Official title: Pilot RCT for Cognitive-behavioural & Mindfulness-based online programs for female sexual dysfunction

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1 – THE NEED FOR A TRIAL

We propose a randomized controlled pilot trial to test and compare the efficacy of two online interventions for sexual dysfunction in women.

1.1 What is the problem to be addressed?

Female Sexual Dysfunction (FSD) is defined as frequent and long-lasting problems in one or more areas of sexual desire, arousal, orgasm, or pain, accompanied by clinically-relevant levels of personal distress.[1] FSD is caused by interdependent biological, psychological, and sociocultural determinants,[2] and can lead to negative physical, emotional, and interpersonal outcomes, such as depression and relational conflict.[3-6] Dominant Western beliefs suggest that sexual response is automatic, pleasurable, and universally sought-after. The reality is that FSD is highly prevalent and affects up to one third (15-30%) of women worldwide.[7,8] Efficacious and accessible treatments are needed to address FSD.

1.2 What is/are the principal research question(s) to be addressed?

The primary aims are to:

1. Determine the efficacy of two online (O) versions of empirically-supported psychotherapies for treating FSD: *Cognitive-Behavioural Therapy (CBT-O)* and *Mindfulness-Based Therapy (MBT-O)* compared to a wait list. Primary endpoints are changes in sex-related distress and sexual desire from pre- to post-treatment and persistence of improvement at 6-month follow-up.
2. Compare CBT-O with MBT-O for treating FSD, measuring pre- to post-treatment change in sex-related distress and sexual desire and sustainment of improvement at 6-month follow-up.
3. Evaluate participant satisfaction and compliance using these online programs with weekly individualized support from a non-expert navigator.

We (Brotto, Stephenson, Velten) are experts in CBT and/or MBT for face-to-face and web-based treatment of sexual difficulties.[9-17] We have worked with Zippan, a professional graphic and digital designer, to develop **eSense:** an online platform to deliver CBT and MBT treatments adapted for web-based, self-directed therapy. We believe that eSense is efficacious, has the potential to improve accessibility and affordability of evidence-based treatment, and has long-term potential to be commercialized. I (Brotto) am lead creator and evaluator of the most widely-validated MBT intervention for FSD,[18] which can be readily adapted for online use. To our knowledge, there is no equivalent CBT intervention for FSD that is comprehensive and available. Therefore, much of our work to date has focused on creation and testing of the CBT "arm" of eSense.

1.3 Why is a trial needed now?

There is considerable evidence that face-to-face CBT and MBT are effective and are considered gold standard treatments for FSD.[15,19] Meta-analyses indicate that CBT for FSD is consistently effective compared to a wait list control group [effect size, d=0.58 for sexual function, and d=0.47 for sexual satisfaction].[20,21] Similarly, a meta-analysis of 11 MBT for FSD studies reported wait list-controlled or pre-post effect sizes of d=0.52 for sexual desire and d=0.91 for sexual satisfaction.[22] CBT and MBT are similar, but there are some important differences that may make each more appealing/effective in some cases (see below for examples). Despite their efficacy, barriers to treatment access exist including: geographic location, cost, anxiety, embarrassment, and lack of available expertise.[16,23-28] As a result, only 19-32% of women with FSD receive professional treatment.[16,22-24,26,27,29-31] *There is an urgent need to improve accessibility to lasting and meaningful treatment for women with FSD.*

Web-based therapy is one way to address this need. In general, web-based therapeutic programs: reduce embarrassment, are available at low cost, can be accessible to women regardless of geographic location, can be created and updated by experts,[28] and can be facilitated by non-experts.[32]

Rationale for choice of "technique-focused" interventions. Psychotherapy outcome research has gradually moved away from "problem-focused" interventions that focus on one diagnosis (e.g., relevant

only for women with orgasm difficulties) and moved toward "technique-focused" interventions targeting underlying maladaptive processes relevant across related diagnoses.[33-34] Such transdiagnostic treatments are acceptable to patients and effective for treating comorbid disorders.[35-37] They are also easier to disseminate, because they reduce time and cost burdens for patients and healthcare systems[38]; increasing access in the general population.[39] The diagnoses in FSD (e.g., problems of desire/arousal vs. orgasm)[1] are highly comorbid,[40] and theoretical models of sexual dysfunction[2] show extensive overlap in causal and maintaining factors such as cognitive distraction and avoidance. In-person MBT studies often recruit women with a range of sexual difficulties.[12,41] As such, *we chose to adapt two interventions (CBT and MBT) that should be efficacious across the range of specific female sexual problems.*

Psychological treatments for FSD: How do they differ?

