**Native tissue repair with or without autologous blood graft augmentation for
pelvic organ prolapse: A randomised controlled trial**

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I have read and agree to follow the NHMRC National Statement
on Ethical Conduct in Research Involving Humans.

Signature \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Funding**

Commercial sponsorship:

The roles of the sponsors (FBW Gyn Plus and Smartfem medical technology Pty Ltd):

* 1. FBW Gyn Plus and Smartfem Medical Technology Pty Ltd are companies of the FBW group.
	2. The IP holder is Smartfem Medical Technology Pty Ltd.
	3. The Smartfem service entity will pay for the graft kit, products which are provided to the patient at no charge, admin, research nurse, research assistant, research manager, statistician, editors, stationary etc.
	4. Smartfem Medical Technology Pty Ltd applies for grants from the government

Patients will be assessed and treated in a private gynaecological clinic (FBW Gynaecology Plus, Adelaide) and will not incur extra out-of-pocket expenses for the treatment.

**Research Sites**

FBW Gynaecology Plus
- 46 Marleston Ave, Ashford, SA, 5035;
- Suite 11, 480 Northeast Road, Windsor Gardens, SA 5078;
- (08) 8297 2822
 – recruitment, treatment administration, data analysis, reporting.

Site of Surgery
- Ashford Hospital, 55 Anzac Highway, Ashford, SA 5035
- North Eastern Community Hospital, 580 Lower North East Rd, Campbelltown SA 5074
 – location of surgery who have been seen at FBW Gynaecology Plus

**Clinical laboratories involved in this trial**

Not applicable

***INTRODUCTION***

Pelvic organ prolapse (POP) is a common gynaecological condition with an incidence of 40-60%, and 12-19% of women undergo surgical correction (1-5). Standard technique of native tissue repair (NTR) relying on damaged tissue is associated with variable success and recurrence rate up to 30-50% initiating the exploration of innovative surgical techniques and grafts to improve long-term outcomes (4, 6-8).

Main risk factors for primary POP are parity, vaginal birth, age, and obesity; additionally, advanced preoperative stage of POP is associated with POP recurrence [1-4] Surgery is preferential for younger women with more severe symptoms related to quality of life, if also affecting bladder, bowel, and sexual function [5]. Use of transvaginal polypropylene mesh is no longer accepted in most of the global market due to unfavourable complications of increased reoperation rates, mesh erosion, dyspareunia, and chronic pelvic pain [2, 6]. Hence, popularity has shifted towards abdominal or laparoscopic sacrocolpopexy and innovative approaches to vaginal mesh management [7, 8].

Other surgical techniques using biological grafts or absorbable mesh to augment POP have been trialled, with systematic reviews based on low quality evidence demonstrating minimal advantage compared with NTR regarding rates of awareness of prolapse or reoperation [9-11]. Low to moderate quality evidence suggests higher recurrence rates for anterior prolapse after NTR than with biological grafts [12].

***Background information regarding autologous graft***

Recent randomised controlled trials (RCTs) comparing various surgical approaches, robotic-assisted techniques, mesh, or sutures conclude insignificant difference regarding effectiveness or incidence of prolapse recurrence, requiring or currently undergoing further investigation [13-20]. Pre-operative ultrasonography has been assessed showing minimal influence on planned surgery [21]. Paravaginal repair techniques with and without biological graft show promising results [22-25]. As an alternative to current techniques, we have considered the novel use of autologous graft in the augmentation of NTR at the time of POP surgery, aimed as a biological support to regenerate damaged native tissue.

Whole blood injections are effective in tissue healing process; a systematic review has shown that autologous whole blood injections have a large effect size in tissue repair [26]. Autologous blood injections optimise healing response by releasing growth factors, cytokines and proteins, which regulate the balance of promoting and reducing biological processes of inflammation, angiogenesis, cell proliferation, and extracellular matrix formation [27, 28]. In vitro and animal models have demonstrated these processes via histological analyses [29-32]. Growth factors that contribute to ligament reconstruction include vascular endothelial growth factor, insulin-like growth factor, platelet-derived growth factor, hepatocyte growth factor, transforming growth factor, and fibroblast growth factor. The autologous and biodegradable properties prevent blood products from inducing foreign body reactions unlike synthetic mesh [29]. RCTs continue to document the ability to accelerate treatments, reduce morbidity, and enhance functional recovery in several medical fields [33]. Moreover, autologous blood graft application has the advantages of decreased invasiveness, cost effectiveness, and easy preparation [34]. These therapies appear safe and effective when performed by an experienced clinician [26].

