did not have the authority to give me permission to access University Hospitals of Leicester (UHL) patients (as I was not employed by UHL). She gave me the contact details of Dr. J. T., who she believed might know who could provide the necessary authorisations. He informed me that he needed to give me permission to access patients. He was concerned that my research could highlight patients experiencing post-operative pain and anxiety who would not otherwise have come to the attention of services. If, as a result, services experienced increased demand this could create problems for commissioning. As services are commissioned to meet an expected level of demand, if demand exceeded expectations due to the findings of the project, this could raise a funding issue. I modified the proposal and added a flowchart of how to respond to elevated levels of pain or anxiety in participants. The main change was that participants would be directed to their G. P., who would refer them on to specialist services, rather than the researcher suggesting specialist services himself. Dr J. T. liaised with his colleagues in Research and Development, who were happy with the alterations.

The next step was to attend the NHS ethics committee meeting. This committee had no

major ethical concerns. One minor concern was related to the blinding of the anaesthetist to the BIS score. It was agreed that if the BIS score exceeded 55 (the safe range is considered to be 40-60), rather than 60, then the anaesthetist would be informed. However, they did not grant ethical approval as, at the meeting, they were informed that the procedure had been changed to lumpectomy, even though the written submission they had already received had been based on mastectomy. This decision of the committee not to grant ethical approval represented a significant setback. As the change of focus from mastectomy to lumpectomy did not raise any additional ethical issues, all the parties who had so far contributed to the planning of the project were surprised. These included not only my supervisor and me but also Dr E. J., Dr J. T. and Mr J. K.

Resubmission to the ethics committee involved significantly more work than a simple amendment. The project proposal and ethics form had to be altered and research had to be done regarding lumpectomy and body image/post-operative pain. I now had to come to terms with the fact I would have to manage and cope with a lengthy delay in the time-table of the project. This delay was especially concerning as, at the peer review stage, the importance of being able to adhere to a strict time-table had been emphasised. It was recognised that a tight schedule was essential because of the large time commitment involved in attending operations, administering pre- and post- questionnaires and recruiting participants. The magnitude of the setback was such that it led me to call into question the feasibility of the whole endeavour. It was important for me, therefore, to manage my sense of crisis and to maintain my resolve and motivation.

Ideally, the processes of collaborating with local contacts in order to design the research, and application to the NHS ethics committee, would occur sequentially with the former

being completed first. Due to time constraints it was felt necessary to complete these two processes in parallel. With hindsight, superimposing these two procedures introduced an element of risk, the risk being that insights gained from work with local collaborators could not be used to inform the ethics application.

The National Research Ethics Service (NRES) website recommends that when re-applying for ethical approval, it is important that the re-application should be submitted to the same ethics committee. However, due to time pressures my supervisor and I decided to reapply at the earliest opportunity, as opposed to waiting until the same Ethics committee reconvened.

The committee to which I re-applied raised a number of additional detailed points, although none of these appeared to be significant ethical issues. For example, an ex-anaesthetist on the panel stated that the muscle relaxant component of an anaesthetic was not to prevent reflex movement by the patient, as I had stated in my project proposal. During the meeting I was not given the opportunity to comment on this statement, and I was informed that this point would be included in the written summary that I would be sent. In discussion with my supervisor we had some difficulty in deciding on the relevance of this point, as it appeared to have no bearing on the ethical issues that were the remit of the committee. Indeed, my supervisor could only surmise that it might refer to the role of muscle relaxant in abdominal surgery, where its effect is to enhance access to the abdominal cavity. However, this role of muscle relaxant was of no relevance to the procedure which was the subject of my research. This meeting was difficult, as my supervisor was unable to attend and I found myself having to manage what felt like a rather confrontational style of questioning, without his support. This involved, for example, a committee member asking

a question and then another member interrupting me as I attempted to answer.

Ethical approval was withheld a second time. The points raised were valid, although they appeared to be amendments rather than fundamental ethical concerns about the nature of the research. I felt that an element of confusion was added by the fact that, in their subsequent letter, a number of points were included that were not raised and discussed in the meeting. For example, the committee questioned my suitability to consent participants, despite my extensive experience working in health psychology settings. What is more, as part of the process of having my research authorised by the Research and Development department, I would be attending Good Clinical Practice Training. Additionally, my suitability to perform consenting procedures would be assessed by the Research and Development department through the use of a role-play scenario.

Also, in their letter the committee questioned the relevance of suggesting to participants experiencing post-operative pain or anxiety, that they contact their G. P., given G. P.'s lack of specialist knowledge. This point was somewhat bewildering as it implied that I should be suggesting to participants which specialists in the Trust they might be referred to, which would have been wholly inappropriate. If the committee had raised this issue with me, in the meeting, I could have informed them that the G.P. is the gateway to appropriate specialist services in the NHS Trust in which the research was to be carried out. Although the response of the ethics committee was frustrating, it did teach me an important lesson: always to re-submit to the same committee when re-applying for ethical approval in order to ensure consistency and continuity in the decision making process.

Because of the adversarial tone of the meeting I anticipated a second refusal to grant

ethical approval, and was therefore better prepared to respond constructively. However, a substantial amount of work was required to address the large number of issues that had been raised. Subsequently, my supervisor and I agreed that I would reapply to the original committee and this committee granted ethical approval after minor amendments.

At this stage, we were informed by the manufacturer of the BIS monitor that they would not give consent for use of the device in this project. Fortunately, Professor Wang was able to borrow a BIS monitor from a colleague.

The next step was to seek approval from Research and Development to carry out the study. I was required to attend Good Clinical Practice training, run by the department. Additionally, I participated in a role play exercise with two members of Research and Development staff, covering the process of gaining consent. Given the number of setbacks I had already experienced, I had come to expect yet another setback at this stage. However, I was aware that this was probably not an accurate view of the situation, and that my clinical skills were completely adequate to discuss the topic area sensitively with potential participants. In fact the staff members who ran the session with me, rated my performance as exemplary. This rating was very welcome and served to enhance my moral and improve my motivation.

A further delay was introduced by the requirement to amend the Site Specific form that constituted part of the Research and Development application. Guidance from the Research and Development department indicated that, as I was not employed by the NHS Trust in which the research was being carried out, my details as Principle Investigator were not relevant to the Site Specific form. Instead, I was required to name my Local

Collaborator (Dr. E. J.).

Once the Research and Development process was completed, it was possible to proceed with implementing the research project. My supervisor had acquired a BIS monitor and informed me he would be able to secure a supply of the disposable electrodes required for its use. At this stage, for reasons that only became clear subsequently, Dr E. J. was not in a position to respond to our attempts at communication for a number of weeks. It transpired she had been involved in a serious accident, and although, fortunately, she had not suffered serious physical injuries, the experience did have a short-term impact on her work duties. Once contact was re-established, preparation could resume for commencing the process of data gathering.

Professor Wang and I both felt that it would be feasible to start data collection in January 2013. However, early in January a general email was sent out informing all members of the University department that Professor Wang had undergone major heart surgery over the Christmas period and would be away from work for at least 2 months, as he was very seriously ill. I was very shocked by this, and concerned for Professor Wang's wellbeing.

Although the email assured everyone that the research committee would decide how to precede with Professor Wang's research students when it next met, I now felt as though I was in a state of limbo. Indeed, I was not sure how to, or whether to, proceed and not sure what the outcome of this situation would be. On the one hand, I felt that I was very close to being able to start collecting data. On the other, I was concerned as Professor Wang had said he would be present during the first data collection, and I was not sure whether he would want me to proceed in his absence.

