PROTOCOL

SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMs) – A POTENTIAL TREATMENT FOR PSYCHOTIC SYMPTOMS OF SCHIZOPHRENIA?

Chief Investigator

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REFERENCES
1. **SUMMARY**

1.1 **Objective**

To study the efficacy of adjunctive raloxifene, a selective estrogen receptor modulator (SERM), in a two-arm double blind, placebo-controlled adjunctive study for the treatment of older women with schizophrenia. All patients receive standard antipsychotic medication.

1.2 **Study Population**

Perimenopausal and postmenopausal females with a current diagnosis of schizophrenia or related disorder according to the Diagnostic and Statistical Manual (DSM-IV) of the American Psychiatric Association.

1.3 **Adjunctive Medication**

1. 120mg/day Raloxifene hydrochloride (SERM)
2. Placebo (an inert substance with no active ingredients)

1.4 **Antipsychotic Medication**

All patients take regular antipsychotic medication as prescribed by the clinical treating team.

1.5 **Study Evaluation**

Data will be collected over a 3-month period for each patient. Visits will be performed at baseline, and then at fortnightly intervals. The main outcome measures will be the following:

1. Psychopathology rating scales to quantify psychotic and affective symptoms (PANSS)
2. Cognitive test battery to quantify changes in cognitive functioning (RBANS)
3. Hormone assays
2. INTRODUCTION

2.1 Background

There is an increasing body of evidence that estrogen may have a modulating effect on the psychotic symptoms of schizophrenia. Selective Estrogen Receptor Modulators (SERMS) are a new and effective form of estrogen therapy which targets receptors in the brain without affecting breast and uterine tissue. The project outlined in this proposal builds on pilot data already collected by our group showing a beneficial effect of adding SERMS to existing antipsychotic treatment in perimenopausal and postmenopausal women with schizophrenia.

The hypothesis that estrogen may be protective against the symptoms of schizophrenia in women (Hafner, et.al., 1991; Seeman & Lang, 1990), has received increasing support from both clinical and basic science research over the last 15 years. The “estrogen hypothesis” was derived from epidemiological, clinical and animal studies, which highlighted gender differences in the onset and course of schizophrenia, as well as the effects of estrogen on brain function.

Epidemiological studies have shown that women with schizophrenia present with “first episode psychosis” on average about 5 years later than men (e.g. Maurer & Hafner, 1995). Clinical studies reveal gender differences in clinical presentation, with more negative symptoms in men and more affective and paranoid symptoms in women (Goldstein, 1988; Goldstein & Tsuang, 1990). Life cycle studies have shown women are at greater risk of experiencing a first episode of psychosis or relapse of existing illness at two periods of major hormonal change: firstly during the postpartum period and secondly during the menopause (Seeman, 1986, 1996). There have also been case reports of women whose schizophrenia symptoms increased at low estrogen phases of the menstrual cycle (Endo, et. al., 1978), and reduced at high estrogen phases (Riecher-Rossler, 1994). These clinical findings fit well with animal brain studies in which estrogen has been shown to influence two major neurotransmitter systems implicated in schizophrenia; dopamine and serotonin. Estrogen has been shown to reduce dopamine concentration and modulate the sensitivity and number of dopamine receptors in the striatum (Bedard et.al., 1984; Dupond et.al., 1981; Foreman & Porter, 1980; Koller et.eta.al., 1980). Sumner and Fink (1998) demonstrated that estrogen modulates serotonin systems by increasing the expression of genes for both the 5-HT2A receptor and the serotonin transporter, in the dorsal raphe nucleus and forebrain of rats.

Estrogen has also been shown to improve cognitive function, particularly in memory functions (Sherwin & Phillips, 1990; Halbreich, 1997). Estrogen interaction with the cholinergic systems that are critically involved in attention processes, learning and memory (Bartus et.al., 1981) may be of great importance in schizophrenia and hitherto have been unexplored.
2.2 Clinical Estrogen Trials In Patients with Schizophrenia and Related Disorders

Following these epidemiological, clinical and animal study results we conducted an open label pilot study (Kulkarni et al., 1996) in which 11 women of child-bearing age with schizophrenia were given a daily dose of 0.02mg oral ethinyl estradiol as an adjunct to antipsychotic drug treatment for eight weeks, and compared with a similar group who received anti-psychotic drug treatment plus adjunctive placebo. The group receiving estrogen made a significantly more rapid recovery from acute psychotic symptoms and also reported improvement in their general health.

