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SAFFRON: Developing a Stepped Approach to improving sexual Function aFteR treatment fOr gyNaecological cancer

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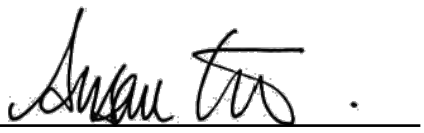
CI Signature: 

SAFFRON: Developing a Stepped Approach to improving sexual Function aFteR treatment fOr gyNaecological cancer

Abstract

Women affected by gynaecological cancer are often not aware of the sexual consequences of both the cancer and its treatment. Most do not receive appropriate advice or help to recover sexual function, and the impact on their sexuality may be profound, both physically and mentally. Despite this there are several potential therapies which can be effective in helping recovery of sexual activity. A major initial challenge is informing and involving the patients in an appropriate and sensitive manner.

This study will develop and evaluate a 'stepped' system of care based on careful assessment of individual needs. The stepped care will use the best available evidence, adapting existing interventions to help women recover their sexual feelings and activity. The initial assessment will determine which step is suitable initially, and women can be progressed from one therapy to another as appropriate. It starts with simple methods, moving on to new talking treatments for more complex cases, based on theories of how we treat loss and depression. Our assessment tool will be applied across the three main gynaecological cancers: cervix, womb and ovary.

Ongoing clinical assessment will be vital for the success of the stepped care model. We will deliver training and supervision to enhance the skills needed by the Clinical Nursing Specialist. An important part of this study will be the characterising the range of women and their willingness to participate in psychosexual help. One-to-one follow up interviews will inform the level of input required for any subsequent Randomised Control Trial. We will use an internationally recognised rating scale for rating sexual function, as well as assessing how illness and treatment affect mood and self esteem, choosing scales which are as brief as possible for participants, in order to minimise drop out through fatigue. We will also measure the overall cost-effectiveness to the public sector of providing this treatment, compared to costs of subsequent use of health and social services.

This pilot study will assess the feasibility of conducting a full scale investigation of a stepped therapy and indicate the potential benefits to the patients, their partners, and to the NHS generally.

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Trial Summary

A two stage study: Stage (1) developing a stepped care system of interventions for psychosexual difficulties in women treated for gynaecological (GN) cancer; Stage (2) an exploratory trial of the stepped care approach to assess feasibility and acceptablity of the interventions, and collect data on sample and effect sizes to inform a larger definitive trial.

Trial design
Feasibility study: Two arm, parallel group, randomized controlled trial.

The brief requests research to develop and test the addition of psychological and behavioural interventions to usual care for women with psychosexual difficulties who have been treated for gynaecological cancer. We propose to develop 3 levels of intervention adapted from current models to be delivered in a stepped care approach. We shall use systematic assessment for entry into and throughout the model which will allow women to move between the three levels if needed. Interventions at each level will be described in detailed written manuals. The finalised approach will be tested in an exploratory randomised controlled trial to assess feasibility, acceptability, willingness to randomise, recruitment rates, and effect size estimates to inform a future definitive phase III randomised controlled trial.

Assessment and intervention to develop a protocol of care to improve psychosexual function in women treated for gynaecological malignancy and to test its feasibility in an exploratory trial. The study will be conducted in two parts. In part one we shall develop: (1) An integrated, stepped care system for the assessment and routine outcome monitoring of women with psychosexual problems (including mood and self-esteem); (2) A series of treatment manuals detailing the interventions provided at each step; (3) A brief training programme for clinical nurse specialists (CNS) and psychological therapists providing the interventions. In part two we shall conduct an exploratory randomised trial to assess (1) referral rates, acceptance of randomisation and attrition (2) uptake of and attrition from the interventions offered; (3) acceptability and feasibility of the trial outcome measures; (4) feasibility and experience of establishing a stepped system for the delivery of the intervention; (5) feasibility of the CNS training; (6) potential effect sizes of the interventions; (7) qualitative data on experiences of women in the trial(8) estimates of the potential magnitude of the effect of the intervention, with confidence intervals to determine whether these are consistent with clinically important effects and (9) estimates required to inform the sample size calculation for a large RCT(10) feasibility of collecting cost and quality of life information for a cost- utility analysis of stepped care compared to TAU in a full trial.

Findings will provide estimates of sample size calculation and treatment effects with confidence intervals to inform the need to conduct a definitive trial.

Target population
Women over age of 18, with adequate English, attending GN-oncology clinic at University Hospitals Bristol or UCLH for follow-up at least 6 months after a course of treatment for any GN malignancy and any stage

Justification for not limiting study to one cancer site
1. The call of HTA asks for all cancer types.
2. Recent systematic review (Abbot-Anderson and Kwekkeboom 2012) advocate comprehensive and systematic assessment of sexual concerns, using reliable and valid measures in large representative samples that include all gynaecological cancer diagnoses, stages of illness, and types of treatment. Rees 2011 suggests broader definition of sexual satisfaction- to be included in our level 2 and 3 interventions.
3. We have used a person-centred, problem-based approach, as there is evidence that extent of treatment not necessarily correlated with sexual dysfunction (Hazewinkel et al 2012, Carpenter et al 2009)

Planned interventions:
Control arm:
Treatment as usual. Women will be seen by their CNS for information, dilation, and advice on topical creams, lubricants as current best clinical practice.

For this study, based on current practice, Treatment as Usual will be as follows:

a) a doctor may recognise the problem at a follow-up visit, either clinically or as a result of a problem checked on the Distress Thermometer.

b) if identified by medical staff, referral to CNS initially (in most cases, but any direct referral to psychologist will be monitored and reported).

c) CNS input will involve assessment, normalizing the experience, supportive counseling, help in discussing the relationship advice on topical lubricants and oestrogen.

d) CNS led clinics in UCLH for dilation after radiotherapy will involve teaching dilator use as well as the contents of C; Therapy radiologist clinics in Bristol for dilation after radiotherapy will involve teaching dilator use, use of lubricants and advice on topical use of oestrogen creams

e) CNS may refer on to a Psychologist if problem does not respond

Psychologist intervention will involve assessment of the woman, body image and self-esteem work, couple assessment using formal measures, psychosexual therapy including modified sensate focus and couple therapy. Women for TAU will only be seen by the CNS NOT trained in the intervention. CNS' trained in the intervention will be asked not to share the content of the new interventions with their clinical colleagues, or include study interventions in the delivery of care to non-trial patients

All treatments in the TAU arm will be recorded from case notes and CNS/Psychologist treatment files to characterize the interventions received. All participating women will receive a patient-held treatment diary to log all treatment contact.