I discussed this with Dr Noelle Robertson (acting course director) and Dr Steve Allan. They both agreed that I should not proceed with the research, since I had not been trained in the use of the BIS monitor. Additionally, the BIS monitor was stored in Professor Wang's office and, as it did not belong to him, I did not feel comfortable taking it without his permission. Dr Robertson and Dr Allan suggested that I contact Professor Wang after 2 weeks, when he was likely to have recovered sufficiently to respond to emails. Another problem with proceeding with the research was a lack of the disposable electrodes used by the BIS to monitor brain activity. In the interim, I discussed with Dr E. J. the possibility of organising a number of training sessions with the BIS monitor.

At the end of January I contacted Professor Wang, who was happy for me to proceed with the research using the BIS monitor stored in his office. He also directed me to liaise with a research nurse (S.) who was involved in another project with him. She was able to demonstrate the use the BIS monitor and to provide me with a number of the electrodes which were surplus to requirements, as the project she was involved in was no longer recruiting participants. When we tested the BIS monitor that Professor Wang had borrowed the machine failed to obtain a reading. The electrodes that S. had provided were out of date. Therefore, in order to determine whether the BIS monitor or the electrodes were faulty, we tested an electrode with a different BIS monitor to which S. had access. The second BIS monitor obtained a reading with an out of date electrode, indicating that the fault lay with the machine that Professor Wang had borrowed. Unfortunately, it was not possible to use the second machine for my data gathering, as this was the apparatus loaned by the manufacturer who had already refused permission for its use.

I also met with Dr. E. J. and had the opportunity to observe a thoracic operation. This dispelled my anxieties concerning witnessing operations, since I did not find the experience distressing.

However, I did realise that it was important to bear in mind the longer-term effects of witnessing major surgical procedures. These included rumination, intrusive thoughts and intrusive images. By reflecting on these experiences, I successfully process and contained their emotional impact upon me.

Dr E. J. facilitated my introduction to the surgical team with which I would be working. I was provided with an induction session by the matron in charge of the theatre, covering theatre procedures and protocols. Once these preliminaries had been completed, it was possible to begin the process of participant recruitment.

Dr E. J. identified potential participants, and either she or I attended their pre-operative clinic. It was important that I was not provided with any of the personal details of potential participants, so that they could not be identified before providing consent. Therefore Dr E. J. provided me with the date and time of the appointment, and the potential participant's initials.

Attendance at the clinics involved the negotiation of a potentially delicate situation. I was introduced by Dr. E. J. to a nurse (H.) whose fulltime role was patient assessment in this clinic. However, there was a regular turnover of the staff working in the clinic, so I would

frequently have to introduce myself for the first time and wait for H. to be available, in order to inform her that I wished to approach a particular patient with regard to participation in the research.

Consenting participants on the wards was a no less complex and delicate a process. On each day of recruitment and data gathering, it was necessary for me to wait until Dr E. J. had seen a particular patient, whilst at the same time preventing my presence from impeding the flow of activities in a busy ward environment. Dr E. J. would assess whether the patient was still willing to be involved in the research. If so, I would then consent them and complete the pre-operative questionnaires. This required tactful management, as patients were attending breast clinics on the same day as and prior to their operations. I had to ensure that participants were consented and questionnaires completed before the first operation, as I would not have time to return to the ward later.

The operating theatre was the third setting that I needed to manage successfully to collect data. This was especially sensitive as infection control protocols had to be taken into account, including which areas were considered sterile. As well as this, monitoring depth of anaesthesia in an operation required responsiveness to a number of different stakeholders. These included anaesthetists, surgeons, nurses, medical orderlies, and theatre matrons. If I collected data from two participants in one day, it usually took at least 10 hours to collect pre-operative data and monitor depth of anaesthesia, for both. A day collecting data could, therefore, be emotionally and physically exhausting and take a number of days to recover from. The BIS monitor that Professor Wang had borrowed was still unable to produce a reading from the electrodes. Therefore, Dr. E. J. agreed that we could use one of the hospital BIS monitors for the research. Another problem encountered

during data collection was that the out of date BIS electrodes sometimes had some difficulty in picking up a signal. However, the members of staff in the surgical team were able to provide a limited number BIS electrodes for use in the research.

An important consideration, in the data gathering process, was how to record data from the BIS monitor. A number of options were considered, including recording the score once every minute on the minute, recording the scores every few seconds and recording the range of scores observed each minute. Recording scores every few seconds allowed for any of these techniques to be used and so was the favoured approach. When Professor Wang returned to work part-time, I was able to discuss this point with him. He informed me that it should be possible to download data from the BIS monitor onto a USB stick, which would be a much less time consuming way of recording data. Unfortunately, the BIS monitor manual I had been supplied with had not corresponded with the model Professor Wang had borrowed, or that which Dr E. J. was able to acquire. As a result, I was unaware how to download the data until this point.

Participant recruitment was slowed by a number of factors. Initially, there were no patients on the operating list that were undergoing the target procedure. When patients were available recruitment was usually possible. Of 18 approached 12 were consented and included in the study. Two refused consent, one declined after discussion with her family, and the second due to recently having had a suspected stroke. One was not eligible for the study due to a diagnosis of bipolar disorder; another participant was not successfully consented as there was not sufficient time prior to the operation.

In order to gather data, a minimum of at least 8 hours was required per participant. This

included at least 5 hours on the day of the operation, and further time to attend pre-operative clinics and collecting data at three follow-up points. A number of additional hours were required to score the questionnaires and enter the data into the necessary spreadsheets.

Timing for follow-up of participants was agreed during the consent process. Sometimes participants did not react well to the anaesthetic and were not available the following day, and so questionnaires were administered two days after the operation. It was important to be sensitive to patients whilst conducting telephone questionnaires, and on one occasion I ended the interview as it seemed that the participant did not feel well, and, with her agreement, I called her back the following day.

One of my key reflections was that the study could potentially involve an important interaction between ethics and methodology. In order to detect an effect there needs to be sufficient variability in the independent variable. However, a crucial ethical issue impinged upon this statistical imperative. If, during the course of data collection, I observed the BIS number moving outside the recommended limits, I was ethically bound to inform the anaesthetist immediately. If the number rises above 60 then this indicates the patient's level of awareness may be too high to protect them adequately. Conversely, should the BIS number fall too far below 40 then this could also indicate that the patient might be at risk. In a number of the operations it was necessary to inform the anaesthetist that the BIS number had exceeded the agreed upper limit of 55. The anaesthetist normally responded by increasing the anaesthetic dose. There is a possibility that my ethically driven intervention could have affected anaesthetic practice in subsequent operations where I was present. This process might have acted to reduce the amount of variability in the

independent variable, i.e. the BIS number. In addition, the very fact that I was required to intervene when the BIS number went beyond acceptable limits, thereby prompting a response from the anaesthetist, might in itself have reduced the BIS number's variability. This could have profound effects on the study's ability to detect a relationship between depth of anaesthesia and post-operative pain.

On occasions, it was also necessary to inform the anaesthetist that the BIS number had dropped below the agreed lower cut off point of 30. However, it is possible to speculate that for psychological reasons some anaesthetists may be more willing to increase an anaesthetic dose to avoid a conscious traumatic experience for the patient, than to reduce an anaesthetic dose to avoid undue suppression of central nervous system function.

This type of interaction between ethical considerations and methodological requirements does become particularly salient in this research design. In this particular NHS Trust, BIS monitors are not routinely used in the surgical procedure studied. Rather, anaesthetists rely upon such indicators as sweating, tear production, heart rate and blood pressure in order to assess depth of anaesthesia. However, the relationship between these standard indicators and depth of anaesthesia has been questioned. Future research in this area will have to be aware of this dilemma.