CBT for sexual dysfunction is change-based, systematically identifying thoughts and behaviours that maintain sexual dysfunction[2,24,42] and replacing them with new thoughts and behaviours in order to improve function and well-being, and ultimately refocus attention to erotic cues and pleasure.[43,44]

MBT for sexual dysfunction is acceptance-based, encouraging present-focused, non-judgmental attention to a target.[45,46] Where CBT challenges specific thoughts and behaviours, MBT encourages open acceptance of the entire spectrum of one's current thoughts and emotions, and a "tuning in" to specific details of both physical and mental events in the body and environment.[47,48] Head-to-head comparisons sometimes show comparable efficacy of CBT and MBT,[49,50] but also superiority of CBT[51] or of MBT.[52] Importantly, recent research—including our CIHR-funded work[53]—indicates that MBT and CBT may have different mechanisms of action.[54,55]

Online delivery of psychological treatments. There is strong evidence from non-sexual conditions, to support the translation of existing face-to-face CBT and MBT therapies into online delivery. Reviews[59,60] and meta-analyses show these to be efficacious,[61,62] with clinical improvements[41,63] and participant satisfaction ratings both comparable to face-to-face.[32] Moreover, online tools are extremely effective at overcoming barriers to access. Several issues should be considered in developing and testing online programs. For example, online psychotherapy ranges from entirely self-administered to therapist-guided.[33] Having *some* (vs. none) individual support and guidance improves outcomes and adherence.[64,65] Interestingly, while individualized supports consistently decrease attrition,[66] research suggests little-to-no difference in outcomes when comparing who provides that support, i.e., facilitators with extensive mental health training *vs*. technicians trained in navigating the intervention only but no therapy training.[67-69]

A systematic review of online treatments[32] compared them with support by licensed clinicians, and found that participants supported by non-experts had either no difference in outcomes, or slightly better outcomes.[70] Additionally, level of therapist experiences did not predict outcomes.[71] The fact that online treatment can be satisfying and efficacious without consistent contact from licensed therapists is important as it *saves costs* and *maximizes access, especially for marginalized and remote populations.*

Online delivery of treatments for sexual dysfunction. Given that web-based therapies are validated for other conditions, it is not surprising that there are similar studies in the area of sexual dysfunction. Four clinical trials of online FSD treatment reported promising effects.[72] For example, one program provided women with FSD access to online CBT modules alongside e-mail contact with a therapist, which led to significant improvements in sexual function maintained after 3 months.[73] Another program combining CBT and MBT found improved communication and emotional intimacy between partners, increased sexual function, and decreased distress.[41] Preliminary data from Velten's (CoA) ongoing web-based study of CBT-O and MBT-O for low sexual desire suggests high satisfaction with treatment and reduced symptoms (63% of participants) after three months.

Limitations of the programs used in prior research include: [1] the programs still included significant contact with a licensed therapist; this limits scalability; [2] they were based on older iterations of current gold-standard protocols; [3] they included minimal multi-media content (primarily text-based); and [4] they did not allow for direct comparison of CBT and MBT. *Our goal is to address these limitations*.

eSense. Since mid-2018, we have worked to create, evaluate (feasibility and usability), and refine an online program called eSense, that can house self-guided CBT-O and MBT-O for FSD**.** Since mid-2018, we have [1] developed the online eSense program, worked with ICOM Productions (expert in technological instructional design), in-house illustrators, and technology experts; and [2] performed 3 feasibility studies and usability testing (see below): eSense is found to be acceptable and feasible.

- *We are now positioned, as recommended by our CIHR reviewers, to perform the pilot RCT to determine the efficacy of the eSense web-based CBT-Online (CBT-O) and MBT-Online (MBT-O) programs.*

Feasibility and efficacy studies

Study 1[74]**:** *Is an online module for delivering CBT-O to women with FSD feasible and e*? Cisgender women (N=17; *M* age=31.9; 41% heterosexual) with Sexual Interest/Arousal Disorder (SIAD), a type of FSD, worked through Module 1 (only) in-person and completed a one-on-one semi-structured interview and online questionnaires. Participants reported a high level of satisfaction with the website's functionality and presentation, as well as reporting greater knowledge, feeling validated and hopeful, and eagerness to complete remaining modules. There were notable pre-post improvements in sexual desire (*d*=0.74), sexual arousal (*d*=1.77), sexual satisfaction (*d*=1.44), and reduced sexual distress (*d*=0.41). Manuscript reviewed with revisions required (**Appendix**).

Study 2**:** We improved the modules based on feedback from Study 1, then asked: *Is delivery of all 8 modules of CBT-O effective for improving sexual function and reducing sexual distress?*, and *Are women satisfied with the online treatment?* Cis women (N=11; *M* age 29.2; 73% heterosexual) with SIAD worked through Modules 1-8 at home, then completed online validated questionnaires and a telephone semi-structured interview. They reported significant pre-post improvements in sexual desire (*d*=-0.93), sexual arousal (*d*=-1.27), sexual satisfaction (*d* =-1.5), overall sexual function (*d*=-1.64), and sexual distress (*d*=1.85). Most women (60%) reported being more than moderately likely to continue using eSense and 100% reported a high level of comprehension. The average satisfaction score (1-5 scale) was 4.2 (see participant qualitative outcomes, **Appendix**).

Study 3**:** *Is each module of CBT-O cohesive when viewed in isolation?* Students (n=40) from Willamette University (CoA Stephenson) were randomly assigned to work through 1 of 7 CBT-O modules, then completed quantitative and qualitative measures. They had minimal information of the structure and purpose of eSense, and none of the other modules. Students had a mean age of 18.7 (SD = .83). More than 30% were in a committed relationship, 58% identified as heterosexual, 3% as gay/lesbian, and 35% as bisexual. Participants rated modules positively for: clarity (8.1/10), order of information (8.2/10), page layout (7.9/10), ease of navigation (8.3/10), and overall appearance (8.4/10) (see outcomes, **Appendix**).