We hypothesise that when an autologous graft created from the combination of whole blood and calcium gluconate is attached to the endopelvic fascia, there is a proliferation of growth factors and acceleration of tissue healing of the endopelvic fascia. According to our knowledge, its use in gynaecological surgery is novel and has not previously been described in the literature.

**OBJECTIVES AND PURPOSE OF STUDY**

The objectives and purpose of this project are to determine the success rate for pelvic floor repair augmented with autologous graft in comparison to traditional pelvic floor repair, also called anterior and posterior vaginal repair, for the treatment of pelvic organ prolapse.

***STUDY DESIGN***

***Participant’s identification and requirement***

Participants will be identified and approached for inclusion within this study through pre-established medical clinics; advertisements will not be used. Recruitment will be conducted at FBW Gynaecology Plus at no cost to the patient.

This is a single-centre, double-blinded [patients and the second surgeon will be blinded] randomised controlled trial of women who undergo NTR for POP. The procedure does not use a sham graft as it could be considered unethical. This study is to compare NTR alone to NTR with autologous graft. It is not possible to blind the surgeon performing the prolapse surgery. However, the surgeon not performing the surgery will assess the patient post-op for data collection to reduce bias. All project investigators are physicians who perform regular gynaecological consultations. The physician carries out a routine history-collecting interview, performs examinations, and conducts the relevant tests to confirm the diagnosis. The second surgeon will perform the examination and assessment after the surgery without the first surgeon involvement in data collection.

|  |  |  |  |
| --- | --- | --- | --- |
| Objective | Endpoint | Statistical Methodology | Comment |
| Primary |
| Efficacy |
| To determine the success rate for pelvic floor repair augmented with autologous graft in comparison to native tissue repair. | Success (Binary), based on change in POPQ.ORRecurrence rate (binary) | Protocol states power calculationLogistic regression would be more appropriate. | Is the primary outcome the recurrence rate or the success rate, as they appear to be completely different. The definitions for both success and recurrence need to be clearly defined and include handling of missing data and drop-outs. |
| Secondary |
| Efficacy |
|  | APFQ | MMRM | There are no secondary objectives to align with these endpoints. |
|  | Standardised VIBe scale | MMRM |  |
|  | Pain VAS | MMRM |  |
|  | Bruising VAS | MMRM |  |
| Safety |
|  | Number of minor and major complications | Descriptive statistics | A safety objective has not been included. |
|  | Infection | Descriptive statistics |  |
|  | Unplanned return to theatre | Descriptive statistics |  |
|  | Catheter for urinary retention | Descriptive statistics |  |
|  | Visceral injury | Descriptive statistics |  |
|  | Venous thromboembolism | Descriptive statistics |  |
|  | Pulmonary embolism | Descriptive statistics |  |
|  | Analgesia | Descriptive statistics |  |

*Inclusion criteria:*

Participants will be considered eligible for this study if they:

|  |
| --- |
| 1. Are female patients over the age of 18 |
| 2. Have been formally diagnosed with pelvic organ prolapse quantification (POPQ) stage 2 of anterior and or posterior compartment with or without apical prolapse, defined as c -1 or less. |
| 3. Understand the conditions of the study fully and are willing to participate for the length of the study in its entirety; |
| 4. Are capable of giving informed consent to their participation in the study. |

*Exclusion criteria:*

The following patients will be deemed unsuitable for inclusion:

|  |
| --- |
| 1. Patients currently suffering any untreated gynaecological cancers.
 |
| 1. Patients with autoimmune disorders requiring anti-platelet medication (antiplatelet drugs weaken the regenerative capacity of autologous blood products and reduces the quality of the graft) [35].
 |
| 1. Patients who are immunocompromised (e.g. lymphoma, AIDS) or have uncontrolled malignant disease.
 |
| 1. Patients on anti-platelet treatment. Using anticoagulants and NSAIDs is not allowed three weeks before and after surgery due to their interference with the scaffold formation.
 |
| 1. Patients who have a mental disability leading to their inability to consent.
 |
| 1. Patients who are pregnant.
 |
| 1. Patients who are uncooperative, known to miss appointments, are unlikely to follow medical instructions, or unable to attend regular scheduled visits.
 |