Intervention arm:
The stepped care intervention will be developed over the first 6 months of the project. Stepped care is widely used within psychological therapies and the 'Improving Access to Psychological Therapies' (IAPT) programme (Improving Access to Psychological Therapies, 2012; Richards et al., 2012) and we shall adapt this approach to develop a 3-step model which will include a clinical assessment and treatment algorithm. All steps will have clear entry criteria and treatment protocols. We will use sessional outcome monitoring standards in IAPT to assess progress (i.e. PHQ-9). Women will first be offered step 1 but based on the structured assessment and predetermined criteria within the treatment algorithm, a number of women will be referred directly to step 2 or 3. Women who do not benefit from step 1 or 2 interventions (this will be informed by the sessional measures. See below) will be referred to step 3.

Step 1: All women with a psychosexual problem who request help and consent to entry to the trial. This will involve structured clinical information delivered by the CNS and
- i) psycho-education and advice on psychosexual problems
- ii) advice on the use of dilators, lubricants and topical creams.

These versions of psychoeducational materials will not be made available to women in the control arm.

Step 2: All women with a psychosexual problem and mild to moderate depressive symptoms (PHQ-9 score 10 to 20) or women who have not responded to step 1, and assessed by the CNS as requiring further help in particular with issues of mood and self-esteem and are requesting further help. Women will be provided in parallel with an enhanced psychosexual intervention based on the work of Brotto et al (2008). The additional element of the intervention at Step 2 will consist of up to six 20-30 minute sessions (Face to Face or telephone) with one follow up session at 12 weeks after the first session. The sessions will address mood and self-esteem issues using existing IAPT materials adapted for use in the trial. The interventions will be delivered by CNS.

Step 3: All women with a psychosexual problem and moderate to severe depressive symptoms (PHQ-9 score greater than 20), are assessed by the CNS as requiring further help in particular with issues of mood and self-esteem and women who have not responded to step 1 and request further help. Women will be provided in parallel with any continuing psychosexual intervention. The additional element of the intervention at Step 3 will be 16 to 20 sessions high intensity intervention NICE recommended treatment for depression(Interpersonal therapy) delivered by a clinical psychologist.

Participants in the control and intervention arms will take part in assessments at 6 weeks, 3, 6 and 12 months and a number of women will be invited to take part in semi-structured qualitative interviews.

Development of the interventions:
The interventions will be developed within the first 6 months of the study. This will include the development of a trial assessment and treatment algorithm. In addition to the production of written materials (guided self-help materials) for the participants, an assessment manual and treatment manuals for each step will also be developed.

Step 1: Best available psycho-educational materials collected for the trial about sexual problems after gynaecological cancer offering self-help, tailored to the individual problems of the woman. Appropriate use of

dilators, advice on lubricants and topical creams in which CNSs are already trained will occur at this stage and be documented.

Step 2: A range of manualised low intensity interventions delivered by study trained CNSs with accompanying workbooks to be developed in first 6 months of trial; they will based on existing psychosexual interventions, body image work and couple work, with a mindfulness component (derived from Brotto et al 2008 - permission has been extended to use and adapt their materials). Mood and anxiety will be addressed if PHQ 9 and GAD7 scores indicate need, using adapted guided self-help booklets from the Camden IAPT programme.

Step 3: Will be a high intensity intervention delivered by a clinical psychologist with experience of working in oncology using Interpersonal Therapy (IPT), (Klerman et al 1984). IPT is a role focused psychological treatment dealing with issues such social relationships, role transitions such as those occasioned by serious illness, loss of fertility and grief and loss generally. It is a NICE recommended treatment for depression. Adaptions will be made to existing manuals to facilitate its use in this study by A Lemma (AL) who is an accredited trainer in IPT. The approach will be detailed in a manual and training and supervision for therapists will be offered by AL.

Following initial development and training, all interventions will be piloted in the clinic and further refinements made. This will involve assessing the comprehensibility and acceptability to participants of the booklets. The assessment procedures and treatment manuals will also be assessed for acceptability and comprehensibility by the CNS and the clinical psychologist.

Measures
We shall use measures that are brief and easy to complete to reduce attrition due to fatigue and collect data on the following possible confounding factors:

At baseline:
Demographics: ethnicity, current relationship status, occupation, education.

At baseline, 3, 6 and 12 months:
Personal history: within a relationship, yes/no; gender of partner;
Cancer history: cancer diagnosis, stage at diagnosis, stage at last appointment (relapse or first line treatment), treatment modality, length of time since end of treatment will be gathered from the ICS database on all GN cancer patients.
Sexual function: Female Sexual Function Index (Rosen et al 2000) (an internationally recognised rating scale which allows women to describe their sexual experience in a range of domains -desire, arousal, lubrication, orgasm, pain and satisfaction);
EORTC sexual function measure: under development by GN Quality of Life Group, due for release before the trial commences
Mood and self esteem: Rosenberg self-esteem measure (Rosenberg 1979)
Hospital Anxiety and Depression Scale (to measure mood in the presence of physical illness)
(Zigmond and Snaith, 1983)
EORTC QLQ-C30 - a cancer specific internationally validated quality of life measure (Aaronson et al., 1993)
Economics: EQ 5D to measure cost effectiveness The EuroQol Group (1990), Brooks (1996) Client Services Receipt Inventory (short form) to assess use of health and social services (Beecham
& Knapp, 2001)

Session measures for all face to face sessions:
PHQ9 A nine item depression scale of the Patient Health Questionnaire (Kroenke et al 2001) Distress Thermometer visual analogue scale adapted for sexual dysfunction (Gessler et al 2008)

Research Governance
Trial Management
The trial will be coordinated through PRIMENT, a fully registered UK CRC Clinical Trials Unit. PRIMENT is collaboration between UCL Mental Health Sciences and the Research Department of Primary Care and Population Sciences. The PI will maintain overall responsibility for the study working in close collaboration with the trial manager to ensure that it is conducted, recorded and reported in accordance with the protocol

and essential standard operating procedures on all aspects of trial management. An independent Trial Steering Group will be set up to monitor the conduct and progress of the trial.