Collectively, these three studies respond to reviewer concerns expressed in our original submission and provide strong evidence of feasibility. Preliminary efficacy data was gathered from the CBT-O arm and showed improvements in distress and sexual function (as reported above). Armed with this evidence that CBT-O is feasible to deliver, usable, well-organized, and satisfactory to participants, we are now well-positioned to carry out a pilot RCT evaluating efficacy of CBT-O and MBT-O, to compare the effects of the two treatments, and to determine the effect sizes for properly powering a future, larger RCT.

1.4 How will the results of this trial be used?

The study will yield effect sizes for primary endpoints of sexual desire and sexual distress that we will use in a subsequent larger RCT application. This study will advance health-related knowledge by providing new data on the relative efficacy of online CBT and MBT for FSD and health outcomes by having the potential to increase access to effective treatment for women living in rural and remote areas as well as those who experience other barriers in accessing face-to-face care. Thus, this research program has a high likelihood of filling a major gap in healthcare of women and eSense has significant potential for commercialization. UBC's University-Industry Liaison Office has committed to supporting this project through to commercialization (see Letter of Support, **Appendix**).

I (Brotto) have expertise with Knowledge Translation (KT) methods. I have held KT grants from CIHR (DGE129657) and MSFHR (#17403, 2017-18; #18793, 2019-20) for social media campaigns, and received UBC's 2020 President's Award for Public Education through Media for KT output. As Executive Director, Women's Health Research Institute, I supervise skilled research managers who have advanced training in KT and implementation science. For this project, we will use integrated and end-of-grant KT, and have an established patient advisory group with whom we meet twice/year. We plan to publish the pilot RCT findings (given dearth of relevant publications). The findings will also be disseminated through traditional conference and rounds presentations, an infographic video, and a public forum for women, co-designed with our patient advisory group. The forum information will be used to design our future RCT.

1.5 Are there any risks to the safety of participants involved in the trial?

Owing to the sensitive nature of sexual content in the intervention, participants will have the option to contact the coordinator (supervised by licensed psychologists Brotto and Stephenson) for guidance on sexually-based concerns. After data have been cleaned and checked (Q2 Y3), participants will be provided unrestricted access to content in both intervention arms, which they can use at their leisure. This adds no cost to our budget. Privacy will be maintained and absolutely no identifying information will be linked to data.

2. THE PROPOSED TRIAL

2.1 What is the proposed trial design?

This is a 3-arm RCT comparing CBT-O and MBT-O to a wait-list control (Study timeline, **Appendix**).

2.2 What are the planned trial interventions?

eSense includes two self-contained programs: CBT-O and MBT-O. Each consists of 8 modules which, based on our feasibility testing, take an average of 8-12 weeks to complete. The MBT intervention being adapted was well-established[75] via many focus groups and pilot studies with women with FSD.[9,45,68] However, we are not aware of an equivalent gold-standard manualized CBT intervention.

CBT-Online: We spent 2 years developing CBT-O; it has short sentences and paragraphs, with headings and sub-headings to maximize readability,[77] uses plain language (high school reading level) to maximize effectiveness for diverse populations (eSense platform sample, **Appendix**). In line with best practices for online therapies, text is interspersed with pictures, diagrams, videos, and audio clips to keep users engaged.[78] With graphic designers, we structured the CBT-O arm for usability and visual appeal. Website hosting and maintenance is provided by Perception Web Management(Letter of support, **Appendix**).

Research on "persuasive systems" (i.e., computerized systems designed to shape or change attitudes and behaviours without coercion or deception[79]) identifies several components associated with increased behavior change.[80] In our adaptation of CBT and MBT to online treatments, we have used as many of these components as possible: reduction (reducing complex behavior changes into simple tasks), tunneling (guiding users through a series of experiences allowing for gradual persuasion that change is possible), rehearsal (providing opportunities to try activities before they are used in real world settings, e.g., with a partner), and dialogue support (offering users praise for effort, sending reminders of "assignments," etc.). We have finalized the CBT-O arm based on our three feasibility studies described above. Table 1 outlines the main topics covered in each of the 8 modules in each arm.

MBT-Online: The 8 modules align directly with the treatment used[75] in our CIHR-funded face-to-face trial of group mindfulness for women with SIAD[81] (see below). We will parallel the existing images, layout, and format of our CBT-O program, and insert the mindfulness-specific content from our effective face-to-face MBT group.[75] We have finalized the content for MBT-O (using other funds) and spent 6 months (Q1-2 of Y1) adapting our CBT-O graphics to MBT-O and have budgeted for illustration costs in the current proposal.

