## Study protocol

## Aims

1. If Therapeutic Ultrasound (TUS) and a standard treatment, is more effective than sham ultrasound and a standard treatment for reducing the severity of local inflammatory breast symptoms and systemic symptoms in women with Inflammatory Conditions of the Lactating Breast (ICLBs); and
2. If high intensity (2 Wcm2) TUS is more effective than low intensity (1 Wcm2) TUS for reducing the severity of local inflammatory breast symptoms and systemic symptoms in women with ICLBs.

## Trial design

This study will be a pragmatic, multi-centre, double-blind, randomised, placebo trial, with random sequence generation and allocation concealment, addressing the aims above. The CONSORT 2010 Flow Diagram has been used to show progress through the phases of the trial (see Figure 1, Appendix 1)1. A pragmatic design has been chosen due to concern over the ability to control for all the other usual care treatments participants are likely to utilise during the trial. The PRECIS-2 tool2 has been used to assess the pragmatic design aspects of the trial (see Table 1, Appendix 2 for scoring rationale):

#### Figure 2: PRECIS-2 wheel for the trial2



## Participants

Participants will be women with ICLBs, defined as lactating women presenting with at least 1 current local breast inflammatory symptom (e.g. pain, redness, heat, swelling3) and at least 1 systemic inflammatory symptom (e.g. fever, chills, aching, lethargy, headache4, 5) this current episode. Any combination of at least 1 local and 1 systemic inflammatory sign/symptom was chosen for the inclusion criteria, as this is in line with previous research and clinical practice5. For inclusion, women must also be over the age of 18 and more than 7 days postpartum, to exclude those with physiological engorgement (the normal sensation of breast fullness with the arrival of breast milk (lactogenesis II) at approximately 3 to 5 days postpartum)6, 7. The exclusion criteria are those that are used for ultrasound (history of breast cancer or breast surgery including breast implants, pacemaker) and preterm or multiple birth. (Figure 1, Appendix 1)

Women will be recruited in Melbourne, from agreed/ participating private physiotherapy practices (for example, Inform Physiotherapy and Womankind Physiotherapy), tertiary public hospitals (Mercy Hospital for Women and Royal Women’s Hospital) and directly from the local community. Flyers will be placed in hospital postnatal packs, and at general practitioner, lactation consultant, midwifery, and maternal child health clinics/centres. Social media adverts will be posted on local community Facebook and Instagram pages. Receptionists, physiotherapists and lactation consultants at two recruitment sites (where the intervention will be provided; Inform Physiotherapy and Mercy Hospital for Women) will be trained to perform a quick eligibility screening if a woman with an ICLB presents, and encouraged to hand out flyers if deemed eligible. Flyers encourage women to contact the primary researcher as soon as their symptoms develop. Home visits will be offered to improve recruitment and follow up.

## Interventions

The following has been reported using the TIDieR checklist and guide8, assuming no COVID-19 restrictions. A women’s health physiotherapist who has used TUS to treat women with ICLBs for over 6 years, will provide the intervention face-to-face at one of three of the recruitment sites in Melbourne, Victoria: 1) A public tertiary women’s hospital; 2) private women’s health physiotherapy practice; and 3) the community (at the participant’s home). The physiotherapist is a staff member at recruitment site 1) and at one of recruitment sites 2). The participant’s baby and or support person may be present. Additional precautions will be taken for COVID-19 as required (Appendix 3).

All participants will receive a standard treatment, comprising of education and advice addressing ICLB risk factors and the common supportive measures outlined in the literature5, 9-12. In addition, all participants will receive up to 3 consecutive days of TUS treatment to their affected breast13, 14, which could be either high intensity TUS, low intensity TUS or sham TUS. Day 1 of treatment will be prioritised for the same day as recruitment, or as soon as appropriate. A standardised script will be used, asking participants to adhere to the standard treatment and not try different treatments or change what they are doing, and informed consent gained. Participants will be asked to remove clothing covering the breast and will be appropriately positioned lying down and draped with towels, allowing optimal exposure of the affected breast. To mitigate the risk of overheating, intact sensation will be confirmed prior to TUS application and participants will be given a TUS standard warnings and safety summary sheet15 prior to and for reference throughout the intervention. Randomisation will be stratified in blocks of 9, within the sites. An online computer program16 will be used to generate the random allocation sequences. Non-trial personnel will prepare sequentially numbered sealed opaque envelopes with A, B or C written on the enclosed paper, signifying group allocation, according to the allocation sequence.The physiotherapist willopen the envelopes sequentially, post baseline outcome measurement. The physiotherapist will have 1 TUS machine (Astar Physiogo 300), with 3 sound heads clearly labelled, A, B or C. These will correspond to pre-set programs (A, B and C) on the TUS machine. One program will be set to deliver high intensity (2 Wcm2) ultrasound, one to deliver low intensity (1 Wcm2) ultrasound and one to deliver sham ultrasound (0 Wcm2). This will be done by a non-trial member and the sham sound head will be altered by the electrophysical company prior to the physiotherapist receiving them, thus, blinding both the physiotherapist and participant to the intervention. The physiotherapist will be able to turn down the intensity for safety. Active TUS will be applied at 1 MHz frequency in continuous mode, reflective of the majority of Australian physiotherapy practice17.