Background and Rationale

Many cancer patients are reported to have sexual difficulties (Ananth, 2003; Anderson 1985, Miles et al 2007), gynae-oncology patients are particularly vulnerable to changes in sexual activity and lack of sexual desire(Stead et al 2003, Aerts et al 2012, Lammerink et al 2012) with sexual difficulty rates estimated between 40 and 100% (Wiggins et al 2007). Women undergo a range of treatments for ovarian, cervix, womb and vulval cancer with different combinations of surgery, chemotherapy, and radiation. Some of these treatments have a deleterious effect on women's internal and external sex organs, surrounding tissues and nerves, and render some menopausal. Following such treatments women report a wide range of difficulties including loss of libido, dyspareunia, vaginal dryness, and orgasmic difficulty. In addition, the symptom burden of gyaenacological cancers is heavy with many women reporting pain, fatigue, changes in bowel function, urinary symptoms including leakage, and depression and anxiety (Casey et al 2011) which interact with menopausal and sexual difficulties, (Barbera et al 2011). Hazewinkel et al (2012), and Carpenter et al (2009) both note the major impact of physical well-being on sexual function, as well as the lack of relationship between extent of treatment and formal scores of sexual function. It is unsurprising that women treated for a gynaecological cancer are at high risk of emotional distress. One prevalence study found 23% satisfying criteria for major depressive disorder (Thompson & Shear, 1998), and Parker et al(2003) found greater depressive symptoms in gynaeoncology patients than in breast, urology or gastro intestinal cancers.

Carpenter et al (2009) suggest that some of this greater distress is related to the very high levels of sexual difficulty experienced after treatment. Carpenter et al (2009) argue that sexual self schema is an important moderator of response, finding that positive sexual self schema was associated with more frequent sexual activity, better sexual responsiveness, and higher global sexual satisfaction across all disease sites and confounders (Andersen &Cyranowski, 1994; Wiederman & Hurst, 1997), suggesting it makes women more resilient to the adverse sexual impacts of gynaecological cancer. Despite their sexual difficulties, many gynaecologic cancer survivors resume intercourse (Andersen et al., 1989a; Stafford & Judd, 2010). Frequency of intercourse in this sample was comparable to available norms for similarly aged women (Laumann et al., 1994), but these and other longitudinal data have shown sexual satisfaction (Gershenson et al., 2007; Lindau et al., 2007) and responsiveness (Andersen et al., 1989a; Gershenson et al., 2007; Hawighorst-Knapstein et al., 2004; Lindau et al., 2007; Weijmar Schultz et al., 1991) to be significantly impaired following treatment.

Patients report that sexuality is rarely addressed by physicians (Stead et al 2003). Lindau et al 2007 found that conversation with a physician about the sexual effects of cancer was associated with significantly lower likelihood of complex sexual morbidity among very long-term survivors; however 62% of 221 participants reported that their physician had never initiated a discussion about sexuality after cancer. In their study of sexuality in a palliative care setting, Vitrano et al (2011) showed that patients considered it important to talk about sexuality and to face such an issue with an experienced professional even though their life expectancy was short. Patients in their study had not had this opportunity. Moreover, some patients were still able to maintain a sufficient sexual activity, in terms of quality and quantity. Faithfull & White (2008) found that cancer nurses were more likely to focus on the technical aspects of sexual recovery post treatment, for example vaginal dilation, and offered minimal advice or opportunities for disclosure for sexual dysfunctions, dissatisfaction with partner relationships or mood and other psychological difficulties. Clinical Nurse Specialists (CNS's) in gynaecological cancer acknowledge that they have an important role in this aspect of care but do not always feel confident or competent to assess or manage patients psychosexual needs, and appropriate referral is then problematic (Stead et al, 2001; Richardson et al, 2007). Recently a national Psychosexual group has been formed of expert nurse 'champions' and their work to date includes a psychosexual assessment guideline document for nurses.

Sexual dysfunctions are defined by Diagnostic and Statistical Manual of Mental Disorders (DSM-IV R) as 'a disturbance in sexual desire and in the psychological and physiological changes that characterise the sexual response' of which 6 apply to women: Sexual desire disorder or decreased libido: hypoactive sexual desire (low interest in sex) and (2) sexual aversion disorder (objections to having the genitals touched); (3) Female sexual arousal disorder; (4) female orgasmic disorder (premature, delayed or absent orgasm following a normal sexual excitement phase); Sexual pain disorders: (5) vaginismus (involuntary spasms of the muscles of the outer third of the vagina that interferes with intercourse) and (6) dyspareunia (pain during intercourse)(King et al 2007; Nazareth, et al. 2003).

A recent review of specific complaints of all cancer patient referrals to the Sexual Health Program of the

Memorial Sloan Kettering Cancer Centre found that most sought help for painful intercourse (65%), vaginal dryness (63%), low sexual desire (46%), and orgasmic disorder (7%) (Amsterdam et al 2006). The first two of these are partially managed through current best treatment, i.e. topical oestrogen, vaginal dilators and

lubricants (Miles et al 2007, Flynn et al 2009). Prevalences reported by cancer site include Tsai et al comparing crude prevalence (66.67%) with age-standardised prevalence (55%) in cervical cancer. Many other studies report ranges from 83% sexual difficulties (Aerts et al 2009), to 66% significant and 46% moderate difficulties (Corney et al 1993). In early stage cervix treated with radical hysterectomy, Serati et al (2009) reported 65.8%.