It might be possible to measure this effect through the use of a control group and an experimental group. Pre- and post- scores would be collected for both groups, but in the control group no BIS monitoring would take place. If the presence of the monitor had the effect of suppressing variability, we might predict that the level of post-operative pain and anxiety would be higher in the control than in the experimental group, since the monitor

would not have been present in the control group.

Overall in the process of designing, organising and carrying out this research, I learned a great deal in a number of different areas. I gained valuable insights into the nature of the bureaucratic processes involved in applying for ethical approval, including the advisability of delaying the application until after input by local collaborators. I discovered the importance of the interaction between ethics and methodology, as regarded the blinding of the anaesthetist to the BIS score. This enhanced my understanding of the ways in which ethical issues can impact on research methodology. I also gained experience in managing the significant input of time and effort that was required to gather data for this project. This gave me a deeper understanding of the limitations inherent in a single-handed research project.

I feel that the lessons I have learned have given me invaluable experience, and equipped me with the skills to perform future reviews of literature and to carry out demanding research in support of my role as a clinical psychologist.

Appendix A

Position of the Researcher

The researcher takes a positivist position for the purposes of this research, in that constructs such as anxiety, pain, and pain locus of control are construed as real entities that can be measured by the use of questionnaires. The trainee has worked in a health psychology role as an assistant psychologist and has facilitated pain management programs. In this role, the trainee first encountered patients who had unexplained post-operative pain, including complex regional pain syndrome and persistent pain following surgery for breast cancer. This was followed by a first year placement in medical psychology. During teaching the trainee encountered the concept of implicit trauma caused by intra-operative wakefulness. The consequences of implicit trauma are thought to involve nightmares, anxiety and panic upon falling asleep. However, no mention was made of pain resulting from implicit trauma. Pain gate theory holds that a pain experience can sensitise the pain system to future experiences of pain and so it was theorised that pain experienced during an episode of intra-operative wakefulness could lead to an increased pain experience post-operatively. Lightly anaesthetised patients might also experience increased post-operative anxiety, which could in turn contribute to post-operative pain.

Appendix B

Chronology of research process

Date	Notes
11/2010-04/2011	Selection of research topic in discussion with Professor Wang and course staff
06/04/2011-16/05/2011	Liaising with Professor Wang's contacts as to study design and selection of target operation (mastectomy)
05/2011 – 07/2011	Development of initial internally reviewed project proposal, including selection of questionnaires and EEG method of depth of anaesthesia monitoring
07/2011 – 08/2011	Amendments to project proposal suggested by course staff
09/2011 – 01/2012	Development of detailed project proposal and completion of IRAS form for Ethics committee submission
03/11/2011	Recruitment of local consultant anaesthetist into the study (Dr EJ)
03/02/2012	Meeting with surgeons to discuss involvement in project
08/02/2012 – 27/02/2012	Seeking permission from Dr JT to access NHS patients for the purposes of research
20/02/2012	Meeting with Dr EJ and surgeon (Mr JK) surgery type changed to lumpectomy (wide local excision of breast tissue for breast cancer)
15/03/2012 -04/2012	Initial Ethics Committee meeting, minor changes suggested, however, ethical approval not given due to change in operation selection from mastectomy to wide local excision
05/2012-05/2012	Amendment of project proposal and resubmission to Ethics Committee
12/06/2012-18/06/2012	Second Ethics Committee meeting with ethical approval not granted
06/2012-08/2012	Work on Amendments to project proposal and third submission to ethics committee
16/08/2012-23/08/2012	Third ethics committee meeting – ethical approval granted
07/09/2012-21/12/2012	Research and development application – amendments to research and development application – Research and Development approval granted
09/2012	Manufacturer of BIS does not give approval for use of machines already on loan to Professor Wang in use of the study
10/2012	Good Clinical Practice certification – Professor Wang arranges to borrow a BIS monitor from a colleague
01/2013	Professor Wang on sick leave
04/02/2013-11/07/2013	Data collection
07/2013-09/2013	Write up of thesis

Appendix C

European Journal of Pain Author Guidelines

http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1532-2149/homepage

Appendix D

Participant Information Sheet and Consent Form

University of Leicester

Dept. Clinical Psychology

104 Regent Road
Leicester
LE1 7LT
T: 0116 223 1639
F: 0116 223 1650

Participation Information Sheet

Study title

'An examination of the impact of depth of anaesthesia on post-operative pain following wide local excision of breast tissue for breast cancer'.

Researcher: Peter Beardsworth, Clinical Psychologist Trainee, University of Leicester

We would like to invite you to take part in our research study. Before you decide we would like you to understand why the research is being done and what it would involve for you. ***One of our team will go through the information sheet with you and answer any questions you have.*** *We suggest this should take about 5 minutes.*
Please feel free to talk to others about the study if you wish.
(Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about the conduct of the study).
Please ask us if there is anything that is not clear

What is the purpose of the study?
This study is to find out what things can increase pain after wide local excision of breast tissue for breast cancer. Specifically the research will look at whether depth of anaesthesia influences post-operative pain. Previous research has indicated that there may be a link between lighter anaesthesia and increased pain immediately after the operation. The findings of the study could have implications for the treatment and prevention of post-operative pain. The study may also be published in appropriate journals.

Why have I been invited?
All those invited to participate are undergoing wide local excision of breast tissue for breast cancer surgery. Members of the surgical team are collaborating in the study and have identified that you might be eligible to take part. This study aims to recruit around 100 participants.

Do I have to take part?

It is up to you to decide to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What will happen to me if I take part?
You will be asked to fill in 4 questionnaires before your operation, which will give us an idea of your levels of anxiety, levels of pre-operative pain, what your views of pain are and any concerns you have about body image. These questionnaires will also be completed 1-2 days following the operation. You will be asked to complete the questionnaires again at 6 weeks and 3 months; these follow ups can be completed by post or telephone. It will take about 15 minutes each time you complete the questionnaires. During the operation the researcher will use an EEG machine to measure your brain wave activity with an electrode attached to your forehead with a sticky pad. This will be used to measure the depth of your anaesthesia during the operation. Your participation with the study will end when you have completed the questionnaires at 3 months. Other than the completion of the questionnaires and the monitoring that occurs during the operation there will be no changes made to the care you receive. In particular, taking part in the research will make no difference to the anaesthetic you receive or how deeply anaesthetised you will be.

What will I have to do?
If you agree to take part in the study you will be required to complete all of the questionnaires at all the measurement points. This can be done at a follow up clinic or via post or telephone. By agreeing to take part you agree that the researcher can contact you via post or telephone at the follow-up points.

What are the possible disadvantages and risks of taking part?
No major risks have been identified for taking part in this study. However, if the data that have been gathered indicate that you are suffering from significant post-operative pain or anxiety then it will be suggested that you contact your G.P. who can put you in touch with appropriate services that may be able to support you. If appropriate we may suggest you inform your surgeon who can also refer you to specialist services if necessary.

What are the possible benefits of taking part?
We cannot promise the study will help you but the information we get from this study may help improve the treatment of people with long lasting post-operative pain.

What happens when the research study stops?
No further action will be required from you once the study stops. However, you can request a summary of the research findings once it is completed.

What if there is a problem?
Any complaint about the way you have been dealt with during the study will be addressed. The detailed information on this is given in Part 2.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2

This completes part 1.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

Part 2 of the information sheet

What if relevant new information becomes available?
The study does not involve any modification to the treatment that you will receive so it is not anticipated that new information about the study will become available that brings into question your further involvement. However if it is determined that you can no longer consent to be involved in the study then no more data will be collected.

What will happen if I don't want to carry on with the study?
You can withdraw from the study at any time, without giving a reason, by informing the researcher or one of your care team who is involved with the project. If you decide to withdraw from the study after initially agreeing then any data that has already been collected will be destroyed and not used in the study. Once you have withdrawn from the study there will be no further follow up or contact from the researcher.

