Efficacy of transversus abdominis plane blocks as part of a multimodal analgesia regime for total abdominal hysterectomies

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SUBMITTED TO THE UNIVERSITY OF CAPE TOWN
In dissertation fulfilment of the requirements for the degree

M Med Anaesthesia

Faculty of Health Sciences

UNIVERSITY OF CAPE TOWN

Date of submission:
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DECLARATION

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Abstract:

Patients who undergo a total abdominal hysterectomy (TAH) experience a significant amount of pain postoperatively. Several multimodal pain regimes have been used in the past to manage these women's pain. Neuraxial anaesthesia is usually not a feasible option in these cases, because of the risks involved. Limited resources with the lack of high care unit beds available when intrathecal opioids are given are also a problem. Effective analgesia includes both improved comfort and decreased opiate side-effects, if morphine requirements can be decreased.

After approval from the University of Cape Town Human Research Ethics Committee, the trial was registered with the South African National Clinical Trial Register (DOH-27-0212-3945) and the South African National Human Research Ethics Council. All patients between the ages of 20-65 with an ASA score I-III were included in a prospective double-blind randomised controlled trial after obtaining written informed consent from them the day before their operation.

Patients were excluded if they were allergic to any of the trial medication (morphine,bupivacaine), had a history of opioid addiction, coagulation disorders, infection at needle insertion site or were unable to give informed consent. If surgery did not for some reason proceed to a TAH, the patient was also excluded.

The patients were visited in the ward the day before their operation to obtain informed consent. All the patients received a patient-controlled analgesia (PCA) pump and this as well as the visual analogue pain scale (VAS) were demonstrated and explained to them. This was done by the same person (principle investigator) for all the patients.

Our aim with this double-blind randomised controlled trial was to study the efficacy of ultrasound-guided transversus abdominis plane blocks in patients undergoing total abdominal hysterectomy. We randomly allocated thirty patients to two groups, a transversus abdominis plane block group (n=15) and a placebo group (n=15). The transversus abdominis plane blocks were done with 0.25% bupivacaine. The placebo group received a sham block with normal saline post induction of anaesthesia. All patients received postoperative morphine patient-controlled

analgesia. Pain scores and morphine consumption were assessed at 0, 6 and 24 hours postoperatively.

Our trial showed a significant between-group difference in morphine requirements (5.2±3.9 vs. 9.7±4.3 mg [p=0.007], and 12.9±8.9 mg vs. 25±12.1 [p=0.006]) for the transversus abdominis plane- compared with placebo group at 6 and 24 hours respectively. There were no significant between-group differences in pain scores. There were no complications associated with any block.

Ultrasound-guided transversus abdominis plane block is an effective addition to a multimodal postoperative analgesia regimen for abdominal hysterectomy.

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Part A: Research Protocol

Efficacy of transversus abdominis plane blocks as part of a multimodal analgesia regime for total abdominal hysterectomies

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Introduction

Patients that undergo a total abdominal hysterectomy experience significant postoperative pain. Multimodal pain regimes have been described to manage their pain. Transversus abdominis plane (TAP) block has only recently been described (2001) as an addition or alternative to the other analgesic regimes.

A limited number of studies have been done on TAP blocks and there is sufficient data to suggest that it shows a significant improvement in pain scores as well as morphine requirements postoperatively. Many of the studies have been done with the landmark technique (blind "pop" technique via the Triangle of Petit). Although there is minimal risk involved in administering the block, there is still a potential risk of bleeding, perforating abdominal organs or a failed block due to injecting the local anaesthetic in the wrong anatomical plane. An ultrasound guided technique has been described to make the block safer and more reliable. Less than 5 studies had been published by December 2010 on ultrasound-guided TAP blocks.

The aim of our research is to study the efficacy of TAP blocks specifically in elective total abdominal hysterectomy (TAH) patients. Only one randomised control trial has been published by December 2010 on using TAP blocks in total abdominal hysterectomies and in this trial the block was done with the landmark technique.

We are aiming to do a small double-blind randomised control trial to demonstrate the efficacy of doing ultrasound-guided TAP blocks for total abdominal hysterectomies in improving patient pain postoperatively, as well as to decrease the morphine requirements. This may assist recovery of patients and hopefully decrease emotional and psychological side-effects of major abdominal surgeries.

Purpose of the Trial

The ***objective*** of this trial is to study the efficacy of ultrasound-guided transverse abdominis plane (TAP) blocks in providing effective postoperative analgesia in patients undergoing elective total abdominal hysterectomy for benign disease.

The ***primary aim*** is to measure morphine consumption and pain scores for 24 hours postoperatively. ***Secondary aims*** include incidences of nausea, vomiting and pruritus.

The ***null hypothesis*** is stating that ultrasound-guided TAP blocks do not provide enhanced postoperative pain relief for elective total abdominal hysterectomy

patients when used as part of a multimodal analgesic regimen.

Background

Patients that undergo a total abdominal hysterectomy experience significant post-operative pain. Multimodal pain regimes have been used. The TAP block via the "Triangle of Petit" has only been described recently by Rafi [1] in 2001. It provides enhanced pain control by blocking the sensory nerves that supply the anterior abdominal wall by injecting local anaesthetics in the plane between the abdominal muscles. There is a fascial sheath between the internal oblique and transversus abdominis muscles. The nerves lie deep to this fascia. Following the work done by Rafi [1], Walter et al. [2] described a technique in 2008 where TAP blocks can be done with ultrasound imaging to make the procedure even more effective and safe.

Because TAP blocks have only recently come into use, there is a limited amount of published literature. A literature search was done using Pubmed and the Cochrane Collaboration with "TAP block" and "transversus abdominis plane block" as keywords. All randomised controlled trials published by December 2010 were reviewed.

Most of the studies were done on general abdominal surgery. A meta-analysis on the clinical effectiveness of transversus abdominis plane blocks was published by Siddiqui et al. [3] in May 2010 where only four randomised controlled studies were discussed. McDonnell et al.[4] established that the 24 hour post-operative morphine requirements in patients that underwent large bowel surgery with TAP blocks done with 0.375% levobupivacaine 20ml (10ml injected each side), was 70% less than in the control group without the TAP blocks. They also published a randomised controlled trial in 2008 [5] that included patients undergoing a caesarean section. They monitored the cumulative morphine requirements for 48 hours postoperatively and reported that the group that had a TAP block required significantly less morphine than the control group.

In 2009 El-Dawlatly et al.[6] showed that the morphine used by patients in the 24 hours after laparoscopic cholecystectomy was significantly reduced by ultrasound-guided TAP blocks done with 30ml 0,5% bupivacaine (15ml in each side). More recently, in 2010, Ra et al. [7] also published a randomised controlled trial on the analgesic effect of the ultrasound-guided TAP block after laparoscopic cholecystectomies. They showed that the intraoperative use of remifentanil, postoperative pain scores and the postoperative demand for rescue analgesia were

significantly reduced in the group that received a TAP bock with Levobupivacaine after induction of anaesthesia.

There was only one other randomised controlled trial that was done with patients that had a total abdominal hysterectomy. Carney et al.[8] published their trial in 2008 after doing TAP blocks with 0.75% ropivacaine using the landmark technique. They showed that TAP blocks reduced postoperative pain scores as well as the mean total morphine requirement in the first 48 hours postoperatively.

In all the above mentioned randomised control studies, the investigators made use of sham injections instead of local anaesthetics in the control group. No complications were reported by using these sham injections.

Methodology

1. Trial design

To address the primary and secondary aims of our trial, we will be doing a double-blind randomised controlled trial, using sham injections in the control group. It has been shown to be a very low risk procedure when the TAP block is performed with the use of ultrasound guidance (no complications reported in the two studies that used ultrasound guided TAP blocks, El-Dawlatly et al. [6] and Ra et al. [7]) Patients will be randomised into two groups of 15 patients. They will be randomly allocated to each group by using a sealed envelope technique. The TAP block group will receive bilateral blocks with 0.25% bupivacaine after induction of anaesthesia. In the placebo group the blocks will be done with normal saline. In the placebo-group, injections of normal saline instead of 0.25% Bupivicaine will be administered by the investigator (who will be blinded to the specific group that the patient belongs to).

The same standard of care regarding the administration of the blocks will be upheld in both trial groups and the safety of administration will be held to the highest standard. It has been shown that a trial of this nature can be safely done in a double-blinded fashion. To ensure that each patient gets the same standard of care and the TAP blocks are performed with uniform technical experience, only one anaesthetist will be performing each block on the patients, namely Dr Owen Porrill.