Table 1: Intervention content

Module	*CBT-O Arm*	*MBT-O Arm*
1	Psychoeducation, introduction to CBT	Psychoeducation, introduction to mindfulness
2	The cognitive model and thought records	Increasing awareness of physical sensations in the body
3	Unhelpful thinking patterns	Exploring movement and body image
4	Cognitive restructuring	Awareness of sexual thoughts and beliefs
5	Behavioral experiments	Working with aversion, self-touch
6	Self-touch and sensate focus	Exploring sexual sensations, knowing our limits
7	Sensate focus with your partner	Integrating the partner into mindful touching
8	Maintaining (and extending) your gains	Maintaining (and extending) your gains

Both CBT-O + MBT-O: Within each module, participants are provided with relevant therapeutic information and activities (e.g., theorized nature of core beliefs, a body scan meditation, etc.), then read narratives about fictional individuals experiencing sexual dysfunction who use the intervention to help manage symptoms. This use of narrative to personalize online interventions has significant benefits. For example, Newby[82] provided stories about fictional characters using CBT techniques to address symptoms of anxiety and depression. They found 89% adherence (much higher than typical rates of online interventions), and high level of satisfaction with treatment. Others have replicated the results.[67] Feedback from our feasibility studies indicates that fictional narratives were helpful in allowing participants to engage with the content.

Some modules include downloadable audio tools (e.g., guided meditations in MBT-O; thought challenging in CBT-O). Each section ends with downloadable files outlining homework activities to be completed before the next module. Participants also complete a weekly journal to reflect on their experiences[83] and inform the agenda for weekly individualized support sessions. This journal is not part of the eSense platform. In module 1 participants are told: "Second, we'd like you to start keeping a journal of your sexual activity. Simply record when sexual activity (either by yourself or with your partner) takes place, what your experience was like, and how you felt about it during and afterward. There is no minimum or maximum length these entries need to be."

Both arms will be supplemented by treatment navigators (*who provide no formal therapy*) (e.g., exploring and challenging negative beliefs about sexual activity). Their role will be clearly described to participants as helping them engage with and navigate through the content. Navigators will meet weekly via Zoom with participants while they are completing the intervention. Each of these weekly sessions will take place on a UBC Zoom account held by the navigator, and each session will be video recorded. Once recorded, it will be labelled by participant ID and module number, and deleted from the Zoom server. Then it will be moved to our lab's OneDrive account. With structured training and ongoing supervision led by the PI (Dr. Brotto) and Drs. Stephenson and Mahar, navigators provide (a) encouragement to engage in the treatment; (b) accountability for completing homework assignments; and (c) answers to practical questions (e.g., "what if I keep falling asleep while meditating?").[84] Velten (CoA) has expertise in training navigators. In her online intervention study (n=260) she developed a navigator training manual and peer support method which will be used.

Participants will have flexibility in the amount of time (1-2 weeks) they spend on each module, as other studies[73,85] have shown flexibility helps with efficacy and real-world utility.[86] Our timeline estimates 8-12 weeks to complete all 8 modules. We will record time required for participants to complete 8 modules.

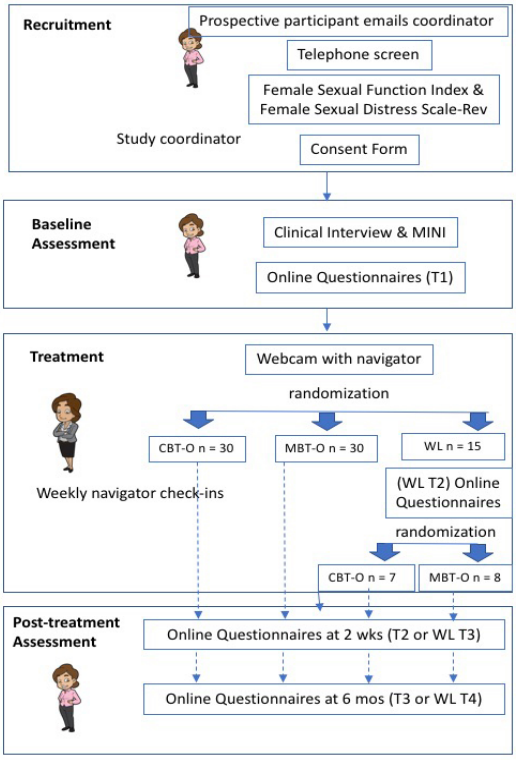
2.3 What are the proposed practical arrangements for allocating participants to trial groups?

Randomization: Participants will be randomized to one of 3 arms in a 1:1:1 sequence (CBT-O: MBT-O: wait-list control) using the Blockrand package in R, with random block sizes. Those in the wait-list group will complete two online questionnaire/assessment batteries before being randomized to one of the active treatment groups**.** As indicated in the Figure (next page), the n=30 women randomized to wait-list will be enrolled in a treatment arm after the wait-list period is complete. No stratification will be used in this pilot study.

Waitlist control: Face-to-face FSD intervention studies consistently find no passage-of-time-only changes in participants assigned to waitlist control groups[11,58]. As such, to maximize the opportunity to estimate treatment effects while minimizing costs of this pilot study, we propose a ***modified waitlist control group***. At study onset, participants will be assigned randomly to the waitlist group; at the end of the waiting period, they will be randomized into 1 of the 2 treatment groups. They will receive 2 assessments: at waiting period start and after randomization to treatment (Fig 1, next page). Pre- and post-waiting period assessments will be compared to check for a passage-of-time effects. Starting at post-waiting period assessment, their data will be combined with the rest of the participants for treatment evaluation analyses.