What if there is a problem?
If you have any concerns or complaints about your involvement with the study then the researcher and others in your care team will do their best to resolve the problem with you. If that is not possible or appropriate then your complaint will be referred to the University Hospitals of Leicester Complaints Department.

Complaints
If you have a concern about any aspect of this study, you should ask to speak to the researcher, who will do his best to answer your questions, on 0116 223 1649. If you remain unhappy and wish to complain formally, you can do this by submitting a formal complaint to the University Hospitals of Leicester Patient Advice and Liaison Department (see contact details below).

Further information and contact details
For further information you can contact the researcher, Peter Beardsworth, on 0116 2231649. This project is supervised by Professor M. Wang (Tel: 0116 223 1648). If you require any impartial support or advice about your participation in this research then you can contact the Patient Advice and Liaison Service:

Patient Advice & Liaison Service
University Hospital of Leicester
Gwendolen House
Gwendolen Road
Leicester
Leicestershire

LE5 4QF

Telephone: 08081788337

Email: pils.complaints.compliments@uhl-tr.nhs.uk

Harm

Although your care will not be altered by your involvement in the study and it is therefore not anticipated that participants are at risk of any harm, if you are caused harm by the study then you will be eligible to compensation as the study is covered by The NHS Litigation Authority Liabilities to Third Parties Scheme (LTPS).

NHS based research

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against Leicester Partnership Trust or University Hospitals of Leicester but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

Will my taking part in this study be kept confidential?

Data collected from you in the study will only be identifiable through a unique identification number. During the course of the study the identification number will be kept on an index with your personal details. This will enable the researcher to link the data each time you complete the questionnaires. Once all the data are collected the index will be destroyed and the data will only be identifiable by the identification number. The data and the index will be stored in a lockable filing cabinet in a locked room at the University of Leicester. The data may be used in future research studies. Only authorised persons will have access to the data including; researchers, sponsors, and regulatory authorities. The data will be stored securely for 5 years and then destroyed.

Involvement of the General Practitioner

We will be informing your G.P. of your involvement in the study.

What will happen to the results of the research study?

The results of the research study will be used by the researcher to produce a Thesis for Doctorate in Clinical Psychology at the University of Leicester. The results will also be used to submit papers to suitable peer reviewed journals. Findings from the study will be made available to the site of the study (Glenfield Hospital). Research findings may also be presented at relevant conferences. Participants will be able to request a summary of the research findings. None of the participants will be identified in any of the reports.

Who is organising and funding the research?

The research is being funded by the University of Leicester and is sponsored by Leicestershire Partnership Trust.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by Northampton Research Ethics Committee.

University of Leicester

Ethics Number:
Participant Identification Number:…..

CONSENT FORM

Title of Project: 'An examination of the impact of depth of anaesthesia on post-operative pain following wide local excision of breast tissue for breast cancer'

Name of Researcher: Peter Beardsworth, Clinical Psychologist Trainee, University of Leicester

Thank you for agreeing to take part in this research project. Please read this consent form, and ask any further questions you would like to about what will be involved. When you are ready please initial all of the boxes, sign and date the consent form.

Consent Statement

1. I confirm that I have read and understand the information sheet dated _____ for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.
2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason.
3. I understand that I will complete a series of assessment questionnaires before the operation, 1-2 days post-operatively, at 6 weeks post operatively and 3 months post-operatively and that these questionnaires may be administered by telephone if necessary and collected in person or returned by post where appropriate.
4. I understand that my depth of anaesthesia during the operation will be monitored using an EEG (electrodes used to measure the electrical activity of the brain).
5. I understand that at the 3 month follow up point my data will be rendered anonymous so I cannot be identified.
6. I understand that if there is any concern about my post-operative progress then the researcher may suggest speaking to my G.P. about appropriate services to aid me in recovery.
7. I understand that data from the interview will be kept securely at the University of Leicester, and destroyed after five years.

8. I understand that my data will be included as part of a Doctoral thesis, and that results may be published in academic journals, presented at conferences, and fed back to Participants and services.

9. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records

10. I agree to take part in this study.

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Appendix E

Letters from ethics committees

NRES Committee East Midlands - Northampton
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS
Telephone: 0115 8839425
Facsimile: 0115 8839294

26 March 2012
Mr Peter Douglas Beardsworth
Clinical Psychologist in Training
Leicestershire Partnership Trust
104 Regent Road
Leicester
LE1 7LT

Dear Mr Beardsworth, **Study title:** **An examination of the impact of depth of anaesthesia on post-operative mastectomy pain**

REC reference: **12/EM/0097**
Protocol number: **N/A**

The Research Ethics Committee reviewed the above application at the meeting held on 15 March 2012. Thank you for attending to discuss the study.

Ethical opinion

The members of the Committee present decided that it was unable to give a favourable ethical opinion of the research, for the following reasons:

- The committee queried why the anonymised data would not be analysed until 3 months after the study is completed. You stated that the data will be stored in a secure place and once the data is anonymised it will not be identifiable.

- The committee asked you why the demographic data would need to be collected as it is only the participant's age that is required for analysis purposes. You confirmed that the other factors are relevant as the will be used for potential future research.

- The committee asked you to clarify what will happen with data that is withdrawn as there are inconsistencies. You stated that in the case of data being withdrawn this would be due to if the researcher was to loose capacity during the study. The committee went on to say that this should be included in the Participant Information Sheet.

- The committee queried whether Dr Jonck should look at standardizing any pre medication as some participants may already be on pain relief, and that the analgesia needs to be specified more clearly. You stated that if they were to standardise the anesthetic then there would not be much of a range, and they do not see this as problematic.

• The committee asked you whether monitoring the BIS score at the top end of 65 is possibly too high and should be considered to look at the score at a much lower range, as this may have safety implications for the participants. You stated that they will discuss this with the anesthetist.

• The committee asked you whether they have considered taking consent from the anesthetist. You confirmed that this would be done within the hospitals policy but did not think that taking informed consent would be necessary as this is already covered.

• The committee stated that the exclusion criteria does not include men and that this could be misleading to participants. You stated that they have recent meetings with the surgeon and that they have decided to change the procedure to a lumpectomy.

• The committee asked you whether the participants would be comfortable knowing that the anesthetist will know their BIS score. You stated that the participants do have the choice of whether or not they would like to part in the study.

• The committee asked you to clarify when participants would receive the Participant Information Sheet and the Invitation. You confirmed that the participants would receive these 2 weeks before giving consent.

• The committee stated that the Participant Information Sheet is lacking information and should be in the NRES standard format. You stated that they would amend this.

• When the Committee queried the exclusion criteria the researcher informed the committee that following a recent meeting with the surgeon they have decided to change the procedure from mastectomy to lumpectomy. The Committee agreed that the study should be resubmitted to be relevant to the procedure lumpectomy as the Application Form and supporting documents that were submitted for review was for the procedure mastectomy.