To estimate the sample size needed to test the hypothesis with sufficient statistical power, we used the results from the trial done by McDonnell et al. [4] as proxy for our population group. By using PASS 2008 (Hintze,J.(2008),Kaysville,Utah) we estimated that a group sample size of 9 patients in each group is needed to achieve

82% power to detect a difference of 3 points in the pain scores postoperatively. This was done with the assumption that the mean pain scores in the control group is 4.0 and the mean pain score in the intervention group is 1.0 with known group standard deviations of 2.8 (control group) and 1.4 (intervention group) and with a significance level (alpha) of 0,05%. A Mann-Whitney and a Student's t-test will be used to analyse the final data, assuming that the actual distribution is uniform due to small sample size.

Sample size estimation was also done by using the morphine requirements as guideline, also using the results from the trial done by McDonnell et al. [4] as proxy to our population group. In this estimation group sample sizes of *15* in each group achieves 99% statistical power to detect a difference of 20mg morphine used in total after 24 hours postoperatively. In the control groups the mean total dose was taken as 30mg and in the intervention group the mean was 10mg with known group standard deviations of 15,0mg (control group) and 10,0 (intervention group) and with a significance level (alpha) of 0,05% using a two-sided Mann-Whitney test assuming that the actual distribution is uniform.

Considering the above sample size estimations, it was decided to recruit 15 patients to each group to incorporate a safety margin for errors.

2. Characteristics of trial population

Number of patients enrolled in the trial

Thirty patients will be enrolled in total (15 patients in each group).

Inclusion and exclusion criteria:

Inclusion criteria:	Females booked for an elective total abdominal hysterectomy
	ASA physical status 1-3
	Adult patients between ages 20-65
Exclusion criteria:	Allergic to bupivacaine or morphine
	History of opioid addiction
	Any abdominal or gynaecological malignancy
	Patients with coagulation disorders
	Infection at the needle insertion site
	Patient refuse to give informed consent to be part of the trial
	Patients not able to give informed consent

Vulnerability

Children or mentally impaired adults will be excluded from the trial.

Location of the research

Patients that are booked on the elective gynaecology list at Groote Schuur Hospital will be approached and enrolled in the trial.

3. Recruitment and Enrollment

Patients will be recruited via convenience cluster sampling once they are booked on the elective gynaecology slate for a total abdominal hysterectomy not associated with any malignant process. Patients will be identified the day before the surgery and they will be seen in the ward as part of their pre-operative assessment by the principle investigator. If the patient qualifies for the trial, the details will be discussed with them. The purpose, methods, effects and complications of the procedure will be explained to them, after which written informed consent will be obtained from them if they are willing to take part in the trial. No commercial publication or advertisement will be used beforehand.

4. Research Procedures and Data Collection Methods

Both groups of patients will receive the same basic standard of care regarding the general anaesthetic and post-operative care. A routine induction of general anaesthesia will be performed using the standard technique. When vital signs are stabilized after endotracheal intubation, the TAP block will be performed by one skilled anaesthetist (Dr Owen Porrill) with the help of ultrasound guidance. A SonoSite S-nerve ultrasound machine will be used in conjunction with Vygon Echoplex needles (100mm).

The TAP block will be done as an aseptic procedure in the flank palpated between the 12th rib and the iliac crest. The neuromuscular plane between the internal oblique muscle and the transversus abdominis muscle will be identified with ultrasound guidance. The needle will be advanced by an ultrasound guided in-plane technique at the anterior axillary line. The first “pop” sensation should be felt as the needle reaches the fascial plane between the external oblique and internal oblique muscles. A second “pop” sensation should be felt as the needle enters the plane between the internal oblique muscle and the transversus abdominis muscle. The exact location of the needle tip will be confirmed via direct ultrasound visualisation.

After confirmation of the correct position of the needle and negative aspiration, 1-2 ml of normal saline will be injected to identify position with water dissection. After

confirmation of correct position the trial drug will be injected and spreading within the fascial layer will be confirmed on ultrasound. A total of 20 ml will be injected on each side using the same technique.

Each patient will receive a standardised post-operative analgesic regime, consisting of a morphine patient-controlled analgesia (PCA) pump, 100mg Indomethacin per rectum 12 hourly and 1g Paracetamol 6 hourly orally. Rescue anti-emetics (Metoclopramide 10mg IVI/IMI) will be prescribed. Patients will be followed-up immediately postoperatively in the recovery room, 6 hours and finally 24hours postoperatively. The presence and severity of pain will be assessed using a visual analogue pain scale (VAS) and the total morphine requirements will be documented. Incidences of nausea, vomiting and pruritus will also be recorded.

It is considered as standard post-operative care for patients undergoing a total abdominal hysterectomy to receive intramuscular morphine boluses 6 hourly as well as indomethacin and paracetamol. Thus, the PCA pump that every patient will receive in this trial for at least the first 24 hours, is regarded as above standard care.

The TAP blocks will be performed by Dr Owen Porrill, who is a consultant anaesthetist at the Department of Anaesthesia, University of Cape Town. He is experienced in doing peripheral nerve blocks with and without ultrasound guidance. The post-operative evaluation will be done by the principle investigator to exclude any observational bias during the evaluation process. A senior anaesthetic registrar or consultant will be asked to prepare the trial drug in pre-marked syringes. The syringes will be marked as the "study drug". Due to the clarity of both solutions, it will not be able to discern the nature of the drug in the syringes. The patients will randomly be allocated to be in the two groups.

It will not be necessary to use any interpreters or other individuals in our trial.

5. Data Safety and Monitoring Plan

Performing a TAP block under ultrasound guidance is a very safe procedure. There have been no complications recorded in the published randomised control trials where the block was performed under ultrasound guidance.

If the block is performed without ultrasound guidance, there is potentially a higher risk of complications. Complications that can occur are minor bleeding at the injection site, accidental intestinal puncture, unexpected diffusion of local anesthetics into additional body parts or even accidental liver puncture. None of these complications are likely to be life-threatening or require intervention due to the

small caliber of the needle used. Using ultrasound guidance reduces the risk of complications.

The procedure will be performed under controlled and aseptic conditions in theatre while the patient will be monitored by the principal investigator and the trial coordinator for any complications. The principle investigator will assess the patients directly postoperatively in the recovery room and will also personally follow-up the patients in the ward for monitoring purposes.

If any unforeseen complication occurs in the ward, the principle investigator will be available to come and examine the patient, address and manage any problems.

6. Data Analysis

Every patient's data will be collected and recorded on a separate data sheet. A number will be allocated to each patient and all data will remain anonymous. The data will not include any personal or confidential information and will be stored in a secured locker in the anaesthetic department at Groote Schuur Hospital.

Patients will be assessed immediately postoperatively as well as 6 hours and 24 hours postoperatively. Their total morphine requirements as well as their pain scores (using a visual analogue pain scale) will be documented. A copy will be made of each patient's completed data sheet and given to the trial coordinator to store securely in his office that is locked at all times in case any back-up information is needed.

The plan for data analysis is to use a Student's t-test and a Mann-Whitney U test.

Description of Risks and Benefits

Potential risks and discomforts

There will be minimal risk involved participating in this trial. The potential risks of complications of a TAP block (bowel perforation, liver perforation etc.) are minimised by doing the TAP block with ultrasound guidance. The patients will be monitored closely intra-operatively and immediately postoperatively to make sure that no complication has occurred.

There have been no recorded complications in any of the randomised control studies where TAP blocks were performed with ultrasound guidance. None of the potential physical complications associated with this procedure is life-threatening and all resolve spontaneously.

Risk classification

The overall risk of the trial is minimal. The risk involved is not more than doing a simple bedside procedure.

Minimizing risk

The block will be done with ultrasound guidance to avoid penetrating the peritoneum or puncturing any intra-abdominal organs. Maldistribution of the local anaesthetics will also be avoided by confirming the position and distribution of the local anaesthetics under ultrasound visualisation.

Potential benefits

The patients will benefit from a standard of care that is regarded as above the normal analgesic post-operative management for a total abdominal hysterectomy, because each patient will receive a Morphine PCA pump. This will ensure that staffing issues/problems in the wards will not cause delays in the patients receiving regular opioid analgesia.

We are aiming to show that it is safe and effective to add a TAP block to the multimodal analgesic management of patients that undergo abdominal hysterectomy. It is a feasible and easy option to provide most patients with an intra-operative TAP block and we hope to prove that it improves their post-operative pain control.

The technique of performing a TAP block is still a new concept, and the benefit of it must still be realised by anaesthetists as well as the surgeons that have to look after their patients postoperatively.

The existing alternative routinely used as post-operative analgesia for these patients is regular intra-muscular morphine injections combined with other oral agents. Due to frequent staff shortages and problems with the patient's prescriptions, the patients often do not receive proper analgesia. This causes severe discomfort and psychological stress among the patients and it delays their recovery after surgery.

Harm: benefit ratio

The benefit involved in doing the TAP block with ultrasound guidance outweighs the harm involved in doing the procedure.

Informed Consent Process

Process

Informed consent will be taken from the patients during the pre-operative visit that will be done the previous day by the principle investigator.

