**Principal Investigator:**

**Fariba Behnia-Willison**

FBW Gynaecology Plus

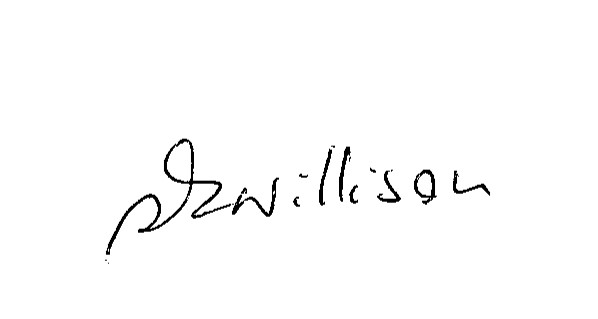
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I have read and agree to follow the NHMRC National Statement on Ethical Conduct in Research Involving Humans.



Signature \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date 01/11/2017

**General Information**

**Protocol Number:** PRP4LS

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5. Instituto Gineco-Oncológico, San Juan, PR 00914

6. Cork Womens Clinic, Western Rd. Cork

**Funding**

Commercial sponsorship: None.

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Patients will be assessed and treated in a private gynaecological clinic (FBW Gynaecology Plus, Adelaide) and will not incur out-of-pocket expenses for the treatment. Medicare will not be billed nor will the patient’s private health fund be charged for the consultation or treatment.

**Research Sites**

FBW Gynaecology Plus, 21 Alexander Ave, Ashford, SA, 5035; (08) 8297 2822

– recruitment, treatment administration, data analysis, reporting.

**Clinical laboratories involved in this trial**

Healthscope Laboratories, Ashford Hospital, Adelaide.

***1.1. INTRODUCTION***

Using a randomised control trial design, the study intends to compare platelet-rich plasma (PRP) against placebo (normal saline) as a treatment for women with symptomatic lichen sclerosus (LS) who present for treatment at FBW Gynaecology Plus and who consent to participate in the study. Specific inclusion and exclusion criteria are listed in Section 4. The study will require a total of 68 participants, 34 per group; the sample size calculations are provided in section 8.

The study aims to build upon recently published results from a pilot study (Behnia-Willison et al., 2016) conducted by the Principal Investigator. This study involved 28 participants who received vulvo-vaginal PRP treatment for LS at FBW Gynaecology Plus to mitigate symptoms. The current study will be carried out in compliance with the principles of good clinical practice and applicable regulatory requirements.

A previous HREC application for this study was submitted to Bellberry (Application ID: 2016-05-452) and considered on 22 June 2016. The submission was rejected. The Principal Investigator and a dedicated research team have carefully reviewed each concern raised by the Committee in its letter dated 24 June 2016 and have addressed all issues. The HREC application was resubmitted in July 2017 (Application ID 2017-07-546). The application has been modified as a response to the HREC questions and comments.

**2 BACKGROUND TO THE DISEASE**

***2.1******Lichen Sclerosus***

Lichen sclerosus (LS) is an acute and often chronic inflammatory dermatosis with autoimmune pathogenesis (Neill et al., 2010). It is a debilitating condition with serious consequences for the patient’s physical, emotional and sexual health (Newman et al., 2015). This condition affects 1.7% of patients referred to general gynaecology (Halonen et al., 2017). Although relatively common, its true incidence is unknown and likely underestimated (Neill et al., 2010). LS is a condition affecting women of all ages; it has a bimodal peak in incidence among prepubertal and post-menopausal women (Halonen et al., 2017).

LS is usually anogenital, but extragenital involvement occurs in 6-20% of patients (Kirtschig, 2016). There is currently no cure or a suitable treatment for all patients with LS. Topical corticosteroid therapy is the mainstay treatment for LS (Sinha et al., 1999). However, it requires continuous application and can be associated with adverse effects (Hengge et al., 2006).