What are the proposed methods for protecting against sources of bias?

During the study, women must agree not to change medications known to have sexual side-effects unless mandated by their physician (medication use data will be collected at each assessment point). Participants will be encouraged to limit/eliminate internet use as a source of additional information about sexual dysfunction during the trial (and asked about this at post-treatment). We have found this request feasible in past[9,87] research. Every 3 months, we will analyze recruitment for group differences in ethno-cultural categories and sexual orientation, and adjust recruitment efforts to ensure that our sample reflects cultural and sexual diversity of the population of Canada and the United States, and is balanced across arms. The coordinator gathering data will not be involved in administering or navigating treatment. To minimize inter-navigator variation, navigators will receive training from Brotto,CoA Stephenson, and Mahar . Specifically, each navigator will receive a reading list of readings relevant to treatment of women's sexual concerns. Navigator-related measures will be evaluated for potential effects on outcomes and controlled for.



Navigator related measures include:
1. Empathy subscale of the Barrett-Lennard Relationship Inventory, a valid measure of perceived provider empathy that predicts outcomes in CBT (this was already uploaded in Rise).
2. Perceived navigator effectiveness with the Working Alliance Inventory, Short Form (this was already uploaded in Rise).
3. In addition, each navigator will keep track of the number of minutes spent with each participant over the course of the 8 modules, and this number will also be used as a moderator.

2.5 What are the planned inclusion/exclusion criteria?

Inclusion criteria: Cis and trans women, aged ≥19y, of any sexual orientation. Women will not be excluded based on menopausal status, as prevalence of distressing sexual concerns is not age-related[88] and continues beyond menopause.[8] In our other studies,[81] mean age is ~42y (22y-65y), so we also expect this age range here. Participants must:
- Be fluent in English (online materials delivered in English).
- Have consistent access to the internet, basic competency in using online platforms (self-report).
- Be in a committed, stable romantic relationship of at least 6 months[89] (because aspects of the interventions require partner participation). Partners may be of any gender.
- Meet telephone screening diagnostic criteria for Sexual Interest/Arousal Disorder.
- Be sexually active with a partner over the preceding 4 weeks (due to the sexual function outcome

measure), and willing to engage in sexual activity with their partner during the study.

Exclusion criteria: Women who:

- Have Sexual Dysfunction that is, in their estimation, attributable to another psychiatric diagnosis, the effect of a substance, a general medical condition (e.g., Multiple Sclerosis), or non-sexual conflict in the relationship, none of which are meant to be addressed by the proposed interventions.
- Poorly managed Anxiety or Mood Disorder (as per degree of life interference assessed at screening).
- Report suicidal ideation on the phone screen assessed using the Depression Anxiety Stress Scale.[92]
- Report visual impairments that would make it difficult to read online materials.
- Are regularly using illegal recreational drugs, prescription narcotics, cannabis, or plan to change their medications over the course of the study.
- On assessment report plans to end their romantic relationship in the next 6 months.

2.6-2.7 What is the proposed duration of treatment? Proposed frequency and duration of follow up?

Assessment points: CONSORT[28] guidelines will be followed in terms of tracking number of participants recruited, randomized, and retained through assessment and treatment. For CBT-O and MBT-O groups, there are 3 assessment points (baseline; post-treatment (within 2wks of completing the 8-module program); and 6-month follow-up). For the wait-list group, there are 2 pre-treatment assessments at waiting period start and after randomization to treatment (4 assessment points; same online questionnaires). No treatment will be given to wait-list participants during this waiting period. However, after the second online questionnaires are complete, they will be randomized to either the CBT-O or MBT-O arm of eSense. All participants will also be sent a mid-treatment link to an online question that asks them to write freely about their reactions to the treatment to date. This is included to examine quality assurance of the intervention. To minimize attrition, honoraria will be linked to completion of each assessment point: $30 for (each) baseline assessment, and $40 at post-treatment and 6-month follow-up assessment points.

Protocol: All participation will be remote, requiring no in-person meetings. Prospective participants will contact the study coordinator at UBC via e-mail, then set up a phone screen for inclusion/exclusion criteria (Fig 1). Consent forms will be sent to prospective participants prior to the scheduled phone screen by the study coordinator. Women will be informed of the length of the intervention (8 modules; 8-12 wks), expectations for homework (1-2 hours/week), and the use of treatment navigators. After meeting the screening criteria, the study coordinator will send prospective participants a personalized link to a Qualtrics questionnaire battery. The first page of the questionnaires will be the e-consent form. Participants must read and electronically sign the consent form before they move on to the baseline questionnaires. The e-consent form will indicate that any questions/issues they raise in interactions with study staff that are worrisome (e.g., suicidal ideation) will automatically prompt the coordinator to contact them. Women who choose not to participate will be provided with other resources (websites, directories of sex therapists, books).