This process will take place in the ward after the patient has been admitted and the routine work-up is completed for her elective surgery. After the pre-operative assessment has been performed, the patient will be evaluated to confirm that there are no contra-indications to her taking part in the trial. If the patient qualifies, the goals and objectives, including all the pros and cons/possible side-effects of the trial will be discussed with the patient in private. If the patient has any doubts or wants to discuss it with her family before giving consent, she will be able to so during the evening visiting hour. The patient will then be seen pre-operatively the next day to confirm that she wants to continue being part of the trial.

Capacity to consent

Patients included in this trial must all be able to give informed consent. Minors and mentally impaired patients will be disqualified. If there is any doubt regarding a patient's capacity to provide informed consent, the patient will not be included in the trial.

Comprehension of information

The trial will be explained to the participants in layman's terms. All the procedures and the pros/cons will be explained in detail. Due to the simple nature of the procedure of performing a TAP block, it will be easy to explain all the detail in non-medical terminology.

The patients will be asked if they understand the information given to them. They will be asked to explain the procedure in their own words at the end of process. Patients will be given a chance to ask questions during and after the process.

Withholding information

Due to the blinded nature of this trial, the patients will not be able to know whether they are in the bupivacaine or the placebo group. All patients will be managed according to the same protocol. All information and observations obtained during the first 24hours postoperatively will be disclosed to them upon their request.

Consent forms

A consent form is formulated specifically for this trial.

An adult consent form will be used in English. It will not be translated into Afrikaans or any other South African language.

Privacy and Confidentiality

The data collected from the patients will not be of a private/personal nature. The patient's name and date of birth will be recorded on a data sheet. A number will be assigned to each patient to ensure correct follow-up and identification of each patient.

The data sheets will be stored in a locker in the anaesthetic department at Groote Schuur Hospital. The department is only accessible by an activated access card. A copy of all the data sheets will be kept in the trial supervisor's office in the anaesthetic department that is locked at all times

The datasheets will be converted to electronic format for statistical analysis. The electronic data will be stored on a two separate flash drives. Each flash drive will be kept locked away with the principal investigator and the supervisor as stated above. Data will be accessible by the investigator, the trial coordinator as well as the statistician that will assist with the statistical analysis at the end of the trial.

Once the trial is completed and all statistical data is confirmed, the data will be kept for 12 months after the trial has been published to be available for any follow-up studies or any queries from peers.

Reimbursement for Participation

Patients taking part in the trial will not receive any compensation.

Sponsorship/Budget

The Western Cape branch of Viking Medical & Surgical Pharmaceuticals has agreed to sponsor the Morphine PCA pumps and Vygon echoplex needles that will be used in this trial. They will not be involved directly in any aspect of this research and will have no influence on any of the results.

What Happens at the End of a Trial?

The goal of this trial is to provide knowledge to treatment of pain after elective hysterectomies. The trial does not involve any investigatory drug or treatment that has to be continued after the first 24hours postoperatively.

At the end of the first 24 hours postoperatively, when the patients will exit the trial, the patients will continue on the routine postoperative analgesia regime. Intra-muscular opiates and oral Paracetamol will be prescribed to all the patients. The primary surgical care will at no point be interrupted.

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Part B: Literature review

Objectives of literature review

Patients who undergo a total abdominal hysterectomy (TAH) experience a significant amount of pain postoperatively. Several multimodal pain regimes have been used in the past to manage these women's pain. Neuraxial anaesthesia is usually not a feasible option in these cases, because of the risks involved and limited resources with the lack of high care unit beds available. Superior analgesia should include improved comfort with decreased side-effects by decreasing morphine requirements while allowing the patient to mobilise earlier.

The aim of our research was to study the efficacy of transversus abdominis plane (TAP) blocks specifically in elective total abdominal hysterectomy (TAH) patients. This is a regional block that has only recently been described and is therefore still a relatively novel technique, especially if done with ultrasound guidance. A limited amount of literature is available on the topic and the aim was to search for randomised controlled trials that included TAP blocks. The literature was reviewed to identify the different block techniques that was utilised. TAP blocks can be done blindly via the Triangle of Petit (landmark technique) or with ultrasound guidance.

Several studies have been published where the analgesic use of TAP blocks have been investigated. There is significant data to suggest that it causes an improvement in pain scores as well as morphine requirements postoperatively. Many of these studies were done with the landmark technique (also known as the blind "pop" technique via the Triangle of Petit). The TAP block is generally a safe block, but there are potential complications, especially when using the blind technique. There is a risk of bleeding, perforating abdominal organs or a failed block due to injecting the local anaesthetic in the wrong anatomical site. An ultrasound guided technique has been described to make the block safer and more reliable.

The TAP block provides enhanced pain control by blocking the peripheral nerves that provide sensory supply to the anterior abdominal wall from level T9-L1. The nerves pass through the transversus abdominis plane in the fascial sheath between the internal oblique and transversus abdominis muscle in the lateral aspect of the abdominal wall between the costal margin and the iliac crest. By identifying this

plane with ultrasound guidance, the needle tip can be visualised and real time spread of local anaesthetics can be confirmed. TAP blocks have been studied in a number of contexts [1-17]. These studies have shown marked improvement in morphine requirements and pain scores by including a TAP block in the analgesia regime.

Literature search strategy

The objective of the literature review was to look at randomised controlled trials and meta-analyses published on the use TAP blocks during the past 10 years. Trials that were published between January 2001 and December 2012 were included.

The focus was on research that looked at treatment strategies for pain control in abdominal surgery patients. The search was limited to randomised controlled trials and meta-analyses involving humans for abdominal surgery. The population group included both adults and children. The intervention was limited to TAP blocks, via the landmark technique and with ultrasound guidance. The comparison could be with any other mode of analgesia, e.g. intrathecal morphine, subcutaneous wound infiltration or patient-controlled analgesia pumps. The outcomes of the studies were assessed in regards to the statistical data as well as safety of the regional block and method of analgesia that was used in the control group.

The electronic databases of the Health Sciences Library of The University of Cape Town were used to access MEDLINE, PUBMED and Cochrane library for the published articles. The MeSH terms and text words used were “TAP blocks”, “transversus abdominis plane blocks” and “randomised controlled trial”. Filters were used to include human trials, focusing on randomised controlled trials and meta-analyses. All age groups of patients were included in the search.

Articles that were published in a language besides English were excluded. Research articles other than randomised controlled trials or meta-analyses were also excluded from the search. If the electronic version of the full text of a relevant article could not be found with the online database, the University of Cape Town Library was used to find the printed versions. The full text of all the articles was critically reviewed by the primary investigator.

Quality criteria

The literature search was limited to randomised controlled trials and meta-analysis that was published between January 2001 and December 2012. These articles were critically reviewed to assess validity towards our proposed research. The outcomes of the studies were assessed in regards to the statistical data as well as safety of the regional block and method of analgesia that was used in the control group.

Summary and interpretation of literature, and its implications for the research

TAP blocks have only recently come into fashion and therefore there is a limited amount of published randomised control trials on the subject.

The TAP block via the "Triangle of Petit" was described by Rafi [1] in 2001. It provides enhanced pain control by blocking the sensory nerves that supply the anterior abdominal wall by injecting local anaesthetics into the neurovascular plane between the abdominal muscles. The transversus abdominis plane is a fascia sheath between the internal oblique and transversus abdominis muscles.

The block was initially done by using a landmark technique through the Triangle of Petit. The Triangle of Petit is superior to the iliac crest, between the latissimus dorsi and external abdominal oblique muscles. A pop is felt when you pass the blunted needle through the fascia layer of the transversus abdominis muscle and the local anaesthetic is blindly deposited in this plane. TAP blocks are generally a safe block to use, but there is potential for complications to occur, especially when this blind technique is used. The potential complications could include extremes like liver trauma, as mentioned by Farooq et al. [2] in a case report.

An ultrasound guided approach was discussed in a letter by Hebbard [3]. Walter et al. [4] continued with this idea and described a technique in 2008 where TAP blocks can be done with ultrasound imaging to make the procedure even more safe and effective.

McDonnell et al.[5] established that the 24 hours post-op morphine requirements were significantly decreased in patients that had large bowel surgery with TAP blocks done with 0.375% levobupivacaine 20ml (10ml injected each side). The morphine requirements in these patients were 70% less than in the control group. They continued their research in this field and published a follow-up randomised control trial in 2008 [6] with patients that had a caesarean section. This was the first of many studies published looking at the use of TAP blocks for caesarean section patients. They monitored the accumulative morphine requirements for 48 hours postoperatively and reported that the group that had a TAP block required less morphine. The patients had lower pain scores and fewer opioid related side-effects than the control group. In the TAP block group the women used less than a third of the morphine dose compared to the control.