In contrast with the majority of sexual therapy interventions where anxiety reduction is often key, management of low sexual desire in the context of gynaecological cancer requires an intervention which additionally addresses the wider range of mediating factors, including loss, life-threat, trauma, change of body image, pre-existing psychological outlook, mood, depression and anxiety symptoms as well as the relationship within which the woman finds herself (Brotto et al 2010, Abbot-Anderson and Kwekkeboom 2012; Mitchell et al, 2011; Rizzo et al., 2011). A wide range of non controlled trials of sexual therapy interventions are reported in reviews by Brotto et al (2010), Abbot-Anderson and Kwekeboom, (2012). These studies across a range of interventions all show small effect sizes, but accompanied by patient satisfaction. Flynn et al (2009) in their Cochrane Review of randomized control interventions for psychosexual dysfunction in women treated for gynaecological cancer concluded 'There is insufficient evidence to support or refute the use of any interventions for psychosexual dysfunction after gynaecological cancer.' Further, they suggested that future trials required multi-centre RCTs with outcome measures validated in gynaecological cancer patients. 'When considering interventions to trial, we would suggest that investigators should focus on interventions that can be delivered by existing members of the multidisciplinary team treating women with gynaecological cancers. It is more likely that such measures, if found effective, will be affordable and capable of being integrated into standard care. An international consensus on outcome measures would greatly facilitate the comparison of interventions in the future.'

This study attempts to address this for the NHS by using the existing multi-disciplinary team to deliver a stepped care approach. This involves CNS delivered interventions at step 1 and step 2 as the major treatment delivery, and only a small minority of more complex psychological issues being treated at step 3 by a level 4 practitioner to whom patients should have access according to peer review (National Institute for Health and Clinical Excellence, 2004; National Cancer Action Team, 2010) .

Evidence explaining why this research is needed now

From the evidence presented above, it is often the case that women affected by gynaecological cancer are not aware of basis information about the sexual consequences of their gynaecological cancer and its treatment, and do not receive appropriate advice or help to recover sexual function, and adapt to their changed body and relationships. It is generally recognised by two Cochrane reviews (Miles et al 2007, Flynn et al 2009) that new interventions are needed for sexual dysfunction in gynaecological cancer and these need to be examined in multi-centre RCTs with agreed outcome measures. There is a sizeable population with these problems to be addressed for there are currently 1.8 million people in England living with and beyond cancer, and 2 million across the UK as a whole. This number is likely to grow by over 3% per year, reflecting the increasing incidence of cancer and better survival rates. By 2030 there are likely to be around 3 million cancer survivors in England (National Cancer Survivorship Initiative, 2012). Since we have the ability to develop suitable treatments, we have a duty to explore them (Richards et al 2011, Richardson et al 2011). The current acceptance of the worth of wellbeing, and conversely the cost of depression, anxiety or unwillingness to engage with the healthcare system - all potential long term effects for the patient group concerned - are drivers for this research (DoH, 2010). Better awareness of mental health issues and depression in general (Barbui&Saraceno, 2012) and in cancer patients (McDaniel, 1995) plus greater acceptance that these symptoms have causes which can be treated or addressed is relevant too. In addition the work is planned at a time when there is more awareness of sexual health, and evidence from cancer user groups (Target Ovarian Cancer, 2009), policy makers (National Council for Hospice and Specialist Palliative Care Services, 2000) and research (Churchill, 2010) of more openness to discuss these matters as a medical need. The potential of CNS's to deliver interventions to help with the consequences of cancer treatment has been recognised by the Department of Health (National Cancer Action Team, 2010b) yet little is known about CNS's training or supervisory needs to provide interventions for psychosexual dysfunction to work alongside psychologists. If care pathways exist for addressing sexual dysfunction in cancer they are currently unique to individual units; providing the evidence for pathways which better meet the requirements of the population will facilitate clinical application of more appropriate and consistent practice. What is currently missing within the literature is a phased proposal that develops an intervention and tests this to facilitate best practice in treatment of sexual dysfunction for all relevant women in gynaecological cancer centres.

Aims and Objectives

1. To establish whether women treated for gynaecological cancer with moderate to severe sexual dysfunction are willing to participate within a randomised trial model and adhere to treatment
2. To indicate likely rates of recruitment to a future evaluation of SAFFRON intervention
3. To pilot a stepped care psychosexual intervention (SAFFRON) on the IAPT (Increasing Access to Psychological Therapies, Richards et al 2012) model and compare its effect on sexual dysfunction to treatment as usual
4. To establish whether the SAFFRON intervention is acceptable to patients
5. To establish whether SAFFRON is deliverable by a GN cancer centre multi-disciplinary team
6. To inform the effect size, sample calculation and outcome measures for use in a larger definitive trial

Research questions

1. Will women agree to be randomized to a sexuality intervention?
2. Are different tumour sites, treatments, cancer stages at approach associated with different rates of uptake of therapy/intervention or recruitment to trial?
3. Is the stepped care system operable within the NHS system as it stands?
4. What is the likely effect of the three levels of intervention on sexual function, mood and self-esteem as measured by standard measures?
5. What is the rate of attrition from each treatment modality?

Research Plan/Methods

Design and theoretical/conceptual framework:

- Feasibility study: Two arm, parallel group, randomized controlled trial.
  The HTA call requires a feasibility study; a new intervention requires a pilot RCT.

Planned inclusion/exclusion criteria:

Target population - inclusion

- Women over 18 (with partners at their choice) treated for any gynaecological malignancy with surgery and/or chemotherapy and/or radiation
- 6 months minimum post end of treatment with sexual function difficulties identified by initial screen (3 clinical questions plus Distress Thermometer used in routine follow-up, Gessler et al 2009)
- Any sexual orientation

Exclusions

- Poor English
- Current drug or alcohol abuse
- Current sexual therapy or psychotherapy

Maximising recruitment

We have identified clinical champions within the teams and will consult weekly to monitor and explore concerns that arise. At UCLH, Olaitan (AO) Gynaecological Oncologist is a co-applicant and former Tumour Board Chair, Summerville (KS) is Lead CNS and co-applicant (Locock et al, 2001; Harvey et al., 2002). At Bristol, Bailey (JB) Gynaecological Oncologist and Cole (SC) Psychologist will be clinical champions.