Aqueous gel will be placed on the 4 cm2 sound head and the physiotherapist will apply the TUS over the area of breast swelling/hardness/tightness, using consistent light pressure and overlapping linear strokes, also extending towards the axilla and nipple18, 19. Participants will be instructed not to inform the physiotherapist if they feel heat, to maintain blinding, unless it becomes more than a comfortable warmth. Duration of application will be dependent on the size of the affected area20, for which the physiotherapist will measure using the sound head:

#### Table 2: Length of ultrasound treatment

|  |  |  |
| --- | --- | --- |
| Size of affected beast area | Measurement | Treatment time |
| ≤ 8 cm2 | ≤ 2 ultrasound heads | 10 minutes |
| 12 cm2 | 3 sound heads |  15 minutes |
| ≥ 16 cm2 | ≥ 4 sound heads | 20 minutes |

The standard treatment will be delivered via 3 different mediums: 1) A video: 3-4 minutes duration, played for participants on a tablet during day 1 TUS intervention (the video will be on the trial’s website for participants later reference); 2) hard paper copy: As an infographic, with a) a laminated copy for participants to view on day 1 during the intervention and b) a pamphlet for them to take home; and 3) electronic copy of the infographic (on the trial’s website; the URL will be given to all participants). The educational material/infographic is designed specifically for this study.

Participants will be encouraged to breastfeed or express prior to the intervention, to ensure their breasts are as soft as possible, and then again as soon as possible/comfortable (or within 20 to 30 minutes) post intervention21. Intervention fidelity22 will be assessed via an online secure survey (REDCap (Research Electronic Data Capture)23, 24) comprising yes/no and slider scale questions checking compliance with the different aspects of the standard treatment, and an open text response question asking about any additional treatments used/trialled. Participants will use a QR code or customised email link to access their survey, completing it at each timepoint (see Figure 1, Appendix 1). At timepoint 4 (T4), 4 extra slider scale and accompanying open text questions will be included in the survey at the end of the intervention, asking participants about their satisfaction and experience with aspects of the trial (secondary outcomes).

Participants may be contacted at 3 and 6 months post their participation in the trial, via email or phone, to ask a few questions about ICLB recurrences.

## Outcomes

Assessment will be blinded. Size of breast hardness area will be the primary outcome, measured via tracing the area of hardness on to gladwrap with a surgical pen. Tracings will be scanned into Adobe and the area calculated electronically. Secondary outcomes will comprise breast milk analysis (sodium and potassium levels in breast milk)25, the BISSI26 and GRC scale27. A drop of breast milk will be placed on the ISE, and the digital sodium and potassium levels recorded. Breast milk samples of up to 5 ml will then be collected from the affected breast into one clearly labelled sterile test tube, put immediately on ice and transported to -20**°**C freezer storage as soon as convenient, for later use in a post-trial study. For the BISSI, its accompanying clinician script will be read to participants26, and scores entered directly into an electronic data collection form (REDCap (Research Electronic Data Capture)23, 24). For the GRC scale, participants will be shown a laminated paper copy of the scale and asked to rate whether their breast condition has improved or deteriorated since the timepoint prior, and scores entered directly into the electronic data collection form. Outcomes will be taken by the physiotherapist at 4 timepoints (see Figure 1, Appendix 1). Timepoint 1 will be taken prior to group allocation. Inter-rater reliability for size of breast hardness area will be assessed at timepoint 2 (T2), with the first 15 participants measured by the trial’s physiotherapist and another women’s health physiotherapist. GRC scale will not be assessed on day 1 (T1) as there is no prior timepoint for comparison. Breast milk analysis will not be performed on day 2 (T2), due to the lag time on changes in sodium levels in the breast milk as the breast recovers28. For this reason, day 10 was chosen for T4 which will be assessment only, no treatment, and performed via home visit.

## References

1. Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *Bmj.* 2010;340: c332.

2. Loudon K, Treweek S, Sullivan F, Donnan P, Thorpe KE, Zwarenstein M. The PRECIS-2 tool: designing trials that are fit for purpose. *BMJ.* 2015;350: h2147.

3. Scott A, Khan K, Cook J, Duronio V. What is “inflammation”? Are we ready to move beyond Celsus? *British journal of sports medicine.* 2004;38(3): 248-249.

4. Amir LH, Lumley J. Women's experience of lactational mastitis: 'I have never felt worse'. *Australian family physician.* 2006;35(9): 745-747.