A meta-analysis on the clinical effectiveness of transversus abdominis plane blocks were published by Siddiqui et al. [7] in May 2010. The analyses included four randomised control trials that were published between 2007 and 2009. The respected studies were done on patient who received different types of intra-abdominal surgeries. Only one of these studies used ultrasound guidance for the TAP blocks. The meta-analysis showed a significant difference in postoperative opioid requirement as well as time to first request for morphine. The trial also had statistically significant decreases in pain scores, but only at 6 hours postoperatively and not for the rest of the observations. They concluded that the TAP block offers comparable analgesia to opioids postoperatively and it reduces the morphine requirements while adding more effective pain relief. They also concluded that it reduces side-effects associated with morphine or other opioids.

In 2009 El-Dawlatly et al.[8] proved that the morphine used by patients 24 hours after they had a laparoscopic cholecystectomy was significantly reduced by doing ultrasound-guided TAP blocks. The blocks were done with 30ml 0,5% bupivacaine (15ml in each side). More recently, in 2010, Ra et al. [9] also published a randomised control trial on the analgesic effect of the ultrasound-guided TAP block after laparoscopic cholecystectomies. They showed that the intraoperative use of remifentanil, postoperative pain scores and the postoperative demand for rescue analgesia were drastically reduced in the group that received a TAP bock with Levobupivacaine after induction of anaesthesia

In 2009 Belavy et al. [10] also improved on the classic landmark technique by doing the blocks ultrasound guided for caesarean section patients. They found that TAP blocks decreased morphine requirements by 40%. In the same year Costello et al. [11] addressed the question of whether TAP blocks were an effective addition to intrathecal morphine analgesia. They found that there was an initial improvement in post-op pain scores and morphine requirements, but after 12 hours there was minimal additional benefit to adding bilateral TAP blocks to intrathecal morphine anaesthesia. Kanazi et al. [12] proved the same point by comparing ultrasound guided TAP blocks to 200ug intrathecal morphine for caesarean delivery.

In 2011 McMMorrow et al. [13] and Loane et al.[14] confirmed the above findings that TAP blocks does not provide superior analgesia when compared to intrathecal morphine, but they did conclude that it was associated with fewer side-effects. As in the above mentioned studies, the looked at the use of TAP blocks post caesarean section.

It is clear that ultrasound guided TAP blocks are safer and more reliable than the standard landmark technique. McDermott et al. [15] had to terminate their trial early due to incorrect needle tip placement and intraperitoneal injection of up to 76% of their cases where the TAP blocks were done with the blind double “pop” technique.

There are two other randomised control trials that were done with patients that had a total abdominal hysterectomy for benign disease. Carney J et al. [16] published their trial in 2008 after doing TAP blocks with 0.75%ropivacaine by using the blind "pop" technique. They concluded that the TAP block reduces postoperative pain scores as well as the mean total morphine requirement in the first 48 hours postoperatively.

Atim et al. [17] also did a prospective, double-blind randomised controlled trial where they evaluated the efficacy of bilateral ultrasound guided TAP blocks compared with subcutaneous bupivacaine infiltration. They only included patients that received a Pfannenstiel abdominal incision. They found that both groups (TAP block group and the group that received subcutaneous bupivacaine infiltration) had decreased pain scores compared to the control group, but the lowest scores were in the TAP

block group at 6 and 24 hours postop. Post-op tramadol consumption rather than morphine consumption was compared between the groups in this trial. The TAP block group again required less tramadol compared to the infiltration and control groups. Both the infiltration and TAP block group however required rescue analgesia. They concluded that ultrasound guided TAP blocks are superior to skin and subcutaneous bupivicaine infiltration.

Identification of gaps or needs for further research

This is still a relatively new and limited field. Future research is needed to look at the complication and success rates. Larger population groups are needed to study local anaesthetic dosing, toxicology of the different drugs used for this block as well as drug concentrations. There is a need for training in doing this block, especially with using the ultrasound guided technique.

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Part C: Publication-ready Manuscripts

Efficacy of transversus abdominis plane blocks as part of a multimodal analgesia regimen for total abdominal hysterectomy

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Summary
Our aim with this double-blind randomised controlled trial was to study the efficacy of ultrasound-guided transversus abdominis plane blocks in patients undergoing total abdominal hysterectomy. We randomly allocated thirty patients to two groups, a transversus abdominis plane block group (n=15) and a placebo group (n=15). The transversus abdominis plane blocks were done with 0.25% bupivacaine. The placebo group received a sham block with normal saline post induction of anaesthesia. All patients received postoperative morphine patient-controlled analgesia. Pain scores and morphine consumption were assessed at 0, 6 and 24 hours postoperatively. Our trial showed a significant between-group difference in morphine requirements (5.2±3.9 vs. 9.7±4.3 mg [p=0.007], and 12.9±8.9 mg vs. 25±12.1 [p=0.006]) for the transversus abdominis plane- compared with placebo group at 6 and 24 hours respectively. There were no significant between-group differences in pain scores. There were no complications associated with any block. Ultrasound-guided transversus abdominis plane blocks are an effective addition to a multimodal postoperative analgesia regimen for abdominal hysterectomy.

Introduction
Patients who undergo a total abdominal hysterectomy (TAH) experience a significant amount of pain postoperatively. Several multimodal pain regimes have

been used in the past. Neuraxial anaesthesia is usually not a feasible option in these cases, because of the risks involved and limited resources in terms of postoperative high care beds. Effective analgesia includes both improved comfort and decreased opiate side-effects, which should allow earlier mobilisation.

A number of studies have investigated transversus abdominis plane (TAP) blocks after various abdominal surgical procedures, and there is data to suggest that it causes a significant improvement in pain scores as well as a reduction in postoperative morphine requirements [1]. Most of these studies were done with the landmark, or blind "pop" technique via the Triangle of Petit [2]. The TAP block is generally safe, but there are potential complications, particularly when using the blind technique. Risks include bleeding, perforation of abdominal organs, or a failed block due to injecting the local anaesthetic in the wrong anatomical site. An ultrasound-guided technique has been described to make the block safer and more reliable [3].

There are only two previous studies of TAP blocks for abdominal hysterectomy for benign disease. The first employed the landmark technique, with its inherent limitations [4,5]. The second investigation used ultrasound guidance [5]. In the latter trial, only Pfannenstiel incisions were performed, and patient-controlled tramadol was administered, with pethidine as rescue in both groups. In view of the paucity of available data on the efficacy of the TAP block post elective abdominal hysterectomy (TAH), we undertook a randomised double-blind controlled trial in patients receiving either Pfannenstiel or midline abdominal incisions. We employed patient controlled IV morphine postoperatively, and examined the efficacy of TAP blocks in the reduction of morphine requirements and improvements in visual analogue pain (VAS) scores.

Methods

After approval from the University of Cape Town Human Research Ethics Committee, the trial was registered with the South African National Clinical Trial Register (DOH-27-0212-3945) and the South African National Human Research Ethics Council. Data are presented in accordance with Consolidated Standards of Reporting Trials (CONSORT) statement. We recruited thirty patients that were scheduled for elective total abdominal hysterectomy (TAH) for benign disease via Pfannenstiel or midline abdominal incision under general anaesthesia. All patients between the ages of 20-65 with an ASA score I-III were included in a prospective

double-blind randomised controlled trial, after obtaining written informed consent on the day before the operation. Patients were excluded if they were allergic to either of the trial medications (morphine, bupivacaine), had a history of opioid addiction, coagulation disorders, required surgery for malignant disease, or were unable to give informed consent. During the preoperative visit, all patients received instruction concerning the function of their patient-controlled analgesia (PCA) pump. In addition, the use of the visual analogue pain score (VAS) was explained. The Universal Pain Assessment Tool was used. The recruitment and explanations were performed by the same investigator in all cases (AM). The patients were randomised to two groups of 15. Allocation was done by envelopes that had been sealed and shuffled. Should any patient not proceed to TAH, the same envelope would be resealed and used for the next recruited patient. The investigators would remain blind to its contents.

After establishment of intravenous access in the operating theatre, routine monitoring was established, and patients received a standard general anaesthetic. The transversus abdominis plane (TAP) block group then received bilateral blocks with 20 ml 0.25% bupivacaine. The placebo group received bilateral sham injections with 20 ml normal saline. The principle investigator who recruited and evaluated the patients postoperatively, the trial coordinator, as well as the patients were blinded to the group allocations. The trial drug was drawn up by an anaesthesiologist not involved in the trial. All the blocks were done by a single anaesthetic consultant, who is experienced in ultrasound-guided blocks (OP). An aseptic technique was used with an anterolateral approach to identify the external oblique, internal oblique and transversus abdominis muscles, and thus the transversus abdominis plane. A SonoSite S-nerve ultrasound machine with a linear array transducer probe was used (SonoSite, Inc., Bothell, WA98021, USA) . The probe was placed superior to the iliac crest. A Vygon echoplex needle was inserted and advanced (Viking Medical & Surgical [Pty] Ltd.). The tip was identified with an in-plane technique until it reached the transversus abdominis plane. After negative aspiration, 1-2 ml sterile water was injected to confirm the plane with hydro dissection. The trial drug was then slowly injected under real-time ultrasound imaging (visualising the spread of the trial drug). The same process was repeated on the opposite side, after which the patient was prepared for surgery and the operation commenced.