To explore the optimal dose of estrogen in this group, we then conducted a dose-finding study of adjunctive estradiol in women of child-bearing age with schizophrenia (Kulkarni et al., 2001), using a safer delivery system (transdermal). This was a three-arm, double blind, placebo controlled, 28-day study in 36 women with schizophrenia. 12 women received 50mcg transdermal estradiol, 12 women received 100mcg transdermal estradiol, and 12 women received transdermal placebo. All women also received standardised antipsychotic drug treatment, The addition of 100mcg transdermal estradiol to antipsychotic drugs provided a significantly greater improvement in the key psychotic symptoms compared to both the 50mcg transdermal estradiol and placebo addition group.

Based on these results, we next conducted a “proof-of-concept” study using a larger sample. This was a 28-day, double-blind, randomized, placebo-controlled trial of adjunctive 100mcg transdermal estradiol compared with transdermal placebo in a total of 93 women with schizophrenia or related disorders. Both groups received standardised antipsychotic medication. Cleaning the data from the large data base, analysing it and, in particular, matching the hormonal data has been completed and the results have now been sent for publication. As shown in Table 1 and Figure 1, the group of women receiving 100mcg transdermal estradiol showed a highly significant improvement in overall psychopathology (Total PANSS), compared to the placebo group. Table 1 also shows that the estrogen group had a significantly greater change on all three subscales of the PANSS and in particular on two key individual items: hallucinations and delusions.
Selective Estrogen Receptor Modulators (SERMs) – A Potential Treatment for Psychotic Symptoms of Schizophrenia?

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**Table 1**

Means and standard deviations of psychopathology (baseline & day 28), change scores and significance levels (p) of change scores for women receiving either 100mcg transdermal estradiol or transdermal placebo.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estradiol</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=51</td>
<td>N=42</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>Day 28</td>
</tr>
<tr>
<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>80.61</td>
<td>67.59</td>
</tr>
<tr>
<td></td>
<td>(20.9)</td>
<td>(16.2)</td>
</tr>
<tr>
<td>Positive</td>
<td>20.73</td>
<td>16.68</td>
</tr>
<tr>
<td>symptoms</td>
<td>(7.3)</td>
<td>(5.6)</td>
</tr>
<tr>
<td>Negative</td>
<td>18.16</td>
<td>15.76</td>
</tr>
<tr>
<td>symptoms</td>
<td>(5.9)</td>
<td>(4.7)</td>
</tr>
<tr>
<td>General</td>
<td>41.80</td>
<td>34.81</td>
</tr>
<tr>
<td>symptoms</td>
<td>(11.4)</td>
<td>(8.6)</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>3.80</td>
<td>3.09</td>
</tr>
<tr>
<td></td>
<td>(1.7)</td>
<td>(1.4)</td>
</tr>
<tr>
<td>Delusions</td>
<td>3.64</td>
<td>3.11</td>
</tr>
<tr>
<td></td>
<td>(1.7)</td>
<td>(1.2)</td>
</tr>
</tbody>
</table>

**Figure 1.** PANSS Total Score Change from Baseline to Day 28 for women of reproductive age receiving either transdermal estradiol or placebo. *** = Significant difference between groups at p<0.001

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### 2.3 Effects of Adjunctive Estrogen on Cognition

Schizophrenia has been shown to be associated with impaired cognition. Measures of cognitive function were added to the protocol approximately half way through the study, to test the potential benefit of adjunctive estrogen on the cognitive function of women with schizophrenia. There is currently cognitive data for a total of 40 participants (23 in the estradiol group and 17 in the placebo group). Analyses (ANOVA) show that the women receiving adjunctive estradiol experienced a
significant improvement in immediate verbal memory compared to women receiving
adjunctive placebo. The estradiol group also showed improvements on measure of
attention and working memory (as measured by the digit span test) compared to the
placebo group whose performance worsened over time. In contrast, the placebo
group improved on a measure of immediate visual memory significantly more than
the estradiol group. Both groups improved in their ability to retain visual material after
a delay, with no significant difference between the two groups.