Much of the management of LS is aimed at controlling symptoms, mainly severe vulvo-vaginal pruritus. Some women with LS are either unresponsive to corticosteroids or hesitate to use them. Other topical treatments include calcipotriol, retinoids, tacrolimus, and pimecrolimus. Photodynamic therapy has also been reported to be beneficial (Olejek et al., 2009). Surgical treatments involve vulvectomy, cryosurgery, and laser ablation (Neill et al., 2010). These procedures can pose a risk of scarring to damaged tissues and disease recurrence (Casabona et al., 2010). Hence, less invasive techniques are of interest. The potential adoption of autologous platelet-rich plasma (PRP) for autoimmune skin conditions such as LS has been discussed in the literature (Boero et al., 2016) and has demonstrated promising results in cohort studies (Casabona et al., 2010) and, more recently, Behnia-Willison et al. (2016) with a sample of 28 patients over a two-year period. Therefore, this study is to evaluate PRP as a treatment for lichen sclerosus in a randomised controlled trial.

* 1. ***The role of platelet-rich plasma (PRP) as a potential alternative treatment for LS***

The use of PRP as a regenerative medical therapy for damaged tissue has yielded positive results in orthopaedic, reconstructive surgery, dentistry, dermatology and musculoskeletal medicine (Eppley, 2006; Foster, 2009; Marx, 1998; Shin, 2012). PRP treatment has shown promising preliminary results in gynaecology too. It is associated with reduced treatment burden in the areas of sexual dysfunction (Runels et al., 2014). Behnia-Willison et al. (2016) reported that most patients treated with PRP experienced improvement in their LS symptoms, with lesions disappearing completely in 28.6% of this pilot study cohort.

The theory behind PRP relates to the activity of concentrated autologous platelets being injected into regions of the body, resulting in activation and release of platelet growth factors. These growth factors interact with cell receptors and instigate signal transduction which then stimulate cell growth and proliferation (Crane & Everts, 2008). Effectively, they can activate stem cells, resulting in new collagen formation and eventual tissue regeneration (Diegelmann, 2004; Knighton, 1982; Rozman, 2007; Shin, 2012; Casabona, 2017).

As a treatment option for vulvar LS, this requires injecting PRP into the affected vulva. This may cause some momentary discomfort to the patient. However, in terms of other risks to patients, the current literature contains no documented danger of hypersensitivity reaction, possible infection, local tissue necrosis, or bleeding.

1. **TRIAL DESIGN**

***3.1 Participant Identification and Recruitment***

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 a randomized, controlled, patient- and observer-blinded trial. Each patient will be randomized in one of the two following groups: platelet-rich plasma (PRP) as the treatment or normal saline as the placebo.

Evaluation of primary and secondary endpoints will be performed by a blinded assessor who is independent of the study treatment and will not know which of the two treatments was received by the patient. The clinicians who will be treating the study subjects will be unblinded. The blindness of the injector cannot be ensured due to the difficulty in masking the study and control treatments that will be injected (different color, etc.).

The patient will be blinded to the treatment they receive. To achieve this, all patients will undergo a blood collection, regardless which of the two treatment groups they will receive. The day of each treatment session, a specially trained site staff member performs the blood draw and prepare the treatment according to the randomization code in a separate but neighboring room. This staff member will then deliver the treatment to the ward where the clinician will inject the randomized product into the patient’s vulva. To preserve patient’s blindness, a screen will be placed over the patient to prevent her from seeing the whole procedure (from blood draw to treatment injection).

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. Once a diagnosis has been reached, the physician will present the patient with treatment options. After the treatment, a letter will be provided by the Principal Investigator to referring physicians, including datasheets of their patient, for that patient’s file.

The patient will be briefed on current mainstream treatments and informed about the study treatment option being investigated. The patient will be provided with an Information Sheet on PRP and its clinical applications, literature references, and treatment algorithm based on recent work undertaken by the Principal Investigator (Behnia-Willison et al., 2016). The patient will be advised if they are eligible to participate in the study by the Principle Investigator completing the enrolment form (attachment 4) which reviews the eligibility and exclusion criteria as outlined in Section 4, and that the patient has already undergone the required diagnostic tests. Vulvar lichen sclerosus scoring is outlined in Table 1. The patient may choose to participate in the study on the day of their initial consultation but will need to completely read the Information Sheet and sign the consent first. Another option is for the patient to give verbal consent at the time of their initial consultation to being contacted by a Co-Investigator or Research Assistant to discuss participating in the study.