The conduct of the general anaesthetic was at the discretion of the attending

anaesthesiologist. Intraoperative opioid and anti-emetic use were not part of our trial protocol. The patients in placebo group received on average 1,5 ug/kg of fentanyl and 0,08 mg/kg of morphine. The patients in the TAP block group received on average 1,4 ug/kg of fentanyl and 0,1 mg/kg of morphine. A standard postoperative multimodal analgesia regime was prescribed. Patients received paracetamol 1g 6 hourly per os, indomethacin 100 mg 12 hourly per rectum, and an anti-emetic (prochlorperazine 12.5 mg intramuscularly) as needed. Each patient received morphine via a patient-controlled analgesia (PCA) pump. A Vygon Freedom 5 disposable PCA device (Viking Medical & Surgical [Pty] Ltd.) was used with morphine 1 mg/ml and droperidol 0.1 mg/ml boluses with a 7 min lock-out time. The PCA pump was connected to a dedicated intravenous line.

Patients were taken to the recovery room after the operation where the baseline assessment was done. Thereafter they were discharged to the gynaecology ward, where they were assessed by the same investigator at 6 and 24 hours postoperatively. Primary outcome variables were morphine requirements and pain scores. Morphine requirements were assessed by inspecting the PCA pumps. A visual analogue pain scale was used to assess their pain at rest as well as with movement. Secondary outcomes (nausea, vomiting and pruritis) were also assessed by direct questioning. Lastly, a note was made with every assessment as to whether the patients received the pain regimen as prescribed in the ward.

The Null hypothesis was that ultrasound-guided TAP blocks do not provide enhanced postoperative pain relief for elective total abdominal hysterectomy patients, when used as part of a multimodal analgesia regimen. To estimate the sample size needed to test this hypothesis with sufficient statistical power, we used the results from the trial done by McDonnell et al. [6] as proxy to our population group. By using the software programme PASS 2008 (Hintze, J. [2008].PASS, Kaysville, Utah), we estimated that a group sample size of 9 patients in each group would be needed to achieve 82% power to detect a difference of 3 points in the postoperative pain scores. This was done with the assumption that the mean pain scores in the control group would be 4.0 and the mean pain score in the intervention group would be 1.0, with known group standard deviations of 2.8 (control group) and 1.4 (intervention group), and with a significance level (alpha) of 0,05%. Sample size estimation was also done by using the morphine requirements as a guideline, using the results from the same trial. In this estimation group sample sizes of *5* in each

group would be needed to achieve 85% statistical power to detect a difference of 30 mg morphine used in total after 24 hours postoperatively. In the control groups, the mean total dose was taken as 40 mg and in the intervention group the mean was 10 mg, with known group standard deviations of 20 mg (control group) and 10 mg (intervention group) and with a significance level (alpha) of 0,05% using a two-sided Mann-Whitney U test, assuming that the actual distribution is uniform. Considering the above sample size estimations, it was decided to recruit 15 patients in each group to incorporate a safety margin for errors. Statistical analyses were performed using Statistica Version 10 (StatSoft, Inc. [2011].STATISTICA, version 10). The continuous data (postoperative morphine consumption and pain scores) were analysed by using Student's t-test. Student's t-test as well as Mann-Whitney U tests were used to compare postoperative pain scores. The descriptive statistics are reported by their mean results and standard deviation. A p value<0.05 was considered statistically significant.

Results

Thirty patients were randomly allocated to 2 groups of 15. One patient in the TAP block group was excluded from the trial after the 6 hour postoperative observation, because she had intra-abdominal bleeding requiring surgical re-exploration. This was unrelated to the TAP block. Another patient in the TAP block group had to be excluded from the 24 hour observation, because the morphine PCA pump was accidentally removed during the night. So, the final analysis included 14 patients in the TAP block group for the 6 hour analysis and 13 patients for the 24 hour analysis. The placebo group consisted of 15 patients for all the postoperative analyses.

The demographics of the two groups were similar. The patients' age, height, weight and body-mass index were compared and no significant differences were noted (Table 1).

There was a significant between-group difference in morphine requirements (5.2±3.9 vs. 9.7±4.3 mg [p=0.007], and 12.9±8.9 mg vs. 25±12.1[p=0.006]) for the TAP block compared with the placebo group at 6 and 24 hours respectively (Table 2, Figures 1 and 2). There were no significant between-group differences in pain scores at rest or on movement (Table 3). There were no complications associated

with any block.

Four patients (two in the placebo- and two in the TAP block group) complained of nausea, but none of them required rescue anti-emetics. Three of these patients complained of the nausea in the recovery room directly after their operation. None of the patients complained about pruritus on direct questioning.

Discussion

We did a prospective double-blind randomised control trial to evaluate whether bilateral ultrasound-guided TAP blocks improve postoperative pain and decrease morphine requirements in patients undergoing elective TAH. Our trial showed that ultrasound-guided TAP blocks significantly reduce postoperative morphine requirements compared with placebo. The mean morphine requirements in the TAP block group decreased by 47% at 6 hours (5.2±3.9 vs. 9.7±4.3 mg [p=0.007]) and by 49% at 24 hours postoperatively (12.9±8.9 mg vs. 25±12.1[p=0.006]). This was despite the fact that, by chance, the TAP block group had more patients with midline incisions. In the placebo group 2 patients compared to 8 patients in the TAP block group had midline incision.

Due to the effective use of patient-controlled IV analgesia, there was no significant between-group difference in pain scores. There was a low incidence of nausea, but the trial was not powered to detect differences in side effects. There were no complications related to the TAP block.

The TAP block via the so-called "triangle of Petit" was described by Rafi [2] in 2001. It provides enhanced pain control by blocking the peripheral nerves that provide sensory supply to the anterior abdominal wall from level T9-L1. The nerves pass through the transversus abdominis plane in the fascial sheath between the internal oblique and transversus abdominis muscles in the lateral aspect of the abdominal wall between the costal margin and the iliac crest. By identifying this plane with ultrasound the needle tip can be seen and real time spread of local anaesthetics can be confirmed. TAP blocks have been studied in a number of contexts, including limited data post TAH [1]. These studies have shown marked reduction in morphine requirements by including a TAP block in the analgesia regimen.

There are two other randomised controlled trials employing TAP blocks for total abdominal hysterectomy for benign disease. Carney et al. [4] used 0.75% ropivacaine in the the blind "pop" technique. They showed a reduction in postoperative pain scores as well as the mean total morphine requirement in the first 48 hours postoperatively. It is clear that ultrasound-guided TAP blocks are safer and more reliable than the standard landmark technique. McDermott et al. [7] had to terminate their trial early due to incorrect needle tip placement and intraperitoneal injection in 76% of their cases where TAP blocks were done with the double “pop” technique. In 2009 Belavy et al. [8] improved on the classic landmark technique by doing the blocks with ultrasound guidance for caesarean section. They found that TAP blocks were associated with a 40% reduction in morphine requirements. A recent editorial calls for the use of ultrasound guidance as standard of care for TAP blocks during caesarean section [9].

Atim et al. [5] performed a prospective, double-blind randomised controlled trial in which they evaluated the efficacy of bilateral ultrasound-guided TAP blocks for TAH, compared with subcutaneous bupivacaine infiltration. They found that both groups had decreased pain scores compared to a control group, but the lowest scores were found in the TAP block group at 6 and 24 hours. Post-operative tramadol consumption was compared between the groups. The TAP block group also required less tramadol compared to the infiltration and control groups. Both the infiltration and TAP block group however required rescue analgesia. They concluded that ultrasound-guided TAP blocks are superior to skin and subcutaneous bupivacaine infiltration. Our trial is only the second to employ ultrasound-guided TAP block for post-hysterectomy pain relief, and differs from the previous trial in that patients with midline and Pfannenstiel incisions were included, and postoperative morphine consumption was studied as part of a multimodal analgesic regimen.

Limitations of our trial include the fact that it was not powered to assess differences in opioid related side effects. The type of surgical incision was not standardized, that is, patients with midline and Pfannenstiel incisions were included. Another limitation to our trial is that it was not powered to assess for safety or reliability due to the small sample size. The issue of potential local anaesthetic toxicity was not specifically addressed, but all doses were within the recommended range. We only assessed patients for the first 24 hours, and although it has been suggested that

TAP blocks are beneficial even after after 48 hours [4,10], we did not extend our monitoring period, due to limited time resources.