The patient will be briefed on current mainstream treatments for pelvic organ prolapse and informed about the study treatment options being investigated. The patient will be provided with a Patient Information Sheet (PIS) on the autologous graft and its clinical applications and a simply formulated summary of the literature. Randomisation will be explained to patients and they will have an equal chance of receiving either routine conventional prolapse surgery or prolapse surgery with autologous graft.The patient may choose to participate in the study on the day of their initial consultation but will need to completely read the Patient Information Sheet and sign the consent first. Patient will be given the opportunity to ask questions about the study and will then be asked if she gives written consent to participate in the study. If the patient declines participation, then the patient is encouraged to make an appointment with her gynaecologist to ensure appropriate follow-up.

If a patient agrees to participate in the study, a co-investigator or research assistant will schedule the patient’s initial study consultation at FBW Gynaecology Plus. This appointment will take place with the principal investigator, who might be the same gynaecologist that made the patient’s diagnosis in the first place. Activities that are expected to occur during this appointment will be explained to the patient and any of the patient’s questions will be answered.

Involvement in this study is voluntary and patients’ ongoing medical care will not be impacted in any way if they choose not to enrol in the study. They will have standard of care for which they were referred. Patients who wish to participate will be required to sign a Participant Consent Form and be informed that they may withdraw from the study at any stage. The Participant Consent Form will be signed prior to the first assessment consultation taking place. A copy of the signed Participant Consent Form will be filed in the participant’s medical record at FBW Gynaecology Plus, Adelaide.

The clinic is in central Adelaide and offers ample free parking. Patients will not incur any personal fees for participating in the study.

*Withdrawal criteria:*

It will be made clear upon commencement of the study that participants are volunteers and are free to withdraw from the study at any point. Reasons for withdrawal will be documented if the participant chooses to provide it. Any participant who does not complete the full treatment regime outlined within the attached documents and/or complete all assessments, will be withdrawn from the study. This will be employed to ensure the quality of the data being analysed. The number of participants withdrawn or excluded from the study will be included in the report. A patient who withdraws from the study at any stage will be advised to see her referring physician to continue with conventional treatment.

***Study process***

*Initial Consultation:*

Patients who express interest will be scheduled to attend their first participant appointment with the principal investigator. The purpose of this consultation will be to obtain consent from the patient, record baseline data, schedule surgery time and subsequent assessment appointments, and assign the patient with a study identifier number. This will be achieved in a standardised manner, by utilising pre-filled envelopes that contain the following documents:

* Study Algorithm Form (for recording surgery and assessment dates as well as existing as a standardisation tool).
* Two Participant Consent Forms (two forms, one for inclusion in the patient’s medical record and the second to be retained with the study files).
* Study Enrolment Form (Supporting document; demographic information collection sheet and inclusion criteria checklist).
* Appointment Card for all treatment and assessment appointments document.
* Assessment Package
* Study Identification Stickers
* Patient’s confidential code numbers.

The following tasks will then be completed:

* The principal investigator will write the participant’s name on the front of the envelope alongside one study identification sticker.
* The Patient Consent Form will be completed, with one form being entered into the patient’s file and the other being filed with the study documents.
* The principal investigator, through discussion with the patient, will complete the Study Enrolment Form. This will ensure that relevant demographic information is collected, as well as ascertaining that the patient meets inclusion criteria.
* One assessment package will be completed. This package is the collection of the ‘treatment outcome measures’ and serves as the ‘baseline’ data of the participant.
* An appointment card will be completed and provided to the participant.

Following the completion of the first appointment, all documentation will be placed inside the envelope and transferred to a Research Assistant. This person will be responsible for formally enrolling the participant into the study by entering the collected details into the study’s database. All documents will remain within the envelope and filed in preparation for the participant’s next documents in the future follow-ups.

As is the case with any medical procedure, all the blood tests, electrocardiogram (ECG) and other assessments will be performed prior to the surgery.