2.4 Summary and Conclusions – from ‘Proof of Concept’ study

Results reported here provide strong evidence that 100mcg transdermal estradiol is
a useful adjunct in the treatment of schizophrenia and related disorders in women of
childbearing age. Preliminary results from cognitive data presented appear to
suggest that estrogen supplementation may provide some neurocognitive benefits.
For this reason, we are continuing to recruit subjects and test their cognition. Only 5
patients withdrew their consent during the study, and in all 5 cases the reason for
withdrawal was because they did not want repeated blood testing. One patient
moved interstate during the study and was lost to follow-up. Compliance with using
the skin patches was not an issue due to the high level of enthusiasm and interest
shown by the patients. Research staff maintained frequent contact with patients
which ensured excellent study adherence.

International concordance with our work is beginning as other sites replicate our
studies (Akhondzadeh et al., 2003 Chakos 2005), and a Stanley Medical Research
Institute (Washington) funded multi-site replica study is to commence in April 2006.

While studies by our group and others have demonstrated the beneficial effects of
adjunctive estrogen in treating schizophrenia over a short period of time, its utility in
ongoing or longer term treatment is restricted by the potential harmful effects of
estrogen itself on breast and uterine tissue (Rossouw et al., 2002). Our studies were
brief for this reason, and we used 100mcg transdermal estradiol without
progesterone over an eight (Kulkarni et al., 1996) or four week (Kulkarni et al., 2001)
period.

2.5 Selective Estrogen Receptor Modulators (SERMs)

With the recent advent of selective estrogen receptor modulators (SERMS), such as
raloxifene hydrochloride, there is the potential to harness the positive estrogenic
effect on CNS neurotransmitter systems without affecting breast or uterine tissue.
While the CNS effects of raloxifene have not been fully studied, its actions are
mediated through binding to estrogen receptors and can thereby regulate gene
expression that is ligand, tissue or gene specific. By inference then, raloxifene would
be expected to impact on dopamine and serotonin pathways in a similar fashion to
unconjugated estrogen. A study on the effect of raloxifene on cognition in healthy,
postmenopausal women found a slight increase in verbal memory performance after
one month of high dose treatment, while no other differences were found after 12
months of treatment (Nickelsen, Lufkin, Riggs, Cox, & Crook, 1999). A recent
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Selecti...

Table 1
Baseline and Week 12 Scores on Variable of Interest

<table>
<thead>
<tr>
<th>Variable</th>
<th>SERM (N=6)</th>
<th>HRT (N=6)</th>
<th>Placebo (N=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Week 12</td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>S.D</td>
<td>Mean</td>
</tr>
<tr>
<td>PANSS Total</td>
<td>73.0</td>
<td>8.4</td>
<td>67.2</td>
</tr>
<tr>
<td>CVLT</td>
<td>39.0</td>
<td>9.9</td>
<td>50.0</td>
</tr>
<tr>
<td>LH</td>
<td>33.0</td>
<td>6.9</td>
<td>27.0</td>
</tr>
</tbody>
</table>

Taking our pilot data into account with Yaffe’s findings, we propose to study 120mg/day oral raloxifene as a potentially new, safe adjunctive treatment in postmenopausal women with schizophrenia.

3. PROPOSED STUDY

3.1 Aim and Hypothesis

Aims
- To examine the impact of adjunctive SERM (120mg oral Raloxifene daily) treatment on the psychopathology of perimenopausal and postmenopausal women with schizophrenia and related disorders.
- To examine the impact of adjunctive SERM treatment on the cognitive functioning of perimenopausal and postmenopausal women with schizophrenia and related disorders.
- To examine the impact of adjunctive SERM treatment on the hypothalamo-pituitary-gonadal axis in perimenopausal and postmenopausal women with schizophrenia and related disorders.

Hypothesis
- That the women receiving adjunctive SERM will have a significantly greater reduction in psychosis symptoms over the course of the study than women receiving adjunctive placebo.
- That the women receiving adjunctive SERM will have a significantly greater improvement in cognitive function than women receiving adjunctive placebo.
4. METHOD

4.1 Research Plan

Design Overview

The study will employ a 12 week, double-blind, randomised, placebo-controlled, adjunctive treatment trial design. Perimenopausal and postmenopausal women with schizophrenia will be randomised to one of two groups:

1. Daily oral Raloxifene 120mg + antipsychotic
2. Daily oral Placebo + antipsychotic

Patients will be currently psychotic but physically well. The antipsychotic medication will be prescribed by the clinical treating team. To control for the use of different antipsychotics, all antipsychotic data will be converted into risperidone equivalents. Patients will be seen at screening, baseline and then each week for 12 weeks. The majority of visits are brief and check compliance and adverse events only. Diagnosis will be confirmed at the screening visit. Menopausal status will be assessed at screening and at week 12. Psychopathology will be measured at baseline and then fortnightly. Hormonal levels will be measured at screening, and at weeks 4, 8 and 12. Cognitive performance will be assessed at baseline and at week 12. Adverse symptoms and treatment compliance will be measured at each weekly visit.