Additional methods of inviting women

- The UCLH web-based patient portal will have material on the study.
- The Macmillan Support and Information Service (integral part of cancer centre) will have written information and all informal support workers will be made aware of the trial
- The sexuality and gynaecological cancer leaflet which forms part of the standard materials available to women will be rewritten with information about the availability of the study.

Maintaining recruitment

We will be vigilant during early stages of study - and if not reaching expected numbers within 6 weeks, we will

approach units within our Gynaecological cancer network. We will present the study within the multi-disciplinary Meeting (MDM) and include a section of MDM agenda with study summary and recruitment to date as agenda item to be raised weekly.

Training
Step 1 training - and training in the assessment process will be by Gessler (SG), Lanceley (Ala), Pilling (SP) and form part of the full day described below.

The step 2 intervention will require a full day training (SG, ALa, SP, KS) for CNSs. They will receive weekly supervision on their case load in group session by ALa and/or KS for the duration of the study. This will allow assessment of fidelity to treatment protocols with direct feedback and continued training during the study.

Step 3 will require IPT training with adaptation by AL and weekly supervision for cases 1 and 2 to ensure fidelity to treatment protocol. Subsequent cases monthly supervision.

Adherence to model of treatment
Adherence to the model of intervention and protocol for delivery will be monitored at all steps. CNS and clinical psychologist sessions will be taped and rated for adherence to the model using standard techniques, as used in the IAPT programme and clinical psychologist sessions will be taped and rated for adherence to the model using standard techniques, as used in the IAPT programme (Reachout Manual, Richards and Whyte 2009, via www.iapt.nhs.uk. Manuals exist for Brotto and Heiman intervention, IAPT and IPT which will all be used as a basis for adherence measures. Assessment will be by senior members of the research team.

The intervention team will receive regular supervision from seniors involving case discussions, reflection on specific difficulties and challenges. The team will be encouraged to feedback on gaps in their training and knowledge for these to be addressed. Field notes will be taken so that detailed knowledge of training and support needs is developed; these can then be considered when developing the protocol for a definitive trial.

Process
Women in treatment arm - baseline assessment.

Step 1.
Mild sexual dysfunction -will be provided by their CNS with the trial psychoeducational and self help materials. At 6 weeks, contacted by RA to complete measures FSFI, PHQ-9 GAD 7. Open-ended conversation. Woman can opt-in to step 2 or be invited to step 2 if score on measures unchanged.

Step 2.
CNS mood and sexual dysfunction intervention. Workbooks and intervention to be chosen from a battery developed for study from Brotto et al materials and adapted IAPT mood workbooks. 6 sessions within nurse led clinic. Sessional measures. Woman's choice to bring partner or not. Assessment at end (3m from baseline). If significant change on FSFI, self esteem, PHQ-9 or GAD 7, offer step 3.

Step 3.
Consists of women stepped up from Step 2 or if severe mood shown on initial baseline assessment, women go straight from baseline assessment to step 3. 16 session weekly IPT adaptation for SD administered by a practictioner psycho-oncologist (minimally band 8A). Sessional measures and end of treatment assessment as per schedule below.

Methods to protect against other sources of bias
As is common in trials of complex healthcare interventions it will not be possible for clinicians and patients to be blind to their assignment to treatment group. However, researchers collecting data at baseline and follow-up will remain blinded. Trial participants will be asked to avoid revealing their allocation to researchers. The trial statistician will remain masked until all data are collected and the final analysis plan is agreed by the research team.

In order to assess the possible leakage of the impact of the trial on Treatment as Usual (as study occurs in a single centre), all participants in both arms will be asked at follow-up to describe any treatments or information they have accessed as some may, by having the possibility of an intervention raised, seek treatment elsewhere.

Sampling:
Proposed sample size

The aim of this study is to establish the feasibility of a larger definitive trial of the proposed stepped care intervention. The critical parameters that will be used to quantitatively assess feasibility are:

a) consent rate
b) proportion in the intervention group who move up at least 1 step on the intervention
c) proportion of all randomised subjects who have a useable (non missing) score for total FSFI (our proposed primary outcome) at 12 months

In order to justify continuation to the main trial minimum values ('success criteria') for these parameters have been set. These are:
a) consentrate of at l east 40%
b) minimum of 30% in the intervention group moving up at least 1 step on the intervention
c) at least 70% of randomised subjects having a useable (non missing) score for total FSFI (our primary outcome) at 12 months follow-up

We will also use the feasibility data to provide an estimate of standard deviation of the FSFI score that will be required for the sample size calculation of the main trial.

A sample size of 100 patients, randomised equally to the 2 treatment groups, has been chosen for this feasibility work. This sample size is shown below to be adequate to ensure sufficient precision to exclude the minimum acceptable values for the 3 critical parameters based on exact, one sided 95% confidence intervals around assumed values for each parameter:

a) Consent rate: We expect that 50% of women will consent to randomisation in the trial. With a sample size of 100 women, this consent rate can be estimated with a lower 95% confidence bound of 44%.

b) Proportion in the intervention group who move up at least 1 step on the intervention: We expect that 80% of the 50 women allocated to the intervention group will step up at least 1 level on the intervention during their treatment period. We will be able to estimate our expected proportion of 80% with a lower 95% confidence bound of 68%.

c) Proportion of all randomised subjects who have a useable score for total FSFI at 12 months: We estimate that 80% of the 100 women randomised in the trial will provide useable data to score the FSFI at 12 months. With 100 women we will be able to estimate 80% with lower 95% confidence bound of 72%.

Data from 100 patients will also be adequate to provide a good estimate of the standard deviation of the primary outcome to inform the sample size calculation for the main trial (Julious, 2005).