We observed that the pain scores in the two groups did not differ, but we did show a marked decrease in morphine requirements between the groups. Another limitation to our trial is that we did not evaluate sedation scores, because this would arguably have shown that the patients who required more morphine would have been more sedated. This in turn can potentially hamper early mobilisation and therefore recovery and time to discharge. The clinical relevance of introducing a TAP block for these patients would be including a regional technique with minimal risks with no added discomfort to the patient and the benefit of comfort without the requirement of excess morphine postoperatively.

The final outcome of this trial is that the performance of bilateral ultrasound-guided TAP blocks in women undergoing TAH is a useful addition to a multimodal analgesia regimen, resulting in a significant reduction in postoperative morphine requirements.

Acknowledgement:

We would like to thank Viking Medical & Surgical who sponsored all the PCA pumps and echoplex needles.

We would also like to thank Professor MFM James for his valuable statistical assistance.

Competing interest:

No external funding and no competing interests declared.

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Table 1: Patient demographics. Values are mean and standard deviation (SD).

	Mean (SD)	Mean(SD)
	Placebo	TAP
Age (years)	48 (6.7)	46.6 (4.7)
Height (meter)	1.63 (0.06)	1.62 (0.04)
Weight (kg)	74.4 (17.8)	65.8 (12.4)
BMI ($kg.m^{-2}$)	27.9 (6.6)	25 (5.3)

Table 2: Postoperative Morphine consumption. Values are mean, p value and standard deviation (SD)

	Mean	Mean	p	SD	SD
	Placebo	TAP		Placebo	TAP
M6 (mg)	9.7	5.2	0.007	4.3	3.9
M24 (mg)	25	12.9	0.006	12.1	8.9

M6 = Morphine consumption at 6 hours; M24 = Morphine consumption at 24 hours

Table 3: Pain scores: Student's t-test. Values are mean and p values.

	Mean	**Mean**	**p**
	Placebo	TAP	
Pain Rest 0	4.2	4.3	0.87
Pain Movement 0	4.6	4.9	0.75
Pain Rest 6	2.4	2.3	0.87
Pain Movement 6	2.8	2.8	0.98
Pain Rest 24	1.4	1.1	0.61
Pain Movement 24	2.0	1.4	0.18

0 = 0 hours postop; 6 = 6 hours postop'; 24 = 24 hours postop

Figure 1: Box & whisker plot of postoperative morphine consumption at 6 hours

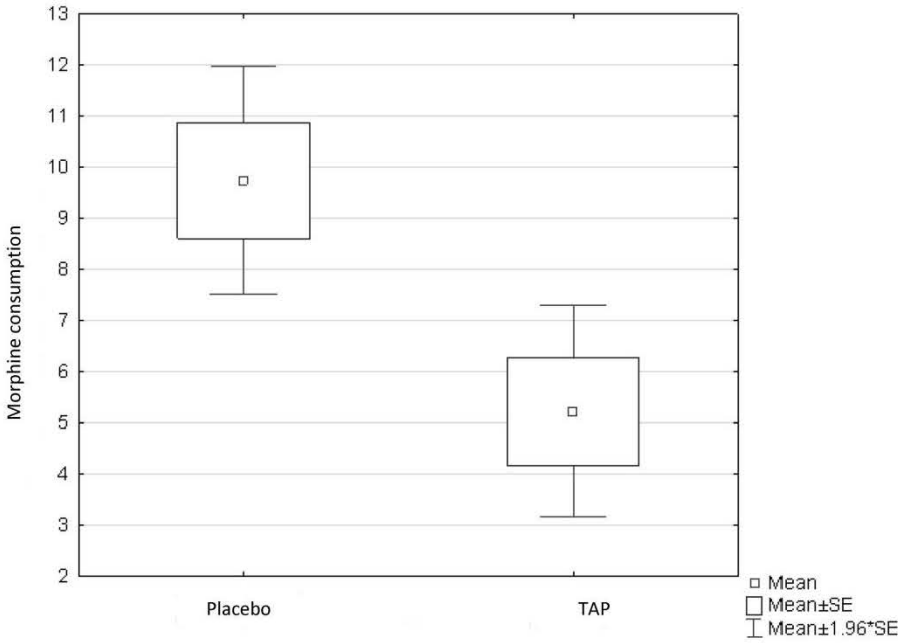
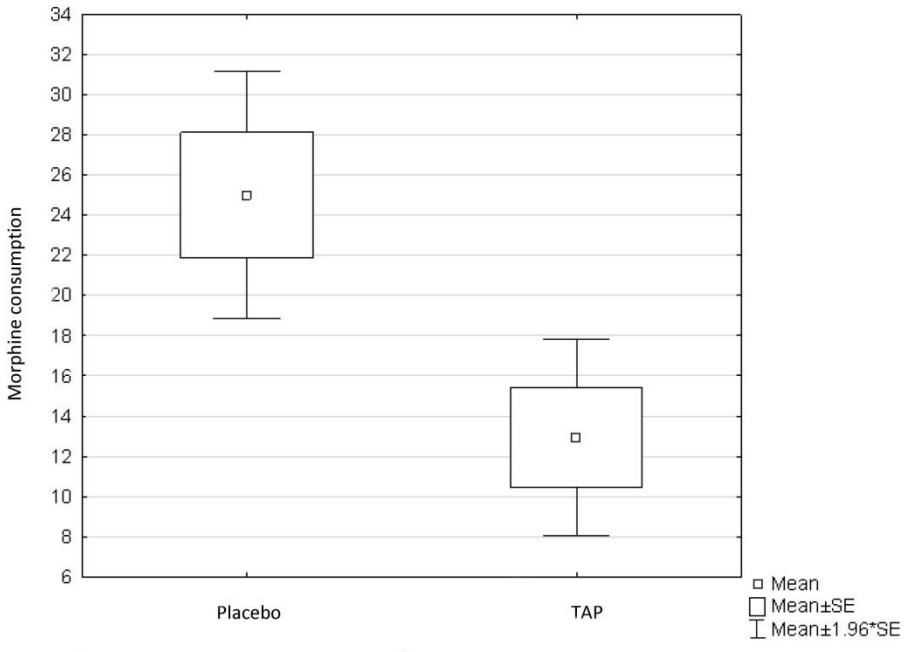


Figure 2: Box & whisker plot of postoperative morphine consumption at 24 hours



Part D: Appendices

a. Consent form
b. Example of search criteria conducted as part of the literature review
c. Official Ethics approval letter from the Faculty Research Ethics Committee
d. Annual progress report: Human Research Ethics Committee
e. Marriage certificate

a. Consent form

INFORMED CONSENT FORM

Informed Consent Form for women who will undergo an elective total abdominal hysterectomy (not related to any malignancies) and who we are inviting to participate in a research trial investigating the beneficial role of transversus abdominis plane blocks inserted with ultrasound guidance in post-operative pain control.

Name of Principal Investigator : Dr Adri Marais/Dr Owen Porrill
Name of Institution : University of Cape Town

This informed consent has two parts:

- *Information sheet (to share information about the trial with you)*
- *Certificate of consent (for signatures if you choose to participate)*

You will be given a copy of the full Informed Consent Form (ICF)

Part 1 : Information Sheet

Introduction

I am Dr Adri Marais, working at Groote Schuur Hospital in the Anaesthetic Department. I am doing a trial to see if we can help to relieve your pain after your operation. We are planning to use a small injection on either side of your stomach after you are asleep in theatre.I am going to give you more information and ask you

to be part of this trial. You can talk to anyone you would like, before making any decision about participating. This form may have words that you do not understand. You can ask me to explain anything as I read the form with you.

Purpose of the Research

Pain relief in women who have had a total abdominal hysterectomy (the operation that you are going to have) can be difficult, especially in the first 24 hours after the operation. The medicine that we currently use is regular pain injection (morphine) and other pain tablets. We would like to know if your pain can be better controlled if we block the nerves in the front part of your stomach. We know that these nerves are the most important nerves involved in the pain after the operation. We would also like to see if women who have received this block would need less pain injections after the operation and therefore have less bad effects of too much morphine, eg nausea, skin itchiness and sleepiness.

Type of Research Intervention

This trial involves doing the two injections, called a transversus abdominis plane block, after you have already been put to sleep by the anaesthetist in theatre. This will be a double-blind randomised controlled trial, which means that half the patients will receive the real injection and the other half will receive a injections with water. We, the docters will not know which patients received the real of the fake injection so that we can treat everyone the same. I will come to see how you are doing in the ward for the first 24 hours after your operation. I will visit you 6 hours and 24 hours after your operation to see if you have pain or not.

Participant Selection

You have been invited to take part in this trial because you are on the operation list to have your womb removed tomorrow.You can help us to improve our services to you and other women who have the same operation in the future.

Voluntary participation

Your participation is entirely voluntary. It is your choice whether to take part in the trial or not. If you choose not to take part, all the treatment you would normally have received at this hospital will continue and nothing will change.