Sample Size / Study Power

Power analysis was conducted using the G-power software (Erdfelder, Faul, & Buchner, 1996), assuming equal group sizes, large effect size for the change score or difference between the first and last time points, and an alpha of 0.05, ninety subjects per group would give a power of 0.95. There is a regrettable dearth of normative cognitive data for post-menopausal women with schizophrenia. As we expect clinically significant differences, we assumed a large effect size, conventionally but arbitrarily defined as 0.40 (the standard deviation of the group means divided by the common standard deviation (Cohen, 1988, 1992) in the case of analysis of variance. Large effect sizes are often assumed for new adjunctive treatments in schizophrenia, due to the levels of improvement already achieved by the baseline treatment. A good example is the well regarded D-cycloserine adjunctive study (Goff et al, 1999). This two group study had n=23, n=24. Clinical trials of new treatments in patients with schizophrenia are urgently needed but very difficult to do. Our track record shows that we can successfully complete difficult studies. In this study we are proposing to recruit 180 older women with schizophrenia who can give informed consent and remain in a 3 month study which we believe will be challenging but within our capabilities. Considering this as a large pilot study will at least show whether a future, expensive, large, and necessarily multi-centre trial is warranted. Statistical consultation and advice is from the Monash University, Department of Epidemiology and Preventive Medicine (Dean McKenzie, Michael Bailey).

4.2 Inclusion/Exclusion Criteria
Inclusion:
- Physically well.
- A current DSM-IV diagnosis of schizophrenia or related disorder.
- Perimenopausal or postmenopausal status (~45-70 years).
- Able to give informed consent.
- PANSS total score ≥ 60 (1 - 7 scale) and a score of 4 (moderate) or more on two or more of the following PANSS items: delusions, hallucinatory behaviour, conceptual disorganization or suspiciousness.
- On a stable dose of antipsychotic medication as prescribed by the clinical treating team, for at least four weeks.
- Evidence of a normal mammogram in the preceding 12 months.
- Documented normal PAP smear, breast, and pelvic examination in the preceding two years.

Exclusion:
- Patients with known abnormalities in the hypothalamo-pituitary gonadal axis, thyroid dysfunction, central nervous system tumours, active or past history of a venous thromboembolic event, or undiagnosed vaginal bleeding.
- Patients with any significant unstable medical illness such as epilepsy and diabetes or known active cardiac, renal or liver disease; presence of illness causing immobilisation.
- Patients whose psychotic illness is directly related to illicit substance use or who have a history of substance abuse or dependence during the last six months, or consumption of more than 30gm of alcohol (three standard drinks) per day.
- Smoking more than 20 cigarettes per day.
- Use of any form of estrogen, progestin or androgen as hormonal therapy, or antiandrogen including tibolone or use of phytoestrogen supplements as powder or tablet.

4.3 Study Design

Schedule of Patient Visits

Screening: Patients will be screened as soon as possible after referral to the study. No study procedures will be implemented prior to attainment of informed consent. Patients will undergo a full psychiatric and medical history and will have a non-invasive physical examination, including weight, height, and waist-hip ratio. A detailed smoking and other drug use history will be completed. Psychopathology will be assessed to confirm severity of symptoms, and diagnosis will be confirmed. Menopausal status will be confirmed. If required a mammogram will be arranged. If required a PAP smear, breast, and pelvic examination will be performed at the Women’s Health Clinic (The Alfred) or via referral to the participants GP.

Randomisation Procedure: Upon entry into the double-blind phase, each patient will be allocated an identification number and randomly assigned to a treatment regimen according to a computer generated pseudo-random code. Equal numbers will be assigned to both treatment arms. Patients, raters and clinicians are “blind” as to whether each patient receives adjunctive SERM or placebo. The Alfred Clinical Trials
pharmacist will organise randomisation and has extensive experience with this procedure.