With the patient’s permission, a Co-Investigator or Research Assistant will contact the patient within one week to discuss the project. At this time, the patient will be given the opportunity to ask questions about the study and will then be asked if they give consent to participate in the study. If the patient declines participation, the Co-Investigator or Research Assistant will explain to the patient that they need to make an appointment with their GP or gynaecologist to ensure follow-up, which is recommended for long-term management of vulvar lichen sclerosus and to exclude vulvar intra-epithelial neoplasia.

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 over the phone 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. Patients who wish to participate will be required to sign a Participant Consent Form and 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.

Patients will be provided with a high level of care during their treatment, including provision of refreshments. The clinic is in central Adelaide and offers ample free parking. Patients will not incur any personal fees for participating in the study.

***3.2 Randomisation and Minimisation of bias***

Patients will be randomised to each group in equal numbers. In order to avoid selection bias, block randomization will be conducted in random block sizes (4:4 and 2:2). This process will be based around the development of unique study identifiers and completed using the random number function in Microsoft Excel. Three columns will be required to perform this: the first column will contain 68 cells with 34 assigned to each group; the second column will contain the study numbers (1000-1068) and the third column will contain the random number generator function in each of the 68 cells. The study number and random number column will both be selected (but not the treatment column) and sorted per the random number column. This will sort the random number column in ascending order, which will randomly assign the study number to each treatment group. A corresponding list of study numbers per treatment group (randomization list) will be stored in a concealed location unknown and inaccessible to the clinical investigators. Sequentially numbered, opaque, sealed envelopes, each containing a random allocation, will be prepared by an unrelated co-worker according to the randomization list.

***3.3 Study Algorithm***

A study algorithm has been attached (Attachment 2). This outlines the following 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 all treatment 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 (Attachment 2; for recording treatment and assessment dates as well as existing as a standardisation tool).
* Two Participant Consent Forms (Attachment 3; two forms, one for inclusion in the patient’s medical record and the second to be retained with the study files).
* Study Enrolment Form (Attachment 4; demographic information collection sheet and inclusion criteria checklist).
* Appointment Card for all treatment and assessment appointments (Attachment 5).
* Assessment Package (Attachment 6).
* Study Identification Stickers.

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 patients’ 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 (see Section 4).
* 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.
* A Clinical Nurse will take photos and/or measure lesions associated with LS at baseline and at each follow up.
* 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 non-clinical Research Assistant. This person will be responsible for formally enrolling the participant into the study by entering the collected details into the SPSS study’s database. In addition, this person will look up the unique Study Identifier to determine the treatment group of the patient. The patient’s name will be recorded in the Master Study Identifier List, but the envelopes will remain unmarked on the outside in regard to the participant’s treatment group. All documents will remain within the envelope and filed in preparation for the participant’s next appointment such as – a standardised template containing patients’ medical history, examination and investigations, as well as a health questionnaire – all of which will be added to the database for statistical analysis and interpretation.

*Treatment appointments:*

All assessments and treatment appointments will be carried out at FBW Gynaecology Plus, Adelaide. For a treatment consultation, the Principal Investigator will complete the Treatment Record Sheet (Attachment 9) within each participant’s envelope and collect a venous sample of blood from the participant as per protocol. This sample will be appropriately identified with the participant’s name and date of birth. This will occur for all participants regardless of the treatment group to which they are allocated. This sample will then be given to the clinical nurse, who will leave the room and perform the following:

* Look up the participant’s unique Study Identifier Code and determine which treatment group they have been randomly allocated to.
* Identify which treatment protocol is required to be followed; PRP or saline.
* Double-check the previous two steps with the research assistant or practice nurse to ensure correct allocation.
* The Principal Investigator take measures to ensure the patient is unable to determine the contents of the syringe.
* If the treatment option is normal saline, the venous blood will be appropriately discarded as per normal clinical procedure.
* Provide the Principal Investigator with the syringe and ensure that the Principal Investigator injects the contents in that consult.
* Collect the used syringe for concealed disposal.
* Record on the Master Study Identifier List the date of the treatment.

The Principal Investigator, practice nurse, and patient are all present to ensure that the injection is administered. The patient’s details are confirmed among the three people using a verbal protocol which includes: stating their full name and date of birth. That is, three people are confirming the details and agree in the administration of any medication; this is a common practice that aims to reduce errors in administration (Conroy et al., 2012) and is commonly referred to as ‘time out’.