Procedures

The injections will be done under clean conditions by an experienced anaesthetist with an ultrasound machine to make sure we give the injection in the right place.

The injections will be done with a drug called Bupivicaine (we use it for similar injections every day) or with clean water. We will inject the medicine/water in both sides of your lower stomach wall between two layers of muscles under your skin (not into your abdominal cavity).
Everyone will be given a routine and safe anaesthetic (no different to any other general anesthetic). You will be given morphine and other pain medication throughout the operation, as usual. We will wake you up immediately after the operation.
After the operation you will be given a morphine pump with which you can give your own pain medication. We will show you how to use it before and after the operation. This pump will make sure that you do not have to wait for a sister to come and give you pain medicine. We do not usually give patients a morphine pump after this kind of operation, because it is too expensive.
I will come so see you once you are awake after your operation to make sure you do not have any pain. I will also come and visit you in the ward just before I go home in the afternoon (6 hours after your operation) and one last time the next day (24hours after your operation). I will also ask you if you had any complaints of bad effects due to the morphine,eg nausea, sleepiness and itchy skin. If the injections in your stomach wall are as successful as we are hoping it to be, you will not need nearly as much other pain medicine to control your pain.

Duration

The trial will take place over the first 24 hours after your operation. During and after that, you will receive normal care by the docters that will be doing your operation.

Risks

The injections are very easy and safe to do. You will already be asleep by then. In some of the other studies that looked at the same injections they found that there is a small chance of bleeding or infection. At the worst the needle might go into the stomach instead of just in the stomach wall. We will be doing the injections with the help of a ultrasound machine so that we can see where we put the injections and make sure that it does not go through the stomach wall. We will clean your skin well before we do any injection.

Benefits

If you take part in the trial it will help us to find out if we can start to give every patient these injections if they have similar big operations. It will help to prove that

your pain is better controlled after the operation and that less morphine is needed. All of this may speed up your recovery.
During the trial you will also receive a better standard of care, because patients do not usually receive a morphine pump after an operation like yours. That will make sure that you are more comfortable and pain free.

Reimbursements
You will not be given any money for taking part in this trial.

Confidentiality
None of the information that we need in this trial is personal in nature. The information that we collect from this trial will be kept safe and private. We will not share any information about you with anyone outside the trial team.

Sharing the Results
The knowledge that we get from the results of the trial will be shared and published, so that other docters may learn from the findings of the trial. Your name will not be mentioned anywhere.

Right to Refuse or Withdraw
You do not have to take part in this trial if you do not want to and may withdraw from the trial at any time. Whether you choose to take part or not, your decision will not make any difference to the treatment that you will receive from me or the docters that will be doing your operation.

Who to Contact

If you have any questions, you can ask them now or later. If you wish to ask questions later you can contact me in any of the following ways below:
Name : Dr Adri Marais
Telephone : 0000000000
Email : email@gmail.com

Part 2 : Certificate of Consent

I have been invited to take part in a trial to see if injections around the nerves in my stomach wall (transversus abdominis plane block) can help to make the pain after my operation better.

I have read everything on this form with the docter. I have had the chance to ask questions about it and any questions I have been asked have been answered so that I can understand everything.

I am willing to be part of this trial.

Print Name of Participant _____

Signature of Participant _____

Date _____
Day/month/year

Signature of witness _____

Date _____
Day/month/year

Statement by the researcher/person taking consent:

I have accurately read out the information sheet to the potential participant, and to the best of my ability made sure that the participant understands that the following will be done:

1. The participants treatment will not change whether she does or does not take part in the trial.
2. All information will be kept private and locked away.
3. She can withdraw from the trial at any time during the research.

I confirm that the participant was given an opportunity to ask questions about the trial, and all the questions asked by the participant have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily.

A copy of this ICF has been provided to the participant.

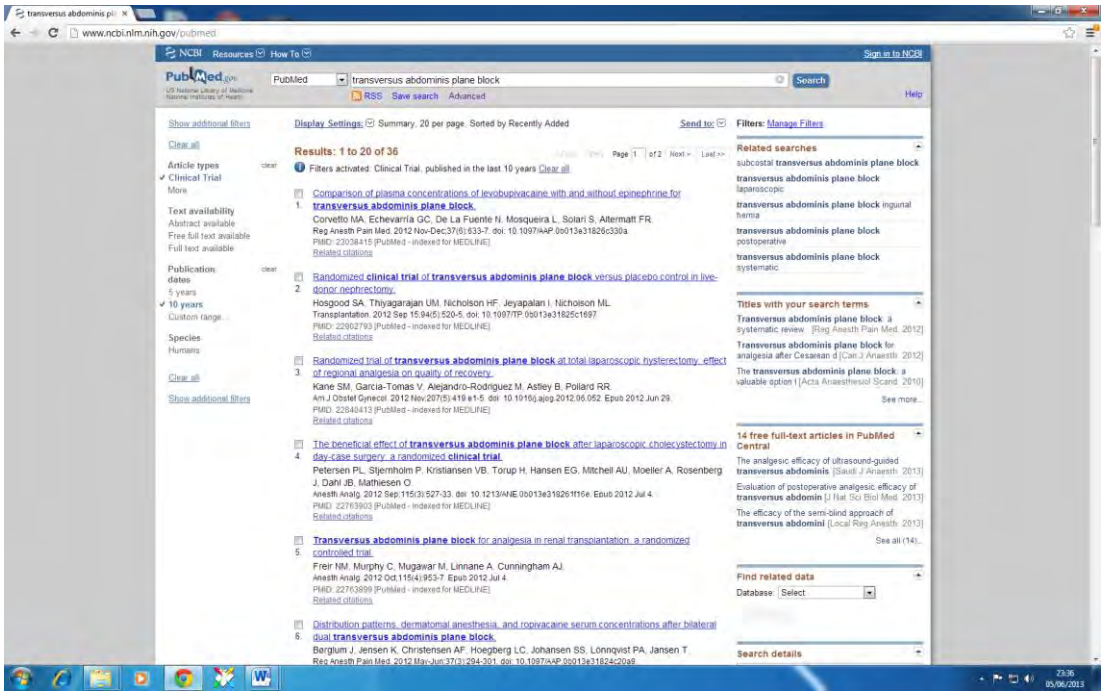
Print Name of Researcher/person taking the consent_____

Date _____

Day/month/year

b. <u>Example of search criteria conducted as part of the literature review</u>

The electronic databases of the Health Sciences Library of The University of Cape Town were used to access MEDLINE, PUBMED and Cochrane library for the published articles. The MeSH terms and text words used were “TAP blocks”, “transversus abdominis plane blocks” and “randomised controlled trial”. Filters were used to include human trials, focusing on randomised controlled trials and meta-analyses. All age groups of patients were included in the search.



c. Official Ethics approval letter from the Faculty Research Ethics Committee

Please see the approval letter below. Please be advised that my name changed from Adri Troskie to Adri Marais. Please see marriage certificate attached

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Human Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: shuretta.thomas@uct.ac.za

11 November 2011

HREC REF: 491/2011

Dr A Troskie
Anaesthesia

Dear Dr Troskie

PROJECT TITLE: EFFICACY OF ULTRASOUND GUIDED TRANSVERSUS ABDOMINIS PLAIN BLOCKS AS PART OF A MULTIMODAL ANALGESIA REGIME IN PATIENTS UNDERGOING AN ELECTIVE TOTAL ABDOMINAL HYSTERECTOMY.

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year till the 28 November 2012.

Please submit a progress form, using the standardised Annual Report Form (FHS016), if the study continues beyond the approval period. Please submit a Standard Closure form (FHS010) if the study is completed within the approval period.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please quote the HREC. REF in all your correspondence.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938

s.thomas

d. Annual progress report: Human Research Ethics Committee

UNIVERSITY OF CAPE TOWN

HUMAN RESEARCH ETHICS COMMITTEE 30 JAN 2013 FACULTY OF HEALTH SCIENCES UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☑ Approved	Annual progress report	Approved until/next renewal date	22/11/2013
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	30/1/2013

Principal Investigator to complete the fo

1. Protocol information

Date form submitted			
HREC REF Number	L911301	Current Ethics Approval was granted until	28 Nov. 2013
Protocol title	Efficacy of ultrasound guided transversus abdominis plane blocks as part of a multimodal analgesia regime for total abdominal hysterectomies		
Protocol number (if applicable)			
Principal Investigator	Dr. Kerri Meyers (Masters Surname Trackie)		
Department / Office Internal Mail Address	Department of Anaesthesia, Groote Schuur Hospital / UCT		

1.1 Does this protocol receive US Federal funding?	☐ Yes	☒ No
1.2 Has sponsorship of this study changed? If yes, please attach a revised summary of the budget.	☐ Yes	☒ No