Accrual and attrition
365 new cancers were diagnosed within UCLH in 2010, and 1474 follow-up patients were discussed in the UCLH Gynae-oncology Multi Disciplinary Meeting that year (Peer review report, CQINS) giving approximately 100 attendances per week Using published figures, over the 9 month recruitment period in this study approximately 550 eligible women are expected to be seen at UCLH (numbers are from UCLH figures which show 1839 women were treated or in follow up for a gynaecological cancer in 2010 (ref UCLH annual review 2010-11), we estimate that 80% of these are likely to be sexually active (aged<75) and previous publications indicate a minimum of 50% of these are likely to have sexual dysfunction(Corney et al 1993, Aerts et al 2009). We therefore expect that the sample size for this feasibility study will be easily achievable in the 9 month period allowed for recruitment. The addition of Bristol, whose throughput is broadly similar, should aid effective recruitment. In 2011-2012, 469 new diagnoses were discussed in their MDT, 23 recurrences and 14 metastases.

The length of recruitment period is to ensure recruitment in the context of a busy clinic, with a culture change required within 2 teams of clinicians (Ryecroft-Malone et al., 2002)

Training and Support

The intervention team will receive regular supervision from senior staff involving case discussions, reflection on specific difficulties and challenges. The team will be encouraged to feedback on gaps in their training and knowledge for these to be addressed. Field notes will be taken so that detailed knowledge of training and support needs is developed; these can then be considered when developing the protocol for a definitive trial.

A didactic training programme alone or even with supervision is unlikely to stimulate and maintain long term changes in behaviour and clinical practice; research suggests that different forms of clinical support are required rather than traditional models of education. (Ryecroft-Malone, 2002) Thus we shall gather evidence

in the pilot phase, for the facilitation required for change in practice to implement a different model of care for the treatment of psychosexual dysfunction (Harvey, et.al.,2002)

Justification of assumptions:
Prevalence levels of sexual dysfunction in this population vary. Tsai et al (2011) compare crude prevalence (66.67%) with age-standardised prevalence (55%) in cervical cancer. Many other studies report ranges from 83% sexual difficulties (Aerts et al 2009), to 66% significant and 46% moderate difficulties (Corney et al 1993). In early stage cervix treated with radical hysterectomy, Serati et al 2009 reported 65.8%. Within our population we do not have figures for those who are un-partnered and not in a sexual relationship. We therefore assume conservatively that an age standardised rate of SD in our population is 50% (ie will answer 'yes' to our three opt-in questions); and of those women, 50% agree to enter the trial (based on take-up of depression therapy trials in primary care) we can estimate recruitment. El et al (2008) found 80% pick-up of a treatment intervention for depression in cancer. Attrition rate: in IAPT, Richards et al 2012 reported attrition rate of less than 30% in psychological intervention trials.

Recruitment rate:
We aim to recruit 2-3 women per week for nine months.

Setting/context:
UCLH Gynaecological (GN) cancer centre, one of two specialist centres *for London Cancer* Integrated Cancer System (ICS), covering a population of 4 million; and University Hospitals Bristol Gynaecological Cancer Centre. In 2010 UCLH saw 365 new GN cancers and 1474 follow-up patients were discussed in its Multi-disciplinary Meeting (MDM). It has a highly integrated structure in a model new cancer centre (opened April 2012) and forms part of an innovative patient-centered gynaecological cancer structure (Pathway) as part of the ICS which is likely to become a model for other services over time. The numbers for Bristol are largely similar, but its setting is within a Cancer Network and covers a very different demographic and clinical structure.

Data collection:
Data Management
We shall use a web based data collection system that has already been successfully developed for two other large multicentre studies run through the MRC GPRF and PRIMENT Clinical Trials Unit. The research assistant will have access to this website and will complete the data entry at the time of seeing the trial participant. Data entered via the website will not contain personal identifiers (e.g. name, address). Each person and service will be given a unique number, which will be linked to participants' names and addresses.
Personal data will be stored in the trial centre in locked filing cabinets. The database will be accessed centrally by the study statistician on a monthly basis and analysed to assess recruitment and retention levels and for data cleaning according to specified Standard Operating Procedures developed by PRIMENT for the management of such data.

Ethical arrangements:
Approval of the local ethics team will be obtained. The research team are cognizant of the fact that this is a vulnerable population who should not be made to feel worse or abnormal by our recruitment requests. Awareness of cultural and personal differences in discussing sexuality will be essential throughout the course of the study and especially at recruitment, which will occur in the context of the important relationship forged between women and their CNS or doctor. Our patient co-applicant (Dunning) has contributed substantially to the outlook and detail of this study including recruitment and will continue to input into the development of materials and conduct of the study. An expert Trial Steering Group will monitor the progress of the study according to national and UCL research governance procedures. All participants will continue to receive standard care and thus none will be disadvantaged. There are no known risks to our stepped care intervention, but clearly all adverse events will be recorded.

Informing potential trial participants of benefits/risks:
We shall inform participants in the TAU arm that they will continue to receive standard care and that their well being will not be compromised by not receiving the new intervention.

Obtaining informed consent:
We shall use the PRIMENT Standard Operating Procedure for obtaining informed consent, which adheres to good clinical practice guidance. In brief, participants will be told that they will be involved in research, the

purpose of the trial, the expected duration of participation, trial procedures, foreseeable risks or inconveniences, expected benefits, whom to contact for further information, their rights as participants, and that participation is voluntary and that they may refuse to participate or withdraw from the trial at any time,

without penalty or loss of benefits. Proposed time for retention of relevant trial documentation: Trial documentation will be retained for 15 years.

Data to be collected:
Data will be collected at baseline and then at 6 weeks, 3 months, 6 months and 12 months after randomization. We shall use measures that are brief and easy to complete to reduce attrition due to fatigue.