*Treatment procedures:*

Randomisation and blinding

This is a double blinded trial [patients and assessing surgeon will be blinded]. Because the procedure does not use a sham graft, it is impossible to blind the surgeons; a safe sham graft with the same structure is not available for pelvic floor repair surgery and can be seen as unethical. Participants will be assigned randomly in a 1:1 ratio to one of two treatment groups (surgery with whole blood graft or conventional surgery). Treatment allocation will be determined by a computer-generated randomisation schedule with block randomisation). Treatment assignments will be placed in consecutively numbered, opaque-sealed envelopes that were opened by the surgeon in the operating theatre before surgery. Patients will be blinded to their treatment assignment. The statistician is blinded by the treatment of the patient. A blood sample will be taken from each patient and labelled for each patient immediately before their surgery to ensure blinding of the patient. The graft is delivered to the surgeon by a scrub nurse who is not a part of the evaluation of the study. The post-operative care is standardised as per protocol used by the surgeon for both groups. Research staff administering and collecting the study questionnaires and outcomes will be blinded to the participant's treatment group for the entire duration of the study. In addition, there is a system in place that the doctors do not have immediate access to the quality of life, which is APFQ, raw data, statistics, and analysis. This is done by nursing staff and research assistants.

The process of manufacturing the autologous blood graft

The manufacturing process for the autologous blood graft was developed and patented by Smartfem Medical Technology. This process is performed at the time of surgery. There is no laboratory preparation for this generated graft. The whole blood is taken from the patient immediately before surgery and prepared in an aseptic and standard operating code for usage at the time of surgery. Patient’s own whole blood will be used to produce individualised graft. Depending on the size of uterovaginal prolapse, multiple grafts are developed. Approximately 20- 40mL of patient blood is taken right before the surgery in the holding bay or operating theatre. In parallel with the surgery, the process of graft making is performed (nearly one hour). Centrifuge is pre-set at 1500-4000 RPM, depending on how long the surgery takes. Sterile PRP tube with patented mixture that has the Therapeutic Goods of Australia (TGA) approval is used as a closed system to extract whole blood. The fresh blood and the patented mixture are centrifuged at 1500-4000 RPM for 35-60 minutes to create an autologous graft in a sterile manner for surgical use following the standard protocols of operative sterility. By the time that the surgical repair is almost completed to the level of endopelvic fascial repair, the graft is prepared and ready to be inserted and attached on the site of the surgery onto the endopelvic fascia to biologically augment the native tissue repair.

Standard operating procedure includes:

The study doctor is responsible for collecting blood specimen by venipuncture and following recommendations according to national guidelines (National Safety and Quality Health Service Standards: Blood Management Standard on www.sahealth.sa.gov.au/) . Avoiding possible backflow from the blood tubes, filling the blood tube completely, removing tube from adapter and immediately mix by gentle inversion of the tube. Whole blood sample can be kept at 18-20 degrees Celsius – which is the standard operating theatre temperature. The process requires labelling of containers or tubes. The patient’s details are confirmed between two theatre staff using a verbal protocol which includes stating the participant’s full name and date of birth. This is a common practice that aims to reduce errors in administration [36] and is commonly referred to as ‘time out’. Each sample will be prepared and immediately used on a participant-by-participant basis, leaving no risk of cross-contamination.

Product release specifications:

Before using the final product for patients, the integrity of the graft is assessed by using 4 non-toothed forceps lifting from its container to the repair site. Please see the picture 01



Picture 01. The autologous whole blood graft.

This will test for its integrity and suture-ability. This is a scaffold for biological support rather than a tough material for mechanical support. The size of the graft is 2.5-5cm depending on the patient’s vaginal length (5cm to 15cm), multiple grafts on one side might be used.

The product is aimed to be safe, sterile, and effective. During the graft manufacturing process in the operating theatre environment, standard operating codes are followed so that sterility is guaranteed.

Traceability and handling:

A close collaboration between individuals who collect blood samples and prepare final graft products and the surgeons, as well as standard labelling of all tubes and containers with full names, date of birth, and date of surgery, will enhance the traceability of our blood products. The patient hospital ID sticker is placed on the container to ensure traceability. So, at any time, the surgical team know “whose blood is this or who will receive the final product.” An appropriately trained clinician (Principal Investigator or Clinical Nurse) will collect the autologous blood sample from the participant right before surgery to make the autologous blood graft in the operating theatre by the gynaecologist where there is only the recipient being operated on.

Handling blood and blood products will be performed considering minimal manual handling of all blood and blood products to ensure products are kept within their recommended temperature ranges, which is 18-20 degrees Celsius. Any blood sample not used during the treatment consultation will be discarded. A serial number will be on each kit for traceability.