I regret to inform you therefore that the application is not approved.
If you would find it helpful to discuss any of the matters raised above or seek further clarification from the Committee Co-ordinator, you are welcome to contact Miss Jessica Parfrement on 0115 8839425.
Options for further ethical review
You may submit a new application for ethical review, taking into account the Committee's concerns. You should enter details of this application on the application form and include a copy of this letter, together with a covering letter explaining what changes have been made from the previous application. We strongly recommend that you submit the new application to this REC. However, you may submit the application to a different REC if you prefer. Alternatively, you may appeal against the decision of the Committee by seeking a second opinion on this application from another Research Ethics Committee. The appeal would be based on the application form and supporting documentation reviewed by this Committee, without amendment. If you wish to appeal, you should notify the relevant Research Ethics Service manager (see below) in writing within 90 days of the date of this letter. If the appeal is allowed, another REC will be appointed to give a second opinion within 60 days and the second REC will be provided with a copy of the application, together with this letter and other relevant correspondence on the application. You will be notified of the

arrangements for the meeting of the second REC and will be able to attend and/or make written representations if you wish to do so. The contact point for appeals is:
Joan Kirkbride
Tel: 01325 746167
Mobile: 07979 806425
Email: joan.kirkbride@nres.npsa.nhs.uk

Documents reviewed

Membership of the Committee

The documents reviewed at the meeting were: *Document*	*Version*	*Date*
Investigator CV		05 February 2012
Letter from Statistician		08 February 2012
Letter of invitation to participant	1	05 February 2012
Other: Academic Supervisor CV		
Other: Letter from Funder		31 January 2012
Participant Consent Form	1	05 February 2012
Participant Information Sheet	1	05 February 2012
Protocol	1	05 February 2012
Questionnaire: Short Form McGill pain Questionnaire		
Questionnaire: Self-Evaluated Questionnaire		
Questionnaire: Pain Locus of Control Questionnaire		
Questionnaire: Numerical Rating Scale 101		
Questionnaire: Pre-operative body image screening question	1	05 February 2012
Questionnaire: Post-operative body image screening question	1	05 February 2012
REC application		15 February 2012
Referees or other scientific critique report		06 February 2012

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

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees 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

Here you will find links to the following:
a) Providing feedback. You are invited to give your view of the service 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
b) Re-submission/Appeal.

12/EM/0097 Please quote this number on all correspondence

Yours sincerely

Mr Ken Willis
Chair

Email:
jessica.parfrement@nottspct.nhs.uk
Enclosures:

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

NRES Committee East Midlands - Northampton
Attendance at Committee meeting on 15 March 2012

Committee Members: *Name*	*Profession*	*Present*	*Notes*
Mr John Aldridge	Senior Lecturer in Nursing	Yes	
Dr Timothy Bedford	Consultant Anaesthetist	Yes	
Ms Elaine Blackshaw	Clinical Trial Manager	Yes	
Mr Derek Butters	Industrial Pharmacy Consultant and Locum Pharmacist	Yes	
Mr Alan Caswell	Lay Member	Yes	
Mrs Lorenza Francescut	Research Technician	Yes	
Mrs Yael Vinciguerra	Lay Member	Yes	
Mr Clive Wilkinson	Lay Member	Yes	
Mr Ken Willis	Medical Devices Manager	Yes	

NHS
Health Research Authority

NRES Committee East Midlands - Nottingham 1
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Telephone: 0115 8839436
Facsimile: 0115 8839924

18 June 2012

Mr Peter Douglas Beardsworth
Clinical Psychologist in Training
Leicestershire Partnership Trust
104 Regent Road
Leicester
LE1 7LT

Dear Mr Beardsworth

Study title:	**An examination of the impact of depth of anaesthesia on post-operative lumpectomy pain**
REC reference:	**12/EM/0213**
Protocol number:	**N/A**

The Research Ethics Committee reviewed the above application at the meeting held on 12 June 2012. Thank you for attending to discuss the study.

Ethical opinion

- You were asked how participants would be identified. You confirmed the anaesthetist would identify participants who might be eligible to participate in the study. The Anaesthetist will then ask the potential participant whether the student can approach them to discuss the study.
- The Committee asked you whether the anaesthetist would be present when consent was given. You confirmed that you would be as it could cause some anxiety and the anaesthetist would be better placed to answer questions.
- The Committee asked when Participants would be approached. You confirmed it would be in the follow up clinic which is usually 2 weeks before surgery.
- The Committee asked you if there is only one Anaesthetist working on the study. You confirmed that at present there is only one but you are looking to recruit others.
- You were asked about depth of anaesthesia. You explained that it is not as straight forwarded as the deeper the better. It needs to be deep enough to prevent post operative pain but too deep can have side effects for the patient. The patient should not be able to recall surgery and drugs are given to prevent recall. The current discussion surrounds whether the patient should be unconscious or unable to recall.
- The Committee queried whether the same anaesthetist would produce the same level anaesthesia which they are comfortable with. You explained that currently depth of anaesthesia is not currently measured using a BIS so it is hoped there will be some variability within the results.
- You were asked why you are using the Median for his results. The Committee were concerned that results may be clustered around a certain point affecting your results. You advised if that was the case you would seek advice from a Statistician to ensure the results make sense.

- The Committee advised you the Participant Information Sheet is too vague and needs to give more background regarding the issues relating to depth of anaesthesia and post operative pain. The Committee explained to you the Participant is essentially in the dark as to the risk factors surrounding depth of anaesthesia.
- The Committee asked you whether high anxiety level results will be shown due to the surgery. You explained you would expect some to have a high score but hoped there would be some variability.
- You explained to the Committee you were from a pain background and had experienced people with post operative pain following Mastectomy. Following discussions with his Supervisor and a Colleague you had decided to look at the Lumpectomy cohort.
- The Committee asked you which patients would be included. You advised it would be those undergoing lumpectomy. The Committee asked whether the name of the procedure would be consistent as local surgeons can often give different names for the same procedure. You accepted the point that it may cause some confusion to Patients.
- The Committee explained to you that patients may interpret the use of the term Chronic in the Participant Information Sheet as meaning really bad rather than "long lasting". You were advised to consider rewording the section.
- The Committee advised you it was not clear what types of aesthetic were being used.
- The Committee explained to you your terminology is inconsistent throughout the papers and there are still references to Mastectomy which should have been removed.
- The Committee informed you that participants may not understand the term Battery of Assessments.
- The Committee asked you if you had measured how long it would take to complete the Assessments. You advised you had not, The Committee asked whether there was sufficient time for the Participants to complete the Tests prior to surgery and was it fair to ask them to do so. The Committee advised you that you need to be upfront with the Participant as to what they are being asked to do and how long it will take.
- You were asked what you would do if the Participant showed signs of not wanting to participate any further. You explained if the participant showed any signs of distress you would not continue any further.
- The Committee asked you who would read the BIS and how much time would it take. You explained that it would be done by yourself. It involves attaching a pad to the forehead and as such only takes moments to do.
- You were asked whether the 10 minutes allowed to complete questionnaires was based upon experience. You advised in your experience most people could complete them in 10 minutes but some people may take longer.
- The Committee asked whether the Body image questionnaire was a validated questionnaire. You advised it wasn't. You explained the issue of body image had been picked up by your peer review and the questionnaire was devised in response to it as a lot of patients in this group have concerns over body image.
- The Committee advised you the Title of the Participant Information Sheet and Consent Form should match.

The members of the Committee present decided that it was unable to give a favourable ethical opinion of the research, for the following reasons:

- You need to define the patient group including the variables and how they would be measured.
- The procedure to obtain consent needs to outlined in detail as to how consent will be gained and by who. You should consider if it is appropriate for the Researcher to obtain consent.

- It is not clear whether the Anesthetists have been provided with a Participant Information sheet and whether they know what is involved.
- The Participant Information Sheet needs to be more specific and should spell out the correlation between depth of anesthesia and post operative pain.
- The Participant Information sheet needs to be clear as to what is expected of them and how long it is expected to take.
- The term Chronic Pain needs to be explained in lay language in the Participant Information sheet.
- You need to provide information as to how 'low' and 'high' levels of anesthesia are defined.
- You should provide detailed information as to the types of anesthesia used with correct definitions. The purpose of a muscle relaxant is not to prevent patients moving.
- Participants who develop post operative pain need to be properly signposted to specialist help and not to their GP who may not be able to provide any specialist advice regarding chronic pain.
- It is not clear when the Battery of Assessments will be completed and whether it is appropriate to complete them on the day of surgery.
- A coherent time line should be produced with the help of the clinical team as to what will happen when and how long it will take.
- You should address what would happen if a participant showed a high level of anxiety after completing the questionnaires prior to surgery.
- The Title of the Participant Information Sheet and Consent Form should match

I regret to inform you therefore that the application is not approved.