2. List of documentation

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

3. Protocol status (tick ✓)

☐	Open to enrolment
☐	Closed to enrolment (tick ✓)
☐	Research-related activities are ongoing
☐	Research-related activities are complete, long-term follow-up only
☑	Research-related activities are complete, data analysis only
☐	Study is closed → Please submit a Study Closure Form (FHS010)

4. Enrolment

Number of participants enrolled to date	30
Number of participants enrolled, since last HREC Progress report (continuing review)	30
Additional number of participants still required	0

5. Refusals

Total number of refusals (participants invited to join the study, but refused to take part)	0

6. Cumulative summary of participants

Total number of participants who provided consent	30
Number of participants determined to be ineligible (i.e. after screening)	0
Number of participants currently active on the study	30
Number of participants completed study (without events leading to withdrawal)	30
Number of participants withdrawn at participants' request (i.e. changed their mind)	0
Number of participants withdrawn by PI due to toxicity or adverse events	0
Number of participants withdrawn by PI for other reasons (e.g. pregnancy, poor compliance)	0
Number of participants lost to follow-up	0
Number of participants no longer taking part for reasons not listed above. Please provide reasons below:	0

7. Protocol violations and exceptions (tick ✓ all that apply)

☑	No prior violations or exceptions have occurred since the original approval
☐	Prior violations or exceptions have been reported since the last review and have already been acknowledged or approved

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

☐	Unreported minor violations that have occurred since the last review, as well as significant deviations not yet reported, are attached for review

8. Amendments (tick ✓ all that apply)

☑	No prior amendments have been made since the original approval
☐	Prior amendments have been reported since the last review and have already been approved
☐	New protocol changes/ amendments are requested as part of this continuing review (See note below)

Note: If new protocol changes are being requested in this review, please complete an amendment form (FHS006). Specific changes in the amended protocol and consent/assent forms must be **bolded**, *italicised* or tracked and all changes must include a rationale.

9. Adverse events

9.1 Please provide below or attach a narrative summary of serious adverse events and/ or unanticipated problems since the last progress report. Please indicate changes made to the protocol and informed consent document(s) as a result (if not already reported to the HREC).

No adverse events with any of our patients

9.2 Have participants received appropriate treatment/ follow-up/ referral when indicated (e.g. in the case of abnormal or incidental clinical findings, distress or anxiety)?

☐ Yes	☐ No	☑ Not applicable

If yes, please describe:

10. Summary of Monitoring and Audit Activities (tick ✓)

10.1 Was this study monitored or audited by an external agency (e.g. MCC, FDA)?

☐ Yes	☐ No	☑ Not applicable

10.2 Did a Data and Safety Monitoring Board publish a report?

☐ Yes	☐ No	☑ Not applicable

10.3 If yes, please identify the agency and attach a summary of the findings.

Agency Name		Report attached	☐ Yes	☐ No	☐ Not applicable
		DSMB report attached	☐ Yes	☐ No	☐ Not applicable

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

10.4 Has there been any agency, institutional or other inquiry into non-compliance in this study, or any finding of non-compliance concerning a member of the research team?	
☐ Yes	☑ No
If yes, please explain:	

11. Level of risk (tick ✓)

11.1 In light of your experience of this research, please indicate whether the level of risk to participants has:	
☐	Increased
☐	Decreased
☑	Shown no change
If there has been a change, please explain:	

11.2 Please provide a narrative summary of recent relevant literature.
TAP Pockets in total abdominal hysterectomies (Ahmed et al.). - decreased pain scores and decreased Tramadol consumption

12. Statement of conflict of interest

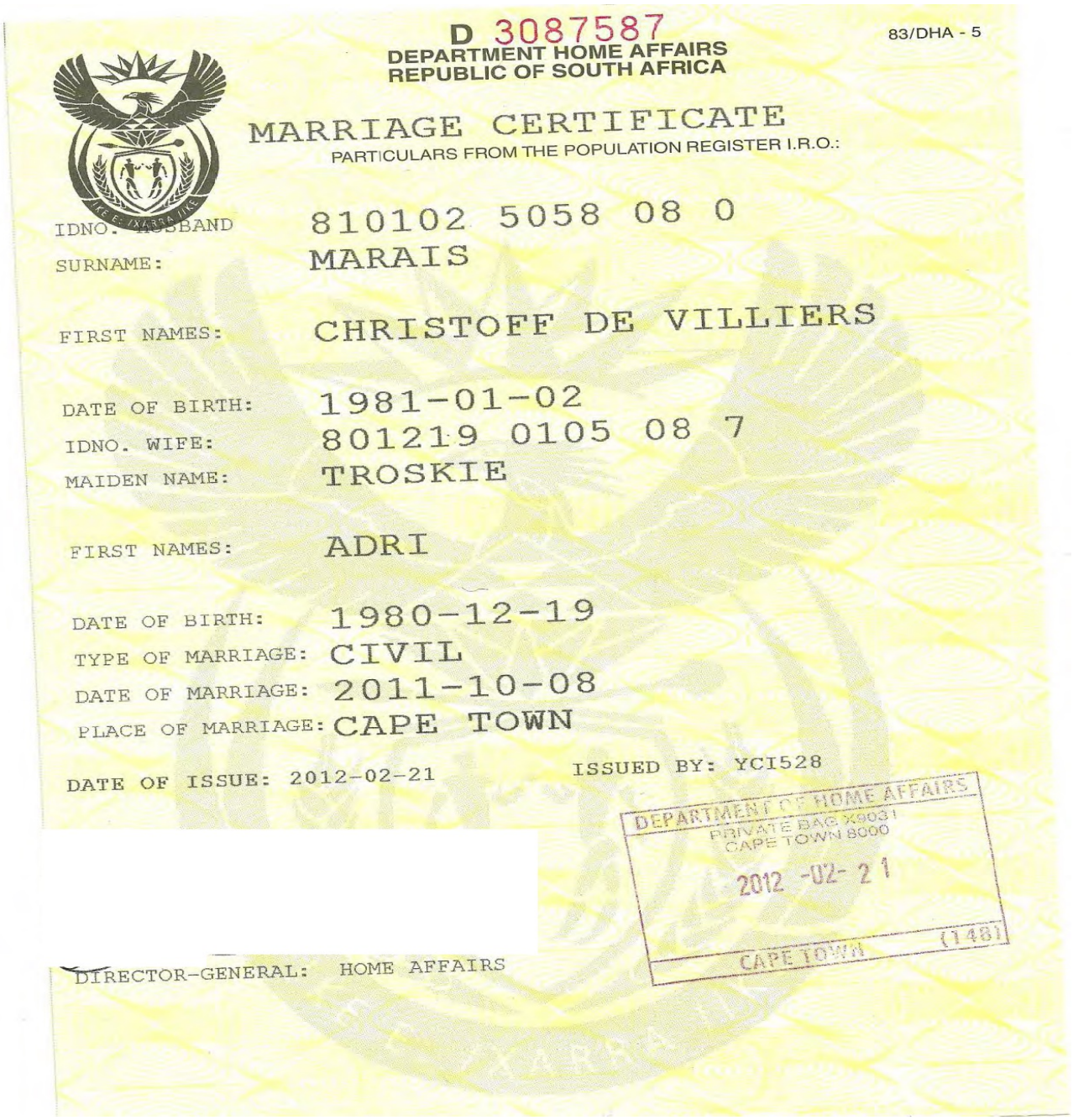
Has there been any change in the conflict of interest status of this protocol since the original approval? (tick ✓)	
☐ Yes	☑ No
If yes, please explain and if necessary attach a revised conflict of interest statement (Section #7 in the New Protocol Application Form (FHS013).	

13. Signature

My signature certifies that I will maintain the anonymity and/ or confidentiality of information collected in this research. If at any time I want to share or re-use the information for purposes other than those disclosed in the original approval, I will seek further approval from the HREC.			
Signature of PI		Date	29/11/13

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

e. <u>Marriage certificate:</u>



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DEPARTMENT HOME AFFAIRS
REPUBLIC OF SOUTH AFRICA

MARRIAGE CERTIFICATE

PARTICULARS FROM THE POPULATION REGISTER I.R.O.:

IDNO. HUSBAND 810102 5058 08 0

SURNAME: MARAIS

FIRST NAMES: CHRISTOFF DE VILLIERS

DATE OF BIRTH: 1981-01-02

IDNO. WIFE: 801219 0105 08 7

MAIDEN NAME: TROSKIE

FIRST NAMES: ADRI

DATE OF BIRTH: 1980-12-19

TYPE OF MARRIAGE: CIVIL

DATE OF MARRIAGE: 2011-10-08

PLACE OF MARRIAGE: CAPE TOWN

DATE OF ISSUE: 2012-02-21

ISSUED BY: YCI528

DEPARTMENT OF HOME AFFAIRS
PRIVATE BAG X9031
CAPE TOWN 8000
2012 -02- 21
CAPE TOWN (1481)

DIRECTOR-GENERAL: HOME AFFAIRS