5. Amir LH, Trupin S, Kvist LJ. Diagnosis and treatment of mastitis in breastfeeding women. *Journal of human lactation : official journal of International Lactation Consultant Association.* 2014;30(1): 10-13.

6. Berens P, Brodribb W. ABM Clinical Protocol #20: Engorgement, Revised 2016. *Breastfeeding medicine : the official journal of the Academy of Breastfeeding Medicine.* 2016;11(4): 159-163.

7. LactaResearch Group. LactaPedia: Physiological engorgement. In: Boss M, Hartmann P, eds. Frauenfeld (CH): Family Larsson-Rosenquist Foundation; 2018.

8. Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ.* 2014;348: g1687.

9. Amir LH, Academy of Breastfeeding Medicine Protocol Committee. ABM clinical protocol #4: Mastitis, revised March 2014. *Breastfeeding medicine : the official journal of the Academy of Breastfeeding Medicine.* 2014;9(5): 239-243.

10. World Health Organization. Mastitis: causes and management. World Health Organization; 2000.

11. Foxman B, D'Arcy H, Gillespie B, Bobo JK, Schwartz K. Lactation mastitis: occurrence and medical management among 946 breastfeeding women in the United States. *American Journal of Epidemiology.* 2002;155(2): 103-114.

12. Kvist LJ, Hall-Lord ML, Rydhstroem H, Larsson BW. A randomised-controlled trial in Sweden of acupuncture and care interventions for the relief of inflammatory symptoms of the breast during lactation. *Midwifery.* 2007;23(2): 184-195.

13. Kvist LJ, Wilde Larsson B, Hall-Lord ML, Rydhstroem H. Effects of acupuncture and care interventions on the outcome of inflammatory symptoms of the breast in lactating women. *International Nursing Review.* 2004;51(1): 56-64.

14. Lavigne V, Gleberzon BJ. Ultrasound as a treatment of mammary blocked duct among 25 postpartum lactating women: a retrospective case series. *Journal of Chiropractic Medicine.* 2012;11(3): 170-178.

15. Robertson VJ, Chipchase LS, Laakso EL, Whelan KM, McKenna LJ. *Guidelines for the clinical use of electrophysical agents*. St Kilda Road Central, Victoria: Australian Physiotherapy Association; 2001.

16. Haahr M. RANDOM.ORG: True Random Number Service; 1998. <https://www.random.org>. Accessed 5 June 2020.

17. Diepeveen LC, Fraser E, Croft AJE, Jacques A, McArdle AM, Briffa K, et al. Regional and Facility Differences in Interventions for Mastitis by Australian Physiotherapists. *Journal of human lactation : official journal of International Lactation Consultant Association.* 2019;35(4): 695-705.

18. Cooper B. Physical therapy intervention for treatment of blocked milk ducts in lactating women. 1429749. Ann Arbor: Quinnipiac University; 2005:31.

19. Neill L, Eske E, Yip WH, Gurram L, De Oliveira BIR, McArdle A, et al. Comparing perceived heating effect and intensity of therapeutic ultrasound between breast tissue and calf muscle in lactating women: An observational study. *International Breastfeeding Journal.* 2020.

20. Demchak TJ, Stone MB. Effectiveness of clinical ultrasound parameters on changing intramuscular temperature. *Journal of Sport Rehabilitation.* 2008;17(3): 220-229.

21. Morishita K, Karasuno H, Yokoi Y, Morozumi K, Ogihara H, Ito T, et al. Effects of therapeutic ultrasound on range of motion and stretch pain. *J Phys Ther Sci.* 2014;26(5): 711-715.

22. Murphy SL, Gutman SA. Intervention Fidelity: A Necessary Aspect of Intervention Effectiveness Studies. *American Journal of Occupational Therapy.* 2012;66(4): 387-388.

23. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics.* 2009;42(2): 377-381.

24. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. *Journal of Biomedical Informatics.* 2019;95: 103208.

25. Lai CT, Gardner H, Geddes D. Comparison of Inductively Coupled Plasma Optical Emission Spectrometry with an Ion Selective Electrode to Determine Sodium and Potassium Levels in Human Milk. *Nutrients.* 2018;10(9): 1218.

26. Cooper M, Lowe H, McArdle A. Development of a novel patient focussed symptom severity index for use in assessing and treating inflammatory conditions of the lactating breast: a Delphi study. *International journal of evidence-based healthcare.* 2020.

27. Kamper SJ, Maher CG, Mackay G. Global rating of change scales: a review of strengths and weaknesses and considerations for design. *J Man Manip Ther.* 2009;17(3): 163-170.

28. Fetherston CM, Lai CT, Hartmann PE. Relationships between symptoms and changes in breast physiology during lactation mastitis. *Breastfeeding medicine : the official journal of the Academy of Breastfeeding Medicine.* 2006;1(3): 136-145.

## Appendices

### Appendix 1