**Baseline Visit:** A separate baseline visit will be conducted once pathology results have been received from the blood sample taken at the screening visit. If results confirm that the subject meets the inclusion criteria, study medication will be dispensed, and the remainder of the baseline procedures will be performed. These include psychopathology, cognitive testing, adverse events and medication compliance.

**Evaluation Visits:** All visits will be performed ± two days of the scheduled visit date. At the evaluation visits, researchers will check and record compliance and adverse events, perform psychopathology rating scales, and collect the blood sample for hormone assays as per the table below. Most of the visits are home visits and we have considerable success in patient retention through this approach. In our experience, weekly contact is welcomed by older women patients and enhances study retention and adherence to treatments. Visits at baseline, weeks 4, 8 and 12 involve outcome assessments, while other weekly visits are brief.

### 4.4 Frequency of Testing

Table 1 outlines the frequency and procedures to be completed for each study visit:

<table>
<thead>
<tr>
<th>Measure</th>
<th>Screening</th>
<th>Baseline</th>
<th>W2</th>
<th>W4</th>
<th>W6</th>
<th>W8</th>
<th>W10</th>
<th>W12</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.I.N.I</td>
<td>X</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Physical &amp; psychiatric History &amp; Assessment</td>
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<td></td>
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<td></td>
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<tr>
<td>Psychopathology</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive Tests</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIMS/BARS/SAS/ASC</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<td>Compliance</td>
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<td>X</td>
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5 INSTRUMENTS FOR DATA COLLECTION

5.1 Diagnostic

Mini International Neuropsychiatric Interview (M.I.N.I): The M.I.N.I (Sheehan et al. 1998) is a brief structured interview that identifies the presence or absence of major psychiatric disorders. The M.I.N.I has acceptably high validation and reliability scores, and in this study will be administered by a trained researcher prior to randomisation (i.e. at screening) to confirm diagnosis for patients entering the study. The length of the illness will also be recorded as well as past hospitalisation and treatment information.

5.2 Adverse Symptom Checklist

The Adverse Symptom Checklist: The ASC is a 22 item checklist of general and associated side effects. For each patient, the checklist will be administered by the same trained rater at each visit.

Abnormal Involuntary Movement Scale (AIMS): The AIMS will be completed at screening/baseline and at each evaluation visit. The 12-item scale examines any estrogen induced/exacerbated abnormal movements.

Simpson-Angus Scale (SAS): The SAS is a 10-item scale rating the presence and severity (on a 5-point scale) of extrapyramidal side effects (EPSE) of medication, and will be administered fortnightly.

Barnes Akathisia Rating Scale (BARS): The BARS assesses presence, severity and change in drug-induced akathisia, and will be administered fortnightly.

5.3 Psychopathology

Positive and Negative Symptom Schedule (PANSS): The PANSS (Kay, Abraham, & Opler, 1987) will be performed at screening/baseline and at weeks 4, 8 and 12. The PANSS consists of a Positive Scale (7 positive symptom constructs), a Negative Scale (7 negative symptom constructs) and a General Psychopathology Scale (16 symptom constructs). For each patient, the scale will be administered by the same trained rater. The PANSS provides a well standardised method of evaluating and monitoring psychotic symptoms. The rater is trained and recertified against an internationally recognised “gold standard”.

Montgomery Asberg Depression Rating Scale (MADRS): The MADRS will be performed at baseline, then at weeks 4, 8 and 12. Many patients with schizophrenia have co-existing depression, hence monitoring of depression is important.

5.4 Pathology

Hormone Assays (Serum): A single 10ml blood sample will be collected at screening and then at weeks 4, 8, and 12 to measure estradiol, LH, FSH, DHEA-S, prolactin and progesterone levels. The blood sample will be delivered to the Alfred Pathology Department for analysis. Screening hormone assay results will be used to help ascertain menopausal status prior to study entry.
5.5 **Cognitive Tests**

A short neuropsychological test battery will be conducted using the RBANS at baseline and at study completion to quantify changes in cognitive functioning. We will use different versions of the tests to prevent a “practice effect”. The RBANS comprises 12 subtests that are used to calculate five index scores (Immediate Memory; Visuospatial/Constructional; Language; Attention and Delayed Memory) and a total score. The RBANS is included on the advice of neuropsychologists specialising in post-menopausal cognition (V. Henderson, Jean Hailes Foundation).