Prior to beginning eSense (Fig 1), participants will have an initial 15-30 min conversation via zoom with their assigned navigator, who will explain their role. These regularly scheduled[64] meetings have been found to significantly increase participation rates.[83,93] Once treatment begins, navigators will schedule weekly 15-20 min sessions, and these will follow a structured outline that includes: 2-3 min general introduction, 10-15 min to check in on any concerns arising during completion of assigned homework, and 2-3 min to close and schedule their next session. Either the participant or the navigator can request a reassignment if there is not a good "fit." This can happen at any time during the study by informing the study coordinator. Navigators will be: undergraduate psychology students; GPA>3.5; coursework in research methods, clinical psychology or human sexuality; and available to complete training (see letter of support from UBC Psychology chair, **Appendix**). They must be able to commit at least a full year to the project. Navigators will be asked to electronically sign the consent form. These signed consent forms will be stored securely on MS OneDrive. Only the study coordinator and co-investigators will have access

to the consent forms and it will not be stored with other data. Each navigator will be assigned a participant to work through all 8 modules. Navigators will be assigned up to 4 participants at the same time. Navigators can choose to be involved with either CBT-O or MBT-O, or both arms, if they feel comfortable. Their feedback to participants will largely be the same regardless of which arm the participant is in. A new coded variable will be included in the analysis to examine whether a navigator was assigned to an arm based on their preference (1) or no preference (0). Students will be interviewed by Mahar to assess comfort with discussing sexual issues, interpersonal skills and ability for empathic listening. Potential impact of navigators will be assessed statistically prior to the main analyses and controlled for. CoA Mahar will oversee navigator supervision.

We may conduct an exit interview for trans participants and participants who are not exclusively heterosexual so we can receive feedback on how our program could be improved for sexual orientation, gender, and sex-inclusivity. This exit interview would be optional for participants.

2.8-2.9 What are the proposed 1° and 2° outcome measures? How are they measured at follow up?

Our primary outcomes are clinical— sexual desire and sexual distress—and will be used to determine effect sizes needed for a future large RCT. Secondary outcomes will be used to refine the interventions. Questionnaires take ~30min and are completed at all assessment points using Qualtrics.

1° outcomes: Sexual distress will be measured by the Female Sexual Distress Scale-Revised[90] (FSDS-R), used extensively in women's sexuality treatment outcome studies. Sexual desire will be measured by the The Sexual Interest and Desire Inventory (SIDI).

2° outcomes: Treatment satisfaction will be assessed with (i) two face-valid single item measures measured on through the eSense platform at the beginning of modules 2-8 and measures via Qualtrics a week after completing module 8 asking participants to rate helpfulness of content covered in the previous module, and ease of reading the content (1-10 scale); Research suggests a cut-off of 6.5/10 on these measures to indicate acceptable utility and clarity of content[94]; (ii) qualitative feedback about website and homework assignments collected by treatment navigators; (iii) adapted Erectile Dysfunction Inventory of Treatment Satisfaction,[95] a widely used scale measuring satisfaction after treatment for erectile dysfunction. Perceived relationship with navigators is assessed at post-treatment with two measures: (i) Empathy subscale of the Barrett-Lennard Relationship Inventory,[96] a valid measure of perceived provider empathy that predicts outcomes in CBT[97]; (ii) perceived navigator effectiveness with the Working Alliance Inventory, Short Form.[98] Treatment compliance will be measured by: (i) recording number of weeks and treatment sections completed[99]; (ii) eSense website engagement and performance by Google analytics (e.g., page views, # visits/sessions, page views/visit, visit duration, unique/returning users); these metrics are recommended by the E-CONSORT guidelines as important for e-health intervention studies. The platform used to house eSense tracks views of a page and completion of the overall program, enhancing and complementing what analytics can provide; (iii) navigators will ask participants to rate homework completion on a Likert scale ranging from "did not attempt" to "successfully completed all assignments" weekly; (iv) having participants complete the Homework Rating Scale-II (HRS-II)[100] at the beginning of modules 2-8 on the eSense platform and then complete it again week via Qualtrics after completing module 8 to provide a comprehensive measure of experience with the homework; (v) measuring navigator adherence to study guidelines by coding a random 20% of Zoom sessions (participants will be informed of these recordings) for adherence (to be done by Brotto's trainee; no funding requested), using a previous adherence scale we have used.[17,81] Sexual function will be measured using the total score of the Female Sexual Function Index,[91] a validated self-report measure of sexual function.

2.10 What is the proposed sample size; justification for assumptions underlying power calculations?

Based on our findings,[17] we expect large effect sizes for the main outcomes (d=.8 for FSFI and d=1.05 for FSDS-R) in the MBT-O arm. According to power analysis based on these two measures and two treatment

groups, 75 participants are needed to give us 90% power to discover a large size effect of our treatment at alpha level of .05 (PASS, 2019 Power Analysis and Sample Size Software (2019). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/ pass.). Based on Velten's work, we expect ~30% attrition so we will recruit 129 women (n=43 per arm) (control later randomized to treatment). After attrition, we expect to have n=30 in each arm.

2.11 If applicable, are health service research issues to be addressed?

This pilot is aimed at establishing effect sizes, so we will include health economics in a future larger RCT.