Measures:
We shall use measures that are brief and easy to complete to reduce attrition due to fatigue and collect data on the following possible confounding factors:

- At baseline: Demographics: ethnicity, current relationship status, occupation, education.
- At baseline, 3 months, 6 months until at 12 month follow up: Personal history: within a relationship, yes/no; gender of partner;
- Cancer history: cancer diagnosis, stage at diagnosis, stage at last appointment (relapse or first line treatment), treatment modality, length of time since end of treatment will be gathered from the ICS database on all GN cancer patients.
- Sexual function: Female Sexual Function Index (Rosen et al 2000) (an internationally recognised rating scale which allows women to describe their sexual experience in a range of domains -desire, arousal, lubrication, orgasm, pain and satisfaction); EORTC sexual function measure developed for Europe- under development, due for release before trial commences; Mood and self esteem:Rosenberg self-esteem measure (Rosenberg 1979); Hospital Anxiety and Depression Scale (to measure mood in the presence of physical illness) (Zigmond and Snaith); EORTC QLQ-C30 - a cancer specific internationally validated Quality of life measure (Aaronson et al., 1993) Economics: EQ 5D to measure cost effectiveness Client Services Receipt Inventory (short form) to assess use of health and social services (Beecham and Knapp 1992)

Baseline Assessment	6 Weeks	3 Months	6 Months	12 Months
Demographics, personal history	X			
Diagnosis, stage, treatment	X			
FSFI	X	X	X	X
Self-esteem	X	X	X	X
EORTC sexual function questionnaire	X	X	X	X
EORTC QLQ 30	X	X	X	X
EuroQol 5D (EQ-5D)	X	X	X	X
Client services receipt inventory (CSRI) (short form)			X	X
DT	X	X	X	X
HADS	X	X	X	X
PHQ-9	X	X	X	X

Sessional measures for all face to face sessions: PHQ 9, a nine item depression scale (Kroenke et al 2001) and sexual dysfunction adapted distress thermometer (visual analogue scale) (Gessler et al 2008) as this is in routine clinical use within the service - every patient completes it on every clinic visit - and can serve to pick up patients where clinicians may have failed to ask the 3 questions.

The 12 month follow-up period is designed to examine whether effects of the treatment intervention diminish over time (Flynn et al 2009) and is a key part of the call.

At baseline, we shall collect data on factors potentially predictive of outcome: Demographics: ethnicity, current relationship status, occupation, education.
Personal history: within a relationship: gender of partner; self-rated quality of relationship measure Disease information: cancer diagnosis(cervix, ovarian, endometrial, other), stage of disease at diagnosis, time since end of treatment in months
Performance status (0-4) assessed by clinician where 0= no impairment, 4= moribund,as a proxy for physical well-being independent of prognosis at each session and follow-up where possible cancer diagnosis, stage at diagnosis, stage at last appointment (relapse or first line treatment),treatment modality, length of time since end of treatment will be gathered from and cross-checked against the ICS database on all GN cancer patients.

Additional data to be collected
Details on numbers of eligible patients and basic characteristics even for those not randomised to examine how representative the eventual sample is.
record information for each intervention group patient about what level of intervention they received and their movement between steps, their compliance with the intervention
record at follow-up any additional treatments or information women have accessed record timing of drop out from treatment or followup and reasons for drop-out, where ascertainable.

Qualitative investigation
Semi-structured interviews will be conducted at 12 months with a purposive sample patients randomised to the stepped care arm of the trial throughout Part 2 to explore their experience of the process of recruitment to the trial and of receiving the interventions. We shall also interview clinical staff to understand their experiences of recruiting participants to the trial and with senior clinicians and managers about the operation of the SAFFRON intervention and stepped care model. These data will be analysed thematically using the Framework approach (Ritchie et al 2003, Pope et al 2000) with the aid of QSR NVivo qualitative data analysis software and will provide important information on acceptability and potential for harm, as well as potential obstacles and facilitating elements for the intervention.

Data analysis:
Statistical Analysis
Analysis of this feasibility trial will be mainly descriptive. We will measure rates of recruitment, acceptance of randomisation, attrition from treatment and trial and completion rates for the outcome measures (to gauge acceptability and appropriateness of the outcomes). We will also estimate differences (with 95% confidence intervals) for the main trial outcomes between the groups, using appropriate regression methods adjusted for baseline values. Information required for the sample size calculation and analysis plan of the definitive trial will be obtained, including estimates of standard deviation for the primary outcome and correlations between repeated measurements, distributional properties of the data and possible clustering effects. We will investigate if attrition levels are similar across the trial arms and examine the characteristics of participants who drop out and reasons for attrition where available. This will help in understanding the pattern of missingness and to make appropriate plans to handle missing data in the larger randomised trial.

Economic evaluation
We will assess the feasibility of conducting an economic evaluation of a stepped care system of interventions for psychosexual difficulties in women treated for GN cancer compared to TAU and the feasibility and acceptibility of collecting cost and outcome information for use in an economic evaluation.

The anticipated analysis for a main trial would be an incremental cost per Quality Adjusted Life Year (QALY) gained of stepped care compared to TAU, or a cost-utility analysis (CUA). As a CUA has never been conducted for a psychosexual intervention for GN cancer patients,thereliablility and validityof the generic health related quality of life questionnaire required for a CUA, the EQ-5D, is unknown. To provide more information on how the EQ-5D responds to changes in outcomes of interestwe will calculate the correlation between EQ-5D scores and other measures.

We will conduct an initial CUA from a health and social care cost perspective. Patient health and social care resource use will be collected using a short version of the CSRI, modified for cancer patients. Resource use will be costed using nationally published data sources.The cost of training and the intervention will also be calculated. Confidence intervals will be constructed using bootstrapping with replacement and one and two-way senstivity analyses conducted to test key assumptions and areas of uncertainity. The EORTC QLQ 30 can also be used in a CUA, as utility scores for this have been calculated, and we will conduct an additional CUA analysis using these values. We will also assess the feasibility of conducting a CUA using a sexual function measure.

Dissemination and Project Outputs

The main outputs from this research will be:

- New therapeutic materials and therapeutic intervention
- A New format of delivery (stepped care) which will raise the issue of sexuality more widely in follow-up for all women treated for gynaecological cancer

The ultimate aim of this study - and any subsequent RCT - is to change clinical practice through changing Health Care Professionals' engagement with patients, and through altering the perception and knowledge of patients of the effect of cancer and its treatments on sexuality and informing them of the possibility of effective interventions. We would therefore use a variety of approaches, some London and host institution based and some national to disseminate our findings.