6 **MEDICATIONS**

6.1 **Antipsychotic Medications**

All patients will receive antipsychotic medication in addition to their study medication. The antipsychotic medications most likely to be used will be second generation antipsychotics (SGAs). They are associated with metabolic side-effects in some patients and we will carefully monitor weight gain, blood glucose and serum lipids in all patients. The average antipsychotic dose and change in dose (initiated by the patients’ clinicians) will be examined as study co-variates. Patients need to have been stabilised on an antipsychotic for a minimum of four weeks prior to entering this study. We use the PORT guidelines for antipsychotic medication use (Lehman, 1998).

6.2 **Concomitant Treatments**

All patients will participate in standard inpatient and outpatient psychosocial therapies and activities as advised by their treatment team. All medication received during the study (psychotropic and non-psychotropic) will be recorded and included in the analysis. If any concurrent illness caused immobilisation during the study, the hormone therapy would be ceased, and the patient withdrawn, as immobilisation increases the risk of venous thromboembolism.

7 **STATISTICAL CONSIDERATIONS**

In order to compare the two groups over the 12 weeks, contemporary statistical methods such as Generalized Estimating Equation (Hardin & Hilbe, 2003), or multilevel modeling (Singer & Willett, 2003), which do not require complete data for every person, will be employed. An intention to treat approach will be adopted; all persons will be analyzed as belonging to the treatment arm to which they were randomized. Sensitivity analyses, encompassing various scenarios, including ‘worst case’, will be adopted. Post hoc analyses will account for differences between groups with factors such as duration of illness and age. Statistical consultation and advice is from the Monash University, Department of Epidemiology and Preventive Medicine (Dean McKenzie, Michael Bailey).
8. ETHICAL CONSIDERATIONS

8.1 The Use of Raloxifene

While many studies have shown raloxifene to be a safe medication, in some women it has been associated with an increased risk of venous thromboembolic events to the same degree as standard HT. For this reason its use is not recommended for women with active or past history of a venous thromboembolic event. In addition, some women experience leg cramps and hot flushes (which is a common event during menopause). However, the use of raloxifene in perimenopausal and postmenopausal women for a three month period falls within clinical guidelines, and should not pose a problem. There are no known interactive effects between raloxifene and antipsychotic medications, or known impact of raloxifene on prolactin. Of interest are the recent favourable results from a study of the preventative aspects of using raloxifene in women deemed to be at high risk for breast cancer.

8.2 Informed Consent

As in many of our studies, we have found that obtaining informed consent from psychotic individuals is entirely possible and feasible. The methodology of the trial is explained to the patient who is required to be able to restate it to the investigator and demonstrate an understanding of its procedures. Witness signatures also accompany the patient’s signature. Witnesses can be family, friends or treating staff, but not research staff. A plain language statement is included and is kept by the patient for future reference. Patients can withdraw their consent at any time.

8.3 Confidentiality

As for all research studies, the NH&MRC guidelines apply. Thus, all patients will be assigned a non-identifying number. Their information will be kept in a locked cabinet only accessible to the researchers of this study. Data entered on computers will use the patients’ code number for identification. A separate booklet will be used to record data collected at screening, baseline and evaluation visits. All files will be retained by the hospital for a period of 15 years after completion or discontinuation of the trial. Confidentiality of patients’ information is maintained by the researcher, except if clinical care may be compromised.

8.4 Adverse Events

All adverse events will be recorded by the investigator in detail at each visit and reported immediately to the patients treating doctor. Any adverse events occurring during the course of the study will be followed rigorously and in conjunction with the treating clinicians. Patients will be withdrawn from the study if any events compromise their clinical treatment and progress. The research and treatment teams work closely together and from our experience, we are confident that patients receive optimal care.
8.5 Follow Up

Each patient will know which “arm” of the trial she was in at the end of her three month trial. This is to permit her treating clinician to decide whether or not she would benefit from receiving an ongoing SERM adjunct. If the treating clinicians wish, then the patient will receive routine SERM treatment via General Practitioners with advice from the Women’s Health Centre. Data about psychotic symptoms will be collected using PANSS on a three monthly basis by the trained treating clinicians.