The Principal Investigator and the registered Practice Nurses are experienced in the collection and use of PRP. They are certified with a RegenLab PRPTM Certificate to take blood and prepare the PRP using the RegenLab PRPTM kit.

*Role of Australian Co-Investigators*

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.

*Role of International Co-Investigators*

International co-investigators will assist with analysis of the study and repeat the study in their respective countries.

*Assessment consultations*

At each assessment consultation, the Principal Investigator will not be the study doctor to examine the patient. One of the co-investigators will complete the vulvoscopy and an assessment package and place the completed documentation back inside the envelope.

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.

At the conclusion of data analysis, the participant and the Principal Investigator will be informed about the participant’s actual treatment group during the study. The participant will receive a letter about the research findings.

*Dependent variables*

Treatment progress will be assessed by the collection of patient questionnaire and treatment outcome measures specific to lichen sclerosus. Participants will complete the Australian Pelvic Floor Questionnaire and the Dermatology Life Quality Index (DLQI) to assess the participant’s disease burden.

The Australian Pelvic Floor Questionnaire is a tool (Baessler et al., 2010) to assess level of symptoms and severity for bladder, bowel, prolapse, and sexual functions. The latter section is most pertinent for patients with lichen sclerosus. It has been validated for use as an interviewer-administered or patient-completed questionnaire that can be used within routine clinical practice and for research purposes. A copy of this questionnaire has been attached as part of the assessment package (Attachment 6).

The Dermatology Life Quality Index (DLQI) is a validated tool to assess skin disease impact on patient’s quality of life (QOL). Each of the ten questions is scored on a 4-point Likert scale: 0 is ‘not at all’ or ‘not relevant’, 1 is ‘a little’, 2 is ‘a lot’, and 3 is ‘very much’. The scores of individual questions (0-3) are added to yield a maximum score of 30; higher scores suggest greater QOL impairment (Basra 2008).

*Visual analogue scale*

A visual analogue scale will be presented to participants to record a measurable reading of the severity of symptoms (see Figure 1 below). Participants will be asked to indicate (a) the level of their distress in relation to their symptoms, and (b) the level of their distress in relation to their dyspareunia (painful intercourse). This scale represents ordinal level data, as it is not possible to quantify whether a score of 2 to 3 is proportional to a score from 8 to 7.

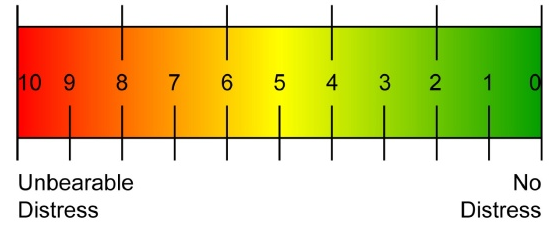


Figure 1. Visual analogue scale indicating subjective distress scores.

A physician-administered clinical score for lichen sclerosus was developed by Günthert et al., (2012). The six clinical characteristics are graded on a three-point Likert scale with grade 0 as normal findings, grade 1 as moderate changes, and grade 2 as severe changes. The score ranges 0 – 12, with total score of 4 or more as significant for vulvar lichen sclerosus in conjunction with the participant having intractable pruritis and soreness with irritation, dyspareunia, dysuria, and incontinence (Naswa and Marfatia, 2015). The lichen sclerosus clinical score is outlined in Table 1, which is based on vulvoscopy findings.

**Table 1: Lichen Sclerosus Clinical Score**

|  |  |  |
| --- | --- | --- |
| **Clinical Characteristic** | **Grade 1 (moderate)** | **Grade 2 (severe)** |
| Erosion | 1-2 small erosions, almost not macroscopically visible | Macroscopically visible and/or > 2 or confluent lesions |
| Hyperkeratosis | </=10% vulva and perineum affected | >10% vulva and perineum affected |
| Fissure | Rhagades affecting the posterior introitus | Generalised vulvar rhagades |
| Agglutination | Partially affecting preputium clitoridis and labial minora | Complete agglutination of both labia minora or majora |
| Stenosis | Narrowing of introitus, which could still be passed by two fingers | Narrowing, which could be passed by less than two fingers |
| Atrophy | Shrinking of labia and clitoris | Labia minor and clitoris were no longer visible |

*Randomisation*

Following the collection of baseline data, participants will be randomised into one of the two treatment groups. The treatment protocols for each of the groups are detailed in Attachment 10 and 11.