Results will be presented to the cancer centre that participated in the research. Participating patients will also be offered the opportunity to receive a summary of the findings or to view the results on the web pages described above. Other forms of dissemination will include the publication of peer reviewed articles, and presentation at conferences and seminars for practitioners, researchers, national policy makers, & users. The quantitative and qualitative study outputs will be assembled to inform the main randomised controlled trial. This will be the subject of a subsequent grant application. For example the qualitative interviews will help to identify deficits and gaps in the treatment manuals, current practices, training and supervisory arrangements which will be revised for the main trial evaluation.

The patient and carer organisations who have been fully involved in the research will also assist with the wider dissemination of the results through their consumer networks. Macmillan are supportive of this endeavour and Julie Latimer, Education Lead of Macmillan London has engaged to roll out any findings. In addition, we will collaborate with the UCLH / UCL Patient and Public Involvement (PPI) in Research Co-ordinator and with the UCLH/UCL press offices to develop contacts with local and national media and to contribute material for the UCL/UCLH websites (including to the dedicated pages on the Research Patients Support Network and PPI in Research). Training courses in *Communicating Science to the Public* will be offered to the researcher.

Plan of Investigation and timetable

Project milestones:
0-6 months -orientation, ethics, research governance, develop intervention and assessment algorithm, write manuals and materials, train CNSs and psychologist 7-15 months -recruitment and intervention
16-27 months - follow-up, qualitative interviews with women and staff, begin qualitative analysis
28-30 months - complete analysis and write

SAFFRON TIMETABLE										
Months	**0-3**	**4-6**	**7-9**	**10-12**	**13-15**	**16-18**	**19-21**	**22-24**	**25-27**	**28-30**
Project Tasks										
Ethics application										
Orientation in gynaecological OPD										
Develop treatment algorithm & manual										
Assemble best available psycho-education										
Develop manuals & workbooks for CNS										
Develop manual for psychological intervention										
Train psychologists										
Train CNS										
On-going CNS & psychologist supervision										
Recruitment			Pilot							
Intervention			Pilot							
Follow-up										
Patient interviews										
Health care professional interviews										
Analysis – qualitative										
Analysis – quantitative										
Write up										
Dissemination										

Project Management

The core research team (SG, AIa, KS; the RA; JB; SP; AL; PF; and MK) will meet monthly to discuss the progress of the trial, and to monitor recruitment and data collection. These meetings will be arranged by the research co-coordinator and chaired by SG. The core team will report to the external and independently appointed Trials Steering Committee. To ensure smooth transition and continuity of membership to the main Trials Steering Committee members will be sought with this in mind. Relevant expertise will be needed on the Trials Committee in terms of statistical advice, user perspective, gynaecological oncology expertise, and psychology. A Data Monitoring and Ethics Committee (DMEC) will be not be set up for this feasibility study but will be required for the main trial.

All aspects of the trial will be managed in accordance with UK Clinical Trials Regulations (2004) and Health Departments Research Governance Frameworks and good clinical practice.

Approval by Ethics Committee

Approval of the National Research Ethics Service (NRES) will be obtained. We will make our application via the Integrated Research Application System (IRAS). We will book for the first available agenda slot at a local research ethics committee (REC) via the Local Allocation System and will be available to attend the committee. NHS Research and Development (R&D) approval will also be sought. We will prepare, plan and obtain ethical and research governance approvals between receipt of notification of award and before 30th September 2013. Study training and treatment manuals will need to be submitted with our application and these need to be developed in Part 1 of the study.

As this is a vulnerable patient group, and the research concerns intimate, private concerns patient confidentiality is particularly important. Since some patients may tire easily, we will also ensure our questionnaire schedule and interviews are kept relatively brief. While there may be concern that semi-structured interviews with patients and carers could place an unacceptable burden on them, there is evidence that patients and carers welcome the opportunity to participate in research and use their experiences to benefit others (Ross, et al 2003). Patients will benefit from their GP being made aware of their sexual difficulties which are often missed. Our previous work with cancer patients suggests that cognitive behavioural therapy and clinical nurse specialist's patient-centered interventions are well received, of potential benefit and do no harm. Patients' travel costs for research sessions will be met by the project funding. An expert independent Trial Steering Group will monitor the progress of the study according to NRES REC governance arrangements. For the feasibility trial we will not establish a Data Monitoring and Ethics Committee but this will be mandatory for the larger trial.

Psychological therapists will access their usual supervision for the duration of the trial. Supervision for the CNS's delivering the step two interventions is met within the study. Clinical supervision is in place within the Dept of Women's Cancer in UCL to support field researchers working with women with cancer at early or advanced stages.

Patient and Public Involvement

We have as a co-applicant Mrs Susan Dunning, an 11 year survivor of ovarian cancer, who has been involved from the inception of this project and attended all the study design meetings and contributed to the psychological focus. She is a Tumour Board representative for the GN cancer Tumour Board, has addressed NICE on appraisal of ovarian cancer drugs and the previous Secretary of State for Health. She has been a Peer Supporter (3 months of weekly contact) within UCLH Gynaecological cancer centre service for 5 years. She has set up a thriving local self support group for ovarian cancer patients and was on the Ovacome committee and has wide knowledge therefore of other women's experience of Gynaecological cancer and its treatment. She emphasized the need to address mood issues without making mental health assumptions within this group. She will continue to attend steering group meetings and will contribute to the materials being written and to qualitative analysis. Macmillan is supportive of this endeavour and Julie Latimer, Education Lead of Macmillan London has engaged to roll out any findings (see dissemination section).

In addition our team has an established relationship with local Cancer Services Partnership Boards made up of people with cancer and their carers which provide active participation in a number of research project: http://www.nlcn.nhs.uk/GettingInvolved. We shall ask them to review patient research information sheets and patient centered information as part of the stepped care model and incorporate their ideas fully into these documents. We shall also liaise actively with the newly formed Patient and Families First Group at Marie

Curie Cancer which has a specific remit to involve user participation at all levels of care and research.

We will also have independent lay members appointed to our Trials Steering Committee to ensure the research activity remains patient-focused.

Please also see section dissemination and project outputs.

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