9. PROPOSED SITES FOR THE STUDY

The Alfred Psychiatry Research Centre (APRC) is ideally placed at The Alfred Hospital to conduct such a study, as the catchment area of The Alfred alone covers a population of approximately 184,000. It is also part of the Bayside Health Service, which incorporates Caulfield General Medical Centre and Sandringham & District Memorial Hospital. The Bayside Mental Health Service is a large mental health service that has both adult and aged psychiatry inpatient and outpatient facilities. The Alfred Aged Psychiatry Service, based at Caulfield, has already provided enthusiastic support for our pilot study in older women with schizophrenia, and has agreed to assist in the follow up arrangements.

APRC has an excellent track record in the area of schizophrenia research, and in particular incorporates the Monash University Research Centre for Women’s Mental Health. The proposed study is in conjunction with Professor Susan Davis, director of The Women’s Health Centre, a renowned specialist menopause centre. The Women’s Health Centre is based at The Alfred Hospital, enhancing ease of collaboration and communication between the two research groups. Both groups have extensive expertise in the design and execution of RCTs.

The second active study site is The Department of Clinical & Biomedical Sciences, an active research unit affiliated with both Barwon Health and the University of Melbourne. Led by Professor Michael Berk, this research unit has an extensive history of conducting clinical research into key aspects of service delivery and innovative treatment options for people living with mental illness. With a broad catchment in and around the Greater City of Geelong, the mental health services of Barwon Health offer, adult and aged inpatient and community psychiatry care to a large number of people.

Pharmaceutical Industry Involvement

Eli Lilly have been approached on four separate occasions to assist in the provision of raloxifene or even to fund the pilot study but are not interested in the “small market” of older women with schizophrenia. Also, pharmaceutical industry funding for this novel use of an existing drug would not allow completely independent and unbiased research, hence my application to NHMRC.

10. SIGNIFICANCE AND FUTURE DIRECTIONS
The development of SERMs opens up a potentially new treatment area for women with schizophrenia. If our innovative study is successful, then there are many possibilities for using SERMs as an adjunct to treatment in a preventative mode with women about to enter menopause. Women with schizophrenia are known to have significantly more relapses of schizophrenia during the perimenopause period. The SERMs are purported to have fewer side-effects on reproductive organs such as the breast or uterus and hence may be a safer adjunct than standard HT in considering the improvement of psychotic symptoms with hormone manipulation. Since the SERMs have been described as “non-feminising estrogens”, they also have the potential to be used to assist in the treatment of psychotic symptoms in men with schizophrenia. Schizophrenia is a serious debilitating disease with increasing social and economic costs to the individual, their family and society. The mainstay of treatment is pharmacotherapy, but a large number of patients with schizophrenia either fail to respond completely or even partially. We desperately need new treatment approaches to improve patients’ quality of life and functioning above the current outcomes with existing treatments. Adjunctive hormonal treatments may offer new opportunities to achieve this.

11. STUDY TIME FRAME

Time estimated for recruitment and completion of data collection is 3 years employing a full-time research assistant at both the Barwon and Alfred sites.

12. STUDY BUDGET

<table>
<thead>
<tr>
<th>1. CONSUMABLES:</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Printing and Stationery production of subject case files and study documents etc. @ $1000 per year/site</td>
<td>$2,000</td>
<td>$2,000</td>
<td>$2,000</td>
<td>$6,000</td>
</tr>
<tr>
<td>Travel costs for staff to screen community clinics, attend meetings &amp; visit participants</td>
<td>$1,500</td>
<td>$1,500</td>
<td>$1,500</td>
<td>$4,500</td>
</tr>
<tr>
<td>Subjects will be reimbursed for out of pocket travel costs such as taxi, parking, train fares etc. $25/visit x 7 visits x 180 subjects</td>
<td>$12,000</td>
<td>$12,000</td>
<td>$12,000</td>
<td>$36,000</td>
</tr>
<tr>
<td><strong>Total Consumables</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>$46,500</strong></td>
</tr>
</tbody>
</table>

| **Total Pathology**                                                            |      |      |      | **$86,400** |