If you would find it helpful to discuss any of the matters raised above or seek further clarification from a member of the Committee, you are welcome to contact the Coordinator Andrea Graham
Options for further ethical review

You may submit a new application for ethical review, taking into account the Committee's concerns. You should enter details of this application on the application form and include a copy of this letter, together with a covering letter explaining what changes have been made from the previous application. We strongly recommend that you submit the new application to this REC. However, you may submit the application to a different REC if you prefer.

Alternatively, you may appeal against the decision of the Committee by seeking a second opinion on this application from another Research Ethics Committee. The appeal would be based on the application form and supporting documentation reviewed by this Committee, without amendment. If you wish to appeal, you should notify the relevant Research Ethics Service manager (see below) in writing within 90 days of the date of this letter. If the appeal is allowed, another REC will be appointed to give a second opinion within 60 days and the second REC will be provided with a copy of the application, together with this letter and other relevant correspondence on the application. You will be notified of the arrangements for the meeting of the second REC and will be able to attend and/or make written representations if you wish to do so.

The contact point for appeals is:

Joan Kirkbride
Head of Operations
National Research Ethics Service
C/o Janet Kelly

Darlington Primary Care Trust
Dr. Piper House
King Street
Darlington
Co. Durham
DL3 6JL

Tel: 01325 746167
Mobile: 07979 806425
Email: joan.kirkbride@nres.npsa.nhs.uk

Documents reviewed

The documents reviewed at the meeting were:

Document	*Version*	*Date*
Covering Letter		
Investigator CV	Mr Peter Beardsworth	06 May 2012
Letter from Sponsor	University of Leicester	
Letter from Statistician	Dr Eric D Gardiner	08 February 2012
Letter of invitation to participant	2	06 May 2012
Other: CV	Professor M Wang	
Other: Letter form Northampton REC committee		26 March 2012
Participant Consent Form	2	06 May 2012
Participant Information Sheet	2	06 May 2012
Protocol	2	06 May 2012
Questionnaire: Short Form McGill Pain Questionnaire		
Questionnaire: Self Evaluation Questionnaire		
Questionnaire: Pain locus of Control Scale - C Form		
Questionnaire: Post Operative body Image Screening question	2	06 May 2012
Questionnaire: Pre operative body image screening question	2	06 May 2012
Questionnaire: Numerical Rating Scale for Pain	1	05 February 2012
REC application	96523/322057/1/304	09 May 2012
Referees or other scientific critique report	University of Leicester	02 December 2011

Membership of the Committee

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

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees 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

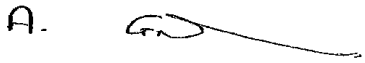
Ethics Service website > After Review

Here you will find links to the following:

a) Providing feedback. You are invited to give your view of the service 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
b) Re-submission/Appeal.

12/EM/0213	Please quote this number on all correspondence

Yours sincerely



Mr Robert Johnson
Chair

Email: Andrea.Graham@nottspct.nhs.uk

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

Copy to: *Mr David Clarke*

NRES Committee East Midlands - Nottingham 1

Attendance at Committee meeting on 12 June 2012

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Walter Bouman	Consultant Psychiatrist	Yes	
Dr Glenys Caswell	Research Fellow	Yes	
Professor Cris Constantinescu	Professor of Neurology	Yes	
Ms Helen Crow	Research Midwife	No	
Dr Ursula Holdsworth	Retired Staff Grade Community Paediatrician	Yes	
Mr Robert Johnson	Expert member	Yes	Chair
Reverend Keith Lackenby	Lay member	Yes	
Mrs Sarah Lennon	Expert member	Yes	
Mr Jon Merrills	Barrister / Pharmacist	No	
Mr Robert Oldroyd	Lay member	Yes	
Dr Noble Philips	General Practitioner	Yes	
Dr Ian Ross	Consultant Physician	Yes	
Mr Ian Thompson	Lay member	No	
Mrs Shirley E White	Lay member	No	

Also in attendance:

Name	*Position (or reason for attending)*
Miss Andrea Graham	REC Coordinator

NHS
Health Research Authority

NRES Committee East Midlands - Northampton
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Telephone: 0115 8839435
Facsimile: 0115 8839294

23 August 2012

Mr Peter Douglas Beardsworth
Clinical Psychologist in Training
Leicestershire Partnership NHS Trust
104 Regent Road
Leicester
LE1 7LT

Dear Mr Beardsworth

Study Title:	**An examination of the impact of depth of anaesthesia on post-operative pain following wide local excision of breast tissue for breast cancer**
REC reference:	**12/EM/0289**
Protocol number:	**N/A**

The Research Ethics Committee reviewed the above application at the meeting held on 16 August 2012. Thank you for attending to discuss the study.

Documents reviewed

The documents reviewed at the meeting were:

Document	*Version*	*Date*
Covering Letter		
Investigator CV		05 February 2012
Letter from Statistician		08 February 2012
Letter of invitation to participant	3	04 July 2012
Other: CV - Professor Wang		
Other: Letter from the funder		30 January 2012
Participant Consent Form	3	04 July 2012
Participant Information Sheet	3	04 July 2012
Protocol	4	04 July 2012
Questionnaire: Numerical scale for pain	1	05 February 2012
Questionnaire: Pain loss of control scale		
Questionnaire: Self Evaluation		
Questionnaire: Short Form McGill Pain		
Questionnaire: Pre-operative body image screening	3	04 July 2012
Questionnaire: Body image screening	3	04 July 2012
REC application	96523/343944/1/233	12 July 2012
Referees or other scientific critique report		02 December 2011

Provisional opinion

- The Committee noted that the BIS score at which you would inform the anaesthetist was still stated as 60 and asked why this hadn't been lowered to 55 as suggested in the previous unfavourable opinion letter. You explained that the previous score at which they had stated they would inform the anaesthetist was in fact 65 and that as requested you had lowered this to the 60 now stated in the current application. The Committee agreed if this was the case that was fine and would check this with the anaesthetist that was present at the Committee meeting when the study was reviewed first. You went on to explain that you had also involved another anaesthetist in the design of the study this time round and that they had also advised 60, but were happy to lower this to 55 if the committee felt it was necessary.

- The Committee suggested that your involve GP's from the start of the study if the were planning to refer participants in distress back to their GP's. You agreed that this could be done.

- The Committee asked you if participants would understand the term 'wide local excision' and queried whether you should use a simpler term. You explained that you had checked what term would be used in normal care and that this was fully understood and therefore had made this consistent across all study documents.

- The Committee asked you whether the depth of anaesthesia would vary enough between participants to make the study worthwhile. You explained that you would use more than one anaesthetist and that different anaesthetists used different techniques. You went on to add that participants would react differently to anaesthetic and were therefore confident there would be enough variation.

The Committee is unable to give an ethical opinion on the basis of the information and documentation received so far. Before confirming its opinion, the Committee requests that you provide the further information set out below.

1. Please replace the word 'battery' with 'series' in point 3 of the Consent Form.

2. Please include PALS details and an external contact within the Participant Information Sheet.

3. Please include contact details within the complaint section found in Part 2 of the Participant Information Sheet.

4. Please amend the committee name in the Participant Information Sheet to Northampton Research Ethics Committee.

5. Please provide a letter for contact to the GP informing them of their patient's participation in the study.

The Committee delegated authority to confirm its final opinion on the application to the Chair.