This study will assess the change in treatment outcome measures between the two groups at 6 weeks to 12 months after first PRP treatment. In doing so, the study will enable a comparison between the different treatment regimens at 3 intervals – 6 weeks, 6 months, and 12 months. The Principal Investigator will perform the treatment and a co-investigator will assess and examine the patients at the post-treatment assessments. Since the co-investigator will not have access to the treatment administration or previous assessment data, this will ensure to eliminate any influence by the pre-treatment data. Patients will receive a total of two treatments of either PRP or normal saline: at baseline and six weeks. Twelve months after the first treatment will be the final visit. They will be asked to fill out QOL questionnaires at each visit.

*Study duration*

The study will run over a minimum of 18 months to account for the initial recruitment period and the recruitment of additional participants in the case of withdrawals. The study will commence when ethics approval is granted. An exact completion date cannot be provided, as this will depend upon the date of ethics approval being granted. The study will require 12 months participation from each participant.

**4 Selection and withdrawal of participants**

*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 lichen sclerosus;
3. Remain symptomatic from vulvar lichen sclerosus despite topical steroid treatment prior to the beginning of the study or women who are unable to use or are intolerant of topical steroid use;
4. Understand the conditions of the study fully and are willing to participate for the length of the study in its entirety;
5. Are capable of, and have given, informed consent to their participation in the study.

*Exclusion criteria*

The following patients will be deemed unsuitable for inclusion:

1. Patients on anti-oestrogens.
2. Patients on systemic immunosuppressant within 12 weeks prior to participating in the study.
3. Patients currently suffering any gynaecological or breast cancers.
4. Patients with autoimmune disorders requiring anti-platelet medication, except Sjogren’s syndrome and lichen sclerosus.
5. Patient who are immunocompromised (e.g. lymphoma, AIDS) or have uncontrolled malignant disease.
6. Patient who have been diagnosed with lichen planus, psoriasis, candidiasis, vulvar intraepithelial neoplasia, or vulvar carcinoma.
7. Patients with vulvodynia.
8. Patients with acute vaginal infection or systemic infection.
9. Patients on anti-platelet treatment.
10. Patients on aspirin.
11. Patients who have a mental disability leading to their inabilty to give consent.
12. Patients who are pregnant.
13. Patients who are uncooperative, known to miss appointments, are unlikely to follow medical instructions, or unable to attend regular scheduled visits.

*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 their referring physician to continue with conventional treatment.

**5 Treatment of subjects**

The vulva will be examined for LS. Vulvoscopy will be performed to exclude any pre-cancerous cells on the vulva, or cancer of the vulva.

Autologous blood samples will be used to create platelet-rich plasma (PRP). There will be no need for cross-matching or storing protocols, as each sample will be prepared and immediately used on a participant-by-participant basis, leaving no risk of cross-contamination. Upon collecting the venous sample, the vial will be labelled with the patient’s name and date of birth, as per normal venopuncture procedure.

An appropriately trained clinician (Principal Investigator or Clinical Nurse) will collect the autologous blood sample from the participant during the treatment consultation. The whole blood sample will subsequently be prepared and administered to the participant according to the treatment protocol (Attachment 10 and 11).

Once the platelet-rich plasma has been removed from the collection device, the remaining constituents will be discarded into biological waste receptacles. Any PRP not used during the treatment consultation will likewise be discarded.

*RegenLab PRP® Concentrating Device*

The RegenLab PRPTM device is owned by the Principal Investigator, who is the first person to use the RegenLab PRPTM device in Australia and has been using it to treat over 1000 patients in three FBW Clinic settings: Adelaide, Geelong, and Noosa. There is no commercial interest to declare between the Principal Investigator and RegenLab PRPTM Corporation.

The RegenLab PRPTM kit is a single-use, closed system that contains all the required equipment to take blood and prepare the plasma in a sterile fashion according to the rules and regulations of the Australian Medical Regulatory protocol.