Surgery:

The scheduled POP surgery with or without autologous graft will be performed in the hospital by two surgeons, Dr Fariba Behnia-Willison (FBW) and Dr Tran Nguyen (TN). Following general anaesthetic, conventional vaginal repair is carried out by a midline incision into the vaginal epithelium is made and the underlying fascial defect is repaired using V-Loc 2.0 delayed absorbable suture (Medtronic). Prior to closing the vaginal epithelium, the autologous graft is sutured or glued to the underlying fascia in the intervention group. The control group will have conventional repair only, which is without autologous graft augmentation. In all patients, the vaginal epithelium is then closed with 2-0 Vicryl (polyglactin 910, Ethicon). Where required, an apical suspension will be also performed with or without concurrent hysterectomy. Apical suspension will be achieved through either a sacrospinous fixation placed with a CapioTM SLIM device with a delayed absorbable monofilament suture (Boston Scientific), a laparoscopic uterosacral ligament fixation (either hysteropexy or colpopexy with 2.0 V-Loc delayed absorbable suture) or a laparoscopic sacrocolpopexy using mesh (approved by TGA). A hysterectomy would be performed following a discussion with the patient or for any suspected pathology.

At completion of surgery, a vaginal pack and in-dwelling catheter will be placed until the next morning prior to a formal trial of void. Routine strict postoperative instructions will be provided to the patient including advice on physical activity, bowel habit and intercourse.

Postop care guide has been described in post-surgery information sheet (IUGA post vaginal repair- attachment 6). All patients will be discharged on five days of oral antibiotics, such as Amoxicillin and Clavulanic acid. Before discharge, the Treatment Record Sheet (Attachment 7) will be completed accordingly.

To quantify bleeding/pain/bruising visual scales will be used by the study doctor. Three scales have been showed in attachment 8 Pain visual analogue scale is from 0 to 10 and bruising visual scale is from 1 to 5. Standardised VIBe scale (0-4) will be used to quantify post-surgery vaginal bleeding [37].

Follow up appointments:

Patient follow-up will be conducted as a phone call from the clinic nurse at 1 week and as a face to face review at 6 weeks, 6 months, and 12 months. They will be advised to monitor and immediately report any adverse events. All adverse events regardless of their relationship with surgery any changes in medication and specific question around pain medication specifically related to the surgery and classifying as opioid/non-opioid will be recorded. At each assessment consultation, the first surgeon (who performed the procedure) will not be the study doctor to examine the patient. One of the co-investigators will complete the check-up and surgical site examination. At the final assessment consultation, participants will have the opportunity to ask any questions before being discharged from the study. They will be advised to arrange a follow-up appointment with their referring physician. The participant will receive a letter about the research findings. The assessment includes completing the The Australian Pelvic Floor Questionnaire (APFQ) and a gynaecological exam at each visit.

***Data collection tools & dependent variables***

Prospective data will be collected on an initial enrolment sheet and entered into the research database. Patient demographic data were collected, including age, BMI, menopausal status, past medical, surgical, familial, gynaecological, and social history, and past/current medications.

Objective outcomes are quantified by the doctors by using the standardised international POPQ system at the time of vaginal examination (13). The subjective outcomes are assessed by APFQ (12). To increase the validity of the POPQ score, all examinations will be performed by the second surgeons (who has not performed the surgery).

The primary outcome is the anatomical success rate of pelvic organ prolapse at one-year post-op. The POPQ pre- and post-op are compared. Success is defined as POPQ less or equal to -1 and no reoperation for anterior and posterior vaginal wall prolapse at one year post operative. Failure is defined as POP-Q greater than 1 ora vaginal bulge at the hymen at Valsalva. Participants not considered a treatment success for the primary outcome will be considered a treatment failure.

Secondary outcomes are:

Secondary outcome include quality of life as assessed by total score of APFQ, which is a validated tool that integrates bladder, bowel, prolapse, and sexual function. Higher scores in each domain suggest greater QOL impairment. Patients will be asked to fill out APFQ questionnaires at baseline and each follow-up visit. Other secondary outcome are minor and major complication rates, infection, severe bleeding (blood loss of 500mls), urinary tract infection (confirmed on urine test), wound breakdown (confirmed on vaginal examination), graft rejection (confirmed on vaginal examination), unplanned return to theatre, urinary retention treated with catheter (confirmed on when bladder scan is greater than 500ml and the patient is unable to void), visceral injury (confirmed in surgery via visual inspection), venous thromboembolism and pulmonary embolism (confirmed on ultrasound or CT-Scan imaging). Another secondary outcome is postop pain score by pain visual analogue scale and amount of analgesia will be compared in both groups.