Further information or clarification required

If you would find it helpful to discuss any of the matters raised above or seek further clarification from a member of the Committee, you are welcome to contact the Committee Coordinator.

When submitting your response to the Committee, please send revised documentation where appropriate underlining or otherwise highlighting the changes you have made and giving revised version numbers and dates.

If the committee has asked for clarification or changes to any answers given in the application form, please do not submit a revised copy of the application form; these can be addressed in a covering letter to the REC.

The Committee will confirm the final ethical opinion within a maximum of 60 days from the date of initial receipt of the application, excluding the time taken by you to respond fully to the above points. A response should be submitted by no later than 21 December 2012.

Membership of the Committee

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

Statement of compliance

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

12/EM/0289	**Please quote this number on all correspondence**

Yours sincerely

pp.

Mr Paul Hamilton
Chair

Email: georgia.copeland@nottspct.nhs.uk

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

Copy to: *Dr David Clarke, Leicestershire Partnership NHS Trust*

NRES Committee East Midlands - Northampton

Attendance at Committee meeting on 16 August 2012

Committee Members:

Name	*Profession*	*Present*	*Notes*
Ms Elaine Blackshaw	Clinical Trial Manager	Yes	
Mr Alan Caswell	Lay Member	Yes	
Mr Chris Foy	Medical Statistician	Yes	
Mrs Lorenza Francescut	Research Technician	Yes	
Mr Paul Hamilton	Retired Local Government Officer	Yes	
Mr Mike Wakeman	Expert Member	Yes	
Mr Clive Wilkinson	Lay Member	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Miss Georgia Copeland	Assistant Committee Co-ordinator

Appendix F

Data Extraction Form

Title of Paper:

Year published:

Journal:

Volume:

Pages:

Authors:

Abstract:

Relevance to lit review:

Findings:

Critical analysis:

Appendix G

Quality Assessment Tools

Strengthening the Reporting of Observational Studies in Epidemiology

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

(Vandenbroucke *et al.,* 2007)

Quality Assessment Check list (Ip *et al.,* 2009)

Appendix H

STROBE and Quality Assessment Checklist scores

	STROBE checklist scores																	
	Title & Abstract		Introduction		Method													
Question	1		2	3	4	5	6		7	8	9	10	11	12				
Study	a	b					a	b						a	b	c	d	e
1	2	2	2	2	2	2	2	na	2	2	1	0	2	2	na	0	1	0
2	2	2	2	2	2	1	2	na	1	2	0	0	2	2	na	2	2	0
3	2	2	2	2	2	1	2	na	1	2	1	0	1	2	na	0	0	1
4	2	2	1	1	2	1	2	na	1	2	1	0	2	2	na	2	2	0
5	2	2	1	2	2	1	2	na	1	2	0	0	2	2	na	2	2	2
6	2	2	2	2	2	1	2	na	2	2	0	0	2	2	na	0	0	0
7	2	2	2	2	2	1	2	na	1	2	1	1	2	2	2	0	0	0
8	2	2	2	2	2	2	2	na	2	2	0	0	1	2	2	0	0	0
9	2	2	2	2	2	1	2	na	2	2	0	0	2	2	na	0	na	0
10	2	2	2	1	2	2	2	na	1	2	1	2	2	2	na	0	0	0
11	2	2	2	1	2	2	1	na	1	2	0	0	2	2	na	2	2	2

	Results											Dicussion							
Question	13			14			15	16			17	18	19	20	21	22	Score	Total Relevant Questions	STROBE %
Study	a	b	c	a	b	c		a	b	C									
1	2	2	2	1	0	1	2	1	2	0	0	2	1	2	0	0	42	32	65.63%
2	2	2	0	2	2	2	2	2	2	0	2	2	2	2	1	0	49	32	76.56%
3	2	2	1	1	0	1	2	2	na	0	2	2	2	2	2	1	43	31	69.35%
4	2	2	0	2	2	2	2	2	2	0	0	2	1	2	2	0	46	32	71.88%
5	2	2	0	2	2	1	2	2	2	0	2	2	1	2	2	1	50	32	78.13%
6	2	0	na	1	2	1	2	0	2	0	0	2	1	2	2	2	40	31	64.52%
7	0	0	0	2	0	1	1	2	na	0	2	2	2	2	1	0	39	32	60.94%
8	2	2	1	2	2	2	0	2	1	0	2	2	1	2	2	0	46	33	69.70%
9	1	na	na	2	0	1	0	1	1	0	2	2	1	2	2	2	38	29	65.52%
10	2	2	1	2	1	1	2	2	2	0	2	2	1	2	2	2	49	32	76.56%
11	2	1	0	2	2	2	2	2	na	0	2	2	2	2	2	2	50	31	80.65%

Quality Assessment Checklist																					STROBE & Quality Assessment Checklist Total score	STROBE & Quality Assessment Total Relevant questions	STROBE & Quality Assessment Overall %
Question	1					2			3					4					Score	Total relevant questions	Quality assessment Checklist %			
Study	a	b	c	d	e	a	b	c	a	b	c	d	e	a	b	c	d	e					
1	2	2	2	2	1	2	2	2	2	2	2	2	1	2	2	0	0	0	15	11	68.18%	57	43	66.28%
2	2	2	2	0	2	2	2	2	2	1	0	2	0	2	0	0	0	0	8	11	36.36%	57	43	66.28%
3	2	2	0	0	1	2	2	2	2	1	0	2	0	2	2	0	0	0	8	11	36.36%	51	42	60.71%
4	2	1	2	1	2	2	2	2	2	1	0	2	0	2	0	0	1	0	10	11	45.45%	56	43	65.12%
5	2	2	2	2	2	2	2	2	2	1	0	2	1	0	2	0	0	0	11	11	50.00%	61	43	70.93%
6	2	2	2	2	1	2	2	1	2	2	0	2	1	2	2	0	0	0	12	11	54.55%	52	42	61.90%
7	2	2	0	0	2	2	2	1	2	1	0	1	0	0	1	0	0	0	3	11	13.64%	42	43	48.84%
8	2	2	0	2	2	2	2	2	2	2	0	2	0	0	2	0	0	0	8	11	36.36%	54	44	61.36%
9	2	2	0	0	2	2	2	2	2	2	1	1	0	0	2	0	0	0	6	11	27.27%	44	40	55.00%
10	2	1	2	1	2	2	2	2	2	1	2	2	2	0	2	0	0	2	15	11	68.18%	64	43	74.42%
11	1	1	0	2	2	2	2	2	2	1	0	2	0	2	2	0	0	0	10	11	45.45%	60	42	71.43%

Questions covered by STROBE and so not counted in Quality Assessment Checklist score

Appendix I
Copies of Questionnaires

Short-Form McGill Pain Questionnaire (SF-MPQ)

www.mapi-trust.org/questionnaires/61

State Trait Anxiety Inventory State and Trait versions (STAI-Y1 and STAI-Y2)

www.mindgarden.com/products/staid.htm

Pain Locus of Control Questionnaire (PLOCQ) using the Health Locus of Control Questionnaire Form C

www.nursing.vanderbilt.edu/faculty/kwallston/mhlcformc.htm

Pre-operative body image screening question

Participant name: _____

Date: _____ Identifying number: _____

Measurement: Pre/Post 1/Post 2/Post 3 (circle)

How much do you feel having a wide local excision of breast tissue for breast cancer will impact on how you see yourself as a woman?

Not at all Could not be worse

0 1 2 3 4 5 6 7 8 9 10

Post-operative body image screening question

Participant name: _____

Date: _____ Identifying number: _____

Measurement: Pre/Post 1/Post 2/Post 3 (circle)

How much do you feel having a wide local excision of breast tissue for breast cancer has impacted on how you see yourself as a woman?