2.12 What is the planned recruitment rate? How will the recruitment be organized? Over what time period will recruitment take place? What evidence is there that the planned rate is achievable?

We will use the combination of methods we often use to recruit women with sexual difficulties.[9,17,43] These include: (i) online postings (e.g., social media, Craigslist, women-specific groups); (ii) sending letters to ~100 BC primary care providers to request they inform patients about the study; (iii) paid advertisements in newspapers; and (iv) posted recruitment ads in the community on public boards (e.g., gyms, community centres, coffee shops, etc.). We have made a commitment to oversampling for trans women, given evidence that they face high levels of sexual dysfunction and tend to be omitted in research.[101] We tailor our methods to ensure a consistent rate of recruitment, and will check sampling every 3 months to ensure we are accessing potential populations of trans women. We are not including trans men or non-binary individuals because the online materials refer to "women" throughout.

2.13–2.14 Are there likely to be any problems with compliance? On what evidence is this based? What is the likely rate of loss to follow up? On what evidence is this based?

Adhering to navigator schedule: If participants exhibit a consistent difficulty in scheduling Zoom sessions and/or has difficulty accessing a webcam of high enough quality to allow for effective interaction, we will allow participant-navigator meetings to take place by phone.

Attrition: Strategies to minimize attrition include: engaging intervention materials; trained, dedicated navigators; explicit discussion of required time commitment; and stepped compensation schedule. The study coordinator will send participants and navigators reminder e-mails about all Zoom sessions (on the day before) and reminders to complete online measures. Two more e-mails will be sent if there is no response.[102] If participants still do not engage in a session or complete scheduled measures, they will be phoned by the study coordinator.[103]

Compliance: We will compare compliance rates to previous research. One systematic review[104] found a typical adherence rate of ~50% in internet interventions for anxiety and depression. Given the aspects of our study meant to maximize adherence (e.g., engaging web content, individualized support, reminder e-mails), we expect our rates to be at least this high. Rates of treatment completion will be compared to other trials of online treatments for FSD and to web-based interventions more broadly. Systematic reviews of drop-out rates from online therapy with minimal support suggest typical attrition of ~30%.[105] Reported rates in online treatment of FSD are comparable (35%)[73] or higher (54%).[83] We will compare our attrition rate to 30% using a one-sided binomial test, to determine if it is significantly higher in our study.

Alternate Treatment: We will propose to participants who report no significant improvement after a year try the alternate treatment. We will also ask participants who drop out if they are willing to try the alternate treatment (if time is not a factor). We will not be collecting data in the alternate treatment as this is not a true test of their participation given that they will have already received one treatment.

2.15 How many centres will be involved?

Though the team of investigators come from 4 different institutions, all study activities will take place in the NPA's laboratory at UBC.

2.16–2.18 What is the proposed type of analyses? What is the proposed frequency of analyses?

Statistical analysis: Effect of treatment will be determined by analyzing baseline (pre) to post-treatment changes after CBT-O and MBT-O on sexual distress (FSDS-R) and sexual desire (SIDI) scores. Sustainability of treatment effects will be evaluated by adding the follow-up measurement point to the model. Both analyses will be conducted using a multilevel mixed effect model analysis with one within-subject factor of time (treatment) based on 2 or 3 measurement points (baseline and post-treatment in the first analysis; plus 6-month follow-up for the second analysis) and one between-subject factor (CBT-O vs MBT-O) as well as their interaction. Interactions will test for differences in the amount of change due to treatment between arms. We will calculate effect sizes and confidence intervals (CI) and use descriptive statistics for measures of treatment satisfaction and compliance. These values will be compared between treatment arms. Treatment length will vary from 8 to 12 wks, so individual length of treatment will be added as a control variable in all initial models. Notable differences will guide changes that may increase satisfaction/compliance before we conduct a larger RCT following completion of the current pilot study.

Missing data: Mixed-effects modelling allows for missing data and uses all available data for estimating model parameters. Incomplete outcome data can restrict the sample size available for tests of interactions. We will impute missing outcome data using multiple imputation techniques. We will run a sensitivity analysis to compare analysis that uses multiply-imputed data to analysis that includes missing data.

2.19 Has any pilot study been carried out using this design?

As detailed in section 1.2, we have spent 2 years developing the CBT-O program of eSense and completing 3 feasibility and usability studies. The MBT-O arm content has been developed, tested, and found effective in a face-to-face format. In 2014, we received CIHR funding (MOP-136876) for a 5-year RCT of 8 sessions of group MBT vs sex education/sex therapy for women (cis, trans) with low desire.[87] The trial included 12-month follow-up and was completed in Dec 2019. 70 women (mean age 39y, range 20y-66y) completed the MBT arm, providing measures of sexual distress (FSDS-R) and sexual desire (sexual interest/desire inventory). Average relationship length was 11y, 81% were Euro-Caucasian, and 75% identified with sexual attraction towards men. Following MBT, we found significant improvement in female sexual distress [paired t-test, $t(57)=6.43$, $p<.001$, Cohen's $d=0.85$ (mean at time 1: 32.3; mean at time 2: 22.9)] and sexual desire [$t(58)=-8.13$, $p<.001$, Cohen's $d=1.06$ (mean at time 1:16.9; mean at time 2: 27.9)]. We are now writing the manuscript of primary outcomes.[81]

In parallel, supported by another 5-year CIHR grant (MOP-123271), we applied MBT to 130 women with Provoked Vestibulodynia (a chronic genital pain condition) and compared it to CBT. We found 8-week MBT was superior to 8-week CBT for improving self-reported pain with vaginal penetration.[46] Improvements in pain, sexual function, and psychological domains persisted at least 1 year. On all other endpoints, MBT and CBT groups were highly effective and had clinically significant outcomes.