<table>
<thead>
<tr>
<th>3. MEDICATION COSTS:</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raloxifene (SERM) @ $3/day x 84 days x 90 subjects</td>
<td>$7,560</td>
<td>$7,560</td>
<td>$7,560</td>
<td><strong>$22,680</strong></td>
</tr>
<tr>
<td>Placebo @ 30c per capsule x 84 days x 90 subjects</td>
<td>$756</td>
<td>$756</td>
<td>$756</td>
<td><strong>$2,268</strong></td>
</tr>
<tr>
<td>Capsules (15,200) @ 50c each</td>
<td>$2,533</td>
<td>$2,533</td>
<td>$2,533</td>
<td><strong>$7,600</strong></td>
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<tr>
<td><strong>Total Medication</strong></td>
<td></td>
<td></td>
<td></td>
<td><strong>$32,548</strong></td>
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</table>
### 4. ALFRED PHARMACY COSTS:

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<tr>
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<tbody>
<tr>
<td>Study setup</td>
<td>$950</td>
<td>$0</td>
<td>$0</td>
<td>$950</td>
</tr>
<tr>
<td>Annual Fee = $450</td>
<td>$450</td>
<td>$450</td>
<td>$450</td>
<td>$1,350</td>
</tr>
<tr>
<td>Annual Cost of blinding all medications @ $80/hour x 40 hours per occasion (To prevent study medication expiring, preparation of study meds will occur annually)</td>
<td>$3,200</td>
<td>$3,200</td>
<td>$3,200</td>
<td>$9,600</td>
</tr>
<tr>
<td>Dispensing fee = $30/dispensing x 3 monthly x 180 subjects</td>
<td>$5,400</td>
<td>$5,400</td>
<td>$5,400</td>
<td>$16,200</td>
</tr>
<tr>
<td>Trial close out fee</td>
<td>$0</td>
<td>$0</td>
<td>$380</td>
<td>$380</td>
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<tr>
<td><strong>Total Pharmacy</strong></td>
<td><strong>$28,480</strong></td>
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</tbody>
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### 5. MEDICAL RECORDS ACCESS:

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</thead>
<tbody>
<tr>
<td>Alfred and Barwon Medical Record Access fee = $4 per subject x 8 main visits x 180 subjects</td>
<td>$1,920</td>
<td>$1,920</td>
<td>$1,920</td>
<td>$5,760</td>
</tr>
<tr>
<td><strong>Total Medical Records</strong></td>
<td><strong>$5,760</strong></td>
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### 6. RESEARCH INSTRUMENTS LICENSE COSTS:

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<tbody>
<tr>
<td>Test instruments include; Cognitive Tests, PANSS, SCID, Adverse Symptom Checklist (approx $15,000)</td>
<td>$5,000</td>
<td>$5,000</td>
<td>$5,000</td>
<td>$15,000</td>
</tr>
<tr>
<td><strong>Total Instrument Costs</strong></td>
<td><strong>$15,000</strong></td>
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### 7. ADVERTISING COSTS:

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<tbody>
<tr>
<td>Advertising for subject recruitment in local and Melbourne newspapers &amp;/or magazines (approx $5000)</td>
<td>$1,667</td>
<td>$1,667</td>
<td>$1,667</td>
<td>$5,000</td>
</tr>
<tr>
<td>Advertising for research staff (Approx $3000)</td>
<td>$1,000</td>
<td>$1,000</td>
<td>$1,000</td>
<td>$3,000</td>
</tr>
<tr>
<td><strong>Total Advertising Costs</strong></td>
<td><strong>$8,000</strong></td>
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**TOTAL DIRECT RESEARCH COSTS**

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<tbody>
<tr>
<td></td>
<td>$83,736</td>
<td>$82,786</td>
<td>$83,166</td>
<td>$249,688</td>
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</tbody>
</table>

### 8. PERSONNEL COSTS

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<tbody>
<tr>
<td>Alfred - NH&amp;MRC PSP4 @ $76,500 per year for 3 years</td>
<td>$76,500</td>
<td>$76,500</td>
<td>$76,500</td>
<td>$229,500</td>
</tr>
<tr>
<td>Barwon - NH&amp;MRC PSP3 @ $64,750 per year for 3 years</td>
<td>$64,750</td>
<td>$64,750</td>
<td>$64,750</td>
<td>$194,250</td>
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<tr>
<td><strong>TOTAL PERSONNEL COSTS</strong></td>
<td><strong>$141,250</strong></td>
<td><strong>$141,250</strong></td>
<td><strong>$141,250</strong></td>
<td><strong>$423,750</strong></td>
</tr>
</tbody>
</table>

**TOTAL PROJECT COSTS**

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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$673,438</td>
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### REFERENCES