Not at all Could not be worse

0 1 2 3 4 5 6 7 8 9 10

Appendix J

Scoring Procedures for Questionnaires

Scoring procedure for MPQ-SF

www.mapi-trust.org/questionnaires/61

Scoring Instructions for the Pain Locus of Control Questionnaire (Form C) Scales

www.nursing.vanderbilt.edu/faculty/kwallston/scoringhlc.htm

Scoring Instructions for the State-Trait Anxiety Inventory

www.mindgarden.com/products/staid.htm

Appendix K
Raw data

Participant Number	Age	MPQSF PRE	Pain Intensity PRE	PPI PRE	MPQSF POST1	Pain Intensity POST1	PPI POST1	MPQSF POST 6 Weeks	PIPOST 6 Weeks
1	68	4	32	1	1	7	1	0	0
2	30	7	15	1	15	45	2	10	30
3	84	2	44	0	8	5	0	0	0
4	68	0	0	1	0	0	0	0	0
5	62	0	0	1	1	15	2	4	0
6	45	11	55	2	7	80	2	MISSING	MISSING
7	70	3	4	0	9	10	2	6	0
8	68	1	1	0	14	40	2	14	8
9	59	0	1	0	9	45	2	0	0
10	51	0	0	0	10	25	0		
11	31	0	0	0	8	20	1		
12	85	1	1	0	1	1	0		
Average	60.08	2.42	12.75	0.50	6.92	24.42	1.17	4.25	4.75
SD	17.95	3.45	19.72	0.67	5.12	23.97	0.94	5.39	10.58

Lighter anaesthesia
Deeper anaesthesia

Participant Number	PPIPOST 6 Weeks	MPQSFPOST 3 Months	PIPOST 3 Months	PPIPOST 3 Months	STAIY1 PRE	STAIY1 POST1	STAIY1 POST 6 Weeks	STAIY1POST 3 Months	STAIY2 PRE
1	0	0	0	0	21	20	25	20	29
2	1	5	18	1	43	26	33	28	37
3	0	0	0	0	26	23	20	20	20
4	0	0	0	0	44	36	27	30	33
5	0	0	0	0	23	31	22	21	28
6	MISSING	MISSING	MISSING	MISSING	53	20	MISSING	MISSING	23
7	0	0	0	0	41	24	22	44	34
8	1				49	32	32		32
9	0				28	21	20		26
10					34	26			26
11					44	38			41
12					59	33			23
Average	0.25	0.83	3.00	0.17	38.75	27.50	25.13	27.17	29.33
SD	0.46	2.04	7.35	0.41	12.29	6.30	5.14	9.30	6.24

Participant Number	PLOC INTERNAL	PLOC CHANCE	PLOC DOCTORS	PLOC OTHER PEOPLE	Body image question PRE	Body image question POST1	Body image question POST6W	Body image question POST3M	BISMINS>50	DEEPER OR LIGHTER anaesthesia
1	19	13	12	5	0	0	0	0	4	DEEPER
2	17	14	11	8	3	4	5	4	2	DEEPER
3	32	31	11	5	0	0	0	0	7	LIGHTER
4	17	18	12	7	3	3	3	3	5	LIGHTER
5	10	18	15	12	3	3	2	2	17	LIGHTER
6	26	11	13	6	5	0	MISSING	MISSING	2	DEEPER
7	12	18	17	15	3	0	0	0	0	DEEPER
8	21	14	7	7	2	0	1		9	LIGHTER
9	14	9	13	14	0	0	0		1	DEEPER
10	23	6	17	12	1	2			10	LIGHTER
11	18	24	10	9	5	4			7	LIGHTER
12	20	23	17	11	0	0			1	DEEPER
Average	19.08	16.58	12.92	9.25	2.08	1.33	1.38	1.50	5.42	
SD	6.05	6.99	3.12	3.47	1.88	1.72	1.85	1.76	4.93	

Appendix L

Descriptive statistics of Pain Locus of Control Questionnaire and Body Image Question (BIQ)

Descriptive Statistics

	N	Range	Minimum	Maximum	Mean	Std. Deviation	Skewness		Kurtosis	
	Statistic	Statistic	Statistic	Statistic	Statistic	Statistic	Statistic	Std. Error	Statistic	Std. Error
PLOCQ Internal	12	22	10	32	19.08	6.052	.639	.637	.712	1.232
PLOCQ Chance	12	25	6	31	16.58	6.986	.576	.637	.266	1.232
PLOCQ Doctors	12	10	7	17	12.92	3.118	-.123	.637	-.399	1.232
PLOCQ Other people	12	10	5	15	9.25	3.467	.344	.637	-1.260	1.232
BIQ PRE	12	5	0	5	2.08	1.881	.250	.637	-1.210	1.232
BIQ POST1	12	4	0	4	1.33	1.723	.658	.637	-1.552	1.232
Valid N (listwise)	12									

Appendix M

Pain Intensity by Depth of Anaesthesia Controlling for Pre-Operative Pain Intensity SPSS Output

Tests of Between-Subjects Effects

Dependent Variable: log10pipost1

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	.181[a]	2	.091	.234	.796
Intercept	6.175	1	6.175	15.919	.003
log10pipre	.072	1	.072	.185	.677
BISSPLIT	.027	1	.027	.069	.799
Error	3.491	9	.388		
Total	19.569	12			
Corrected Total	3.672	11			

a. R Squared = .049 (Adjusted R Squared = -.162)

Estimated marginal means for pain intensity

2. BISSPLIT

Dependent Variable: log10pipost1

BISSPLIT	Mean	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
LOW	1.205[a]	.272	.588	1.821
HIGH	1.097[a]	.272	.481	1.714

a. Covariates appearing in the model are evaluated at the following values: log10pipre = .6438.

MPQ-SF scores by depth of anaesthesia controlling for pre-operative MPQ-SF scores SPSS output table

Tests of Between-Subjects Effects

Dependent Variable: log10mpqsfpost1

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	.157[a]	2	.078	.412	.674
Intercept	1.784	1	1.784	9.369	.014
log10mpqsfpre	.150	1	.150	.788	.398
BISSPLIT	.033	1	.033	.172	.688
Error	1.713	9	.190		
Total	8.826	12			
Corrected Total	1.870	11			

a. R Squared = .084 (Adjusted R Squared = -.120)

Pain Intensity by Depth of Anaesthesia Controlling for Pre-Operative Pain Intensity

Estimated marginal means for MPQ-SF scores

2. BISSPLIT

Dependent Variable: log10mpqsfpost1

BISSPLIT	Mean	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
LOW	.694[a]	.205	.230	1.159
HIGH	.829[a]	.205	.364	1.293

a. Covariates appearing in the model are evaluated at the following values: log10mpqsfpre = .3635.

PPI scores by depth of anaesthesia controlling for pre-operative PPI scores SPSS table

Tests of Between-Subjects Effects

Dependent Variable: PPIPOST1

Source	Type III Sum of Squares	df	Mean Square	F	Sig.
Corrected Model	1.714[a]	2	.857	.970	.415
Intercept	7.656	1	7.656	8.665	.016
PPIPRE	.381	1	.381	.431	.528
BISSPLIT	.914	1	.914	1.035	.336
Error	7.952	9	.884		
Total	26.000	12			
Corrected Total	9.667	11			

a. R Squared = .177 (Adjusted R Squared = -.005)

Estimated marginal means for PPI score

2. BISSPLIT

Dependent Variable: PPIPOST1

BISSPLIT	Mean	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
LOW	1.452[a]	.391	.569	2.336
HIGH	.881[a]	.391	-.003	1.764

a. Covariates appearing in the model are evaluated at the following values: PPIPRE = .50.