Our findings confirm our ability to create distinct CBT and MBT interventions for sexual dysfunction that are feasible and highly efficacious (all pre- to post-effect sizes were $d>0.90$), with benefits lasting up to 12 months follow-up. Since all of these interventions have been delivered in a face-to-face format, the next step to increase access is to move the programs online.

3 – TRIAL MANAGEMENT

3.1 What are the arrangements for day-to-day management of the trial?

Coordination and randomization: Study coordinator (Fig 1) will oversee randomization and data management. Data handling and security: All identifying information and responses to study measures will be linked to Qualtrics housed at UBC. Qualtrics is approved for use by the UBC Research Ethics Board. Participants will not enter information into the host website, so no additional security and encryption are needed. Participants will be assured of the confidentiality of responses at the time of consent.

3.2 What will be the role of each principal applicant and co-applicant proposed?

NPA *Lori Brotto*, *PhD (UBC)*. I am an expert and Tier 2 CRC in Women's Sexual Health. I am a licensed clinical psychologist and co-developed both CBT-O and MBT-O interventions. I am PI of 5 funded psychotherapy trials for sexual dysfunction, and have extensive experience recruiting trial participants. I will supervise the study coordinator and collaborators, co-lead investigator meetings, and direct KT activities. (8 hrs/wk).

Co-Applicants

- ***Kyle Stephenson***, *PhD (Willamette University, Oregon)* is an expert in sexual dysfunction, CBT, and MBT, with >30 publications since 2009. He was awarded New Investigator Award, International Society for the Study of Women's Sexual Health and has extensive experience supervising undergraduate RAs. He is a licensed clinical psychologist in Oregon. He has co-led the creation of both arms and led the 3rd feasibility study using undergraduate students. He will provide co-supervision remotely for the study coordinator, and co-lead investigator meetings with Brotto (8 hrs/wk)
- ***Julia Velten***, *PhD (Ruhr-Universität Bochum, Germany)* has expertise in women's sexual response and functioning (>30 articles and book chapters since 2014). She has published with the NPA on mediators of treatment outcome for MBT. She has considerable experience developing online interventions for sexual dysfunction. She will assist with KT. (2 hrs/wk)
- ***Bozena Zdaniuk***, *PhD (UBC)* is a longitudinal data analysis and complex regression modelling expert. As lead statistician of Brotto's team, she led data management and analysis for two RCTs evaluating mindfulness for FSD.[17,81] She will co-supervise the postdoctoral fellow who will perform all data cleaning, and Bozena will lead all analyses. (8 days over 1 month in Year 3).
- ***Elizabeth Mahar***, *PhD (UBC)* is a Postdoctoral Fellow with seven years of graduate-level training in human sexuality. She will supervise the study coordinator, up to 10 study navigators, and undergraduate volunteers on the project. She will also oversee data management and analyses as well as co-lead all forms of KT, including peer-reviewed manuscripts and public dissemination. (37.5 hrs/wk).

Collaborators: Research Staff + Trainees

- ***Kiarah O'Kane,*** *BA (UBC)* is a level 5 research coordinator who received her BA in 2020. She has extensive experience in research administration and study coordination in both clinical and social psychological areas, including feasibility trials for online interventions. Kiarah will oversee and lead recruitment, ethics, participant screening, payment, distribution of online questionnaires, etc. (37.5 hrs/week).
- ***Natasha Zippan*** *(UBC)* is a trainee who began her BA after a 25 year career as an award-winning graphic designer and art director (Presence Creative). She has designed websites, produced branding, print collateral and digital design for many industries, including health. She also designs CMS sites and apps and is an expert in graphical user interfaces. Zippan art-directed ICOM for *eSense's* CBT-O platform and, as an undergraduate research assistant, led two of the feasibility studies (6 hrs/week).
- ***Ciana Maher*** *(Digital Health Research Manager, Women's Health Research Institute*) specializes in developing/testing digital health interventions in women's health. She will consult with team monthly, and attend team meetings for approximately 20 hours/year for the duration of the project.
- ***Patient Advisory Group*** will be comprised of at least 3 women with lived experience of FSD who will meet with the team of NPA and CoAs twice/year for the duration of the project. Members will be invited from Brotto's registry of women with FSD who participated in past research. Over the past 5 years, Brotto routinely includes patient advisory groups in alignment with recommendations of SPOR.[106]

3.3 Describe the trial steering committee and if relevant the data safety and monitoring committee.

The trial steering committee will comprise Brotto, Stephenson, and Velten. A DSMB is not needed.