***Statistical Design and Analysis Plan***

***Sample size***

Sample size has been calculated from the 12-month POP recurrence rate based on the study of [5]. The recurrence rate after pelvic floor repair surgeries is 30-50%. Based on a 30% recurrence rate, a 50% reduction (around 15 percentage points reduction) would yield a recurrence rate of 15% in the surgery with graft group. The estimated sample size would be n = 134 participants per each arm using two-sided Fisher’s exact method, alpha=0.05, at 80% of power. Assuming an attrition rate of 10%, we would require n=149 patients per group, with a total of 298 patients. A PASS software was used to calculate the sample size.

***Statistical analysis***

Statistical analysis will be completed using R program version 4.3.0. A p-value of 0.05 is selected to assess statistical significance. Means and standard deviations (SD’s) will be calculated for continuous data and proportions for categorical data. The normality assumption will be visually checked by frequency histogram and normal Q-Q plot for continuous measurements. A power calculation will be performed based on recurrence rate of prolapse 6 months and one year post surgery in the intervention group compared with the control arm.

Binary primary outcome will be assessed by Logistic Regression analysis. Continuous numerical data will be analysed by Linear Regression method. As the outcome occurs for each individual with repeated time points, the mixed effect models will capture both fixed effects and random effects within the hierarchical structure of the data. Thus, models will account for the clustering in patients using mixed (for interval scale data – domain score) and melogit (for binary outcomes – QOL). Patients will be treated as random effects, and main effects were group, time and group x time interaction. Models will be adjusted by age (or age group) and BMI as they are clinically important. Missing data for the main variables of interest, as patients who fail to attend appointments will be called for necessary data collection (e.g., completion of the Australian Pelvic Floor Questionnaire).

***Study duration***

The study will run over a minimum of 18 months to account for the initial recruitment period and follow-up. The study will commence when ethics approval is granted. The study will require 12 months follow-up participation from each participant.

**ASSESSMENT OF EFFICACY**

Treatment efficacy will be determined by outcomes (comparing the intervention versus control groups and pre- versus post-treatment differences) on relevant dependent variables.

**ASSESSMENT OF SAFETY**

Timely and complete reporting of adverse events/serious adverse events (AEs/SAEs) will be done; in this study we will implement regulatory requirements in this regard. AEs/SAEs will be monitored hourly during the first four hours after surgery and every four hours during the hospital stay; as well as in all routine post-surgical check-ups by the surgeons. Follow-up AEs monitoring will be conducted at 6 weeks, 6 months, 12 months, and yearly. Additional follow-ups will be tailored according to individual cases. Our team will be available to check on patients as soon as possible if they show signs of AEs/SAEs after discharge. Patients will be provided with a phone number to contact the surgeon if concerned about any AE. If severe complication occurs afterhours, such as haemorrhaging, patients are encouraged to seek urgent medical attention at the nearest emergency department. They will also be provided with a postop information sheet, which included details on what to expect following treatment, and when to report any adverse outcomes, such as infection, bleeding, bruising or pain. At any time and at the time of the initial phone call or presentation, all adverse outcomes will be recorded and entered into digital medical records by nursing staff or doctor. Bleeding is normal up to 6 weeks post-vaginal surgery as long as it does not exceed soaking a sanitary pad. If there is heavy bleeding which requires changing of pad on hourly basis and passing clot, a swab is taken and full blood examination test is measured and action such as return to theatre for further examination or re-suturing would be performed. Often, these kinds of conditions are related to a vaginal infection as the vagina is not a clean environment and closed to the rectum. However, using an autologous graft should reduce the bleeding and risk of pain and infection due to its anti-inflammatory nature and expediating the wound healing and tissue augmentation.