The administration of PRP is considered minimally invasive. Nevertheless, it is acknowledged that from a general society perspective, the diagnosis, treatment, and assessment procedures may be viewed as invasive. Participants in this study will undergo injection into the dermis of their vulva using a small needle. All participants will have the treatment procedure fully explained to them and have the option of withdrawing from the study at any stage. It should be noted that these treatment options present a low level of invasiveness; similar to a small injection of local anaesthetic to remove a mole under the skin. An additional example of the low level of invasiveness is that the size of the needle used for the injection of PRP (30-gauge) is similar to that used by diabetics to inject themselves with insulin (Gill & Prausnitz, 2007). The vulva will be injected with PRP after application of topical local anaesthetic to minimise any discomfort. The protocol will be two treatments of PRP 6 weeks apart.

1. **Assessment of Efficacy**

Treatment efficacy will be determined by outcomes on relevant dependent variables, which are specified in detail in section 3.3.

1. **Assessment of safety**

*Monitoring adverse effects (e.g. emotional, psychological and physical):*

After an adverse event, the patient will be followed up until the adverse event is overcome. Given current knowledge on the risks of PRP (see Section 11), we do not envisage any scenario where this would be a serious issue. PRP presents a possibility of pain, but no serious complications. Barrier-moisturising cream will be provided and analgesia as required.

The methodological design of this study requires all participants to be assessed at six and 12 months after treatment. This design has an inbuilt means of assessing all participants for any unlikely adverse events up to 12 months’ post-treatment. All adverse effects experienced by a participant will be recorded and the ethics committee notified. Significant adverse effects will be reported to the ethics committee.

Many women endure lichen sclerosus for a substantial period before seeking advice. The delay in seeking help can be secondary to embarrassment or fear of the intrusiveness of assessment and treatment. 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 assessment tools are being employed at baseline and at each assessment.

1. **Statistics**

In order to protect the data from bias, the Principal Investigator will play no role in data collection or collation.

The primary outcome is to determine level of symptom relief and lesion reduction or resolution of vulvar lichen sclerosus with PRP by clinical scoring for vulvar lichen sclerosus . The secondary outcomes are to investgate symptoms of lichen sclerosus, such as dyspareunia, sexual function, and quality of life. Additional secondary outcomes are safety and level of discomfort from PRP treatment.

*Sample size calculation*

Based on the pilot study on 28 patients (Behnia-Willison 2016), 80% of the PRP-treated patients experimented an improvement of their condition.  Assuming a difference of 30% between PRP treatment and normal saline placebo at 12 months, an alpha risk of 5% and a power of 80%, a sample size of 31 subjects for the PRP group and 31 subjects for the normal saline group is required. Assuming that up to 10% subjects may be lost to follow-up or withdrawn, a sample size of 34 subjects for the PRP group and 34 subjects for the normal saline group is required, for a total sample size of 68 patients.

1. **Direct access to source data/documents**

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

1. **Quality control and quality assurance**

All study documentation will be managed by an experienced (post-graduate) Research Assistant. All data analysis will be performed by an experienced (post-graduate) statistician.

1. **Ethics**

*Benefits anticipated from study*

The main benefit of this study for participants will be potentially having their gynaecological condition successfully treated in a non-surgical and safe way. 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 with PRP, then this study has the potential to positively reshape the treatments offered to women with lichen sclerosus around the world in a non-hormonal, minimally-invasive manner with no side effects.

*Risks of any harm - including physical disturbance, discomfort, anxiety or pain*

In the recently published results of the pilot study undertaken by the Principal Investigator (Behnia-Willison et al., 2016), patients (n=28) reported minimal to moderate pain in the 24 hours following the procedure. There were no cases of infection, bleeding, haematoma, or other adverse outcomes following the treatment.  
  
The potential risks associated with PRP are outlined below:

* Hypersensitivity reaction – not indicated within the current literature.
* Possible infection – not recorded within the literature.
* Possible bleeding – none documented in pilot studies.

1. **Data handling and record keeping**

All data collected for the purposes of this study will be recorded against the participant’s unique study identifier to ensure participant confidentiality.

Treatment outcome measures will be collated into a password-protected Microsoft Excel spreadsheet and descriptive statistics will be calculated. Subsequent inferential analysis will be performed in SPSS (IBM).

1. **Financing and insurance**

The Principal Investigator’s medical indemnity details are provided in attachment 12.

1. **Publication policy**

Findings from this trial may be disseminated to the scientific community through peer-reviewed journal articles, appropriate conferences, medical education sessions and patient information sessions.

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