There is a separate dataset in our research’s online database to collect and consider information as a reportable AEs/SAEs in details: an identifiable patient, an identifiable reporter/examiner, an event, and the event’s time. All AEs including infection, severe bleeding (blood loss of 500mls), urinary tract infection, wound breakdown, vaginal epithelium separation or ulcer, unplanned return to theatre, urinary retention treated with catheter, respiratory complication, visceral injury, and venous thromboembolism will be evaluated in an additional checklist in each visit and reported when we will conclude our results. AE/SAE will be assessed if related to the graft or vaginal surgery. After an adverse event, the patient will be followed up until the adverse event is resolved. The methodological design of this study requires all participants will receive a phone call from the clinic nurse at 1 week and physically assessed at six weeks, six and 12 months after treatment. This design has an inbuilt means of assessing all participants for any AE up to 6wks and failure rate up to 12 months post-treatment.

There is an independent safety data review committee which has access to our online database [including AE dataset]. All AE experienced by a participant will be recorded and the safety data review committee notified. Any adverse events will be reported to this committee. The committee including two gynaecologists, clinical trial consultant (Professor Paul Rolan) and data analyst,. All safety reports and AEs dataset will be reviewed at least monthly by the committee members and they will meet every three months as a part of research safety monitoring. Additionally, the safety data review will be conducted monthly at the morbidity meeting of the clinical practice.

The medical clinicians involved in this study are highly experienced at supporting patients as they reveal their medical history, express their treatment desire, and deal with their reactions to treatment. The emotional and psychological wellbeing of participants within this study is important to the investigators, which is why the QOL questions are being employed at baseline and at each assessment.

The incidence of serious complications following vaginal repair surgery is between 2.3 and 4.2% in the general population [38-40]; stoppage cut-offs were considered more than 4% for this study. The data recording is up to date and complications will be monitored by a research manager and a research nurse for one week and 6 weeks; as earlier mentioned, safety data review committee will meet every three months. The research team are meeting on a weekly basis to review the progress of the study and if any major complication had occurred as a part of routine control check list. If the percentage of complications exceeds normal ranges (more than 4%), an emergency meeting will be held with safety committee to assess the main causes.

**ROLE OF CO-INVISTIGATORS**

Co-investigators will be involved in patient recruitment, obtaining consent for involvement in the study, following up the patients with the standardised template provided to them, data collection, and data analysis.

**DIRECT ACCESS TO SOURCE DATA/DOCUMENTS**

Digital medical records (including demographics, the heath questionnaires and gynaecological examinations) can be checked at any time. All participants documents will be kept inside the envelope and a non-clinical research assistant will extracted the related data, entered them into the Excel databases.

The Principal Investigator will permit trial-related monitoring, audits, IEC review, and regulatory inspection(s), providing direct access to source data/documents.

**QUALITY CONTROL AND QUALITY ASSURANCE**

Information will be entered by a research assistant with research background, and all data analysis will be performed by a statistician.

**ETHICS**

It is important that the clinician audit their own work, compare it to that of their colleagues, present and publish results in order to provide better care in every aspect of their clinical work.

The study will be conducted in conformity with the principles of the Declaration of Helsinki, with the principles of Good Clinical Practice (GCP), and within Australian laws and regulations.

All patients will be provided with information on their respective treatments, outlining general risks, side-effects and potential complications, possible medical alternatives, and the post-treatment course. Patients who received treatment will be contacted either by email or by standard mail. FBW administration staff will email copies of the Participant Information and Consent Form to patients who have previously agreed to receive online communications from FBW Gynaecology. The remaining patients will receive the documentation by standard mail, along with a self-addressed stamped envelope.

***Benefits anticipated from study***

The main benefit of this study for participants will be potentially having their gynaecological condition successfully treated. This would involve potential remission of the symptoms and signs experienced by the patient, improving her quality of life.

If this study does reveal effective treatment, then this study has the potential to positively reshape the treatments offered to women with POP around the world.

**DATA HANDLING AND RECORD KEEPING**

A digital copy of each patient's record and their documents will also be stored electronically with secure password protection. The system and office IT system has high level Cyber security protection.

Relevant outcomes will be stored in Microsoft Excel and a statistical software. Within the database, individual patients will be de-identified and referred to numerically. Data will be entered and analysed on-site at FBW Gynaecology Plus, with access available to the chief investigator and a trained statistician. Data will be analysed using basic univariate and/or multivariate statistical techniques.

**PUBLICATION POLICY**

Findings from this study may be presented at national and international academic conferences and/or disseminated through peer-reviewed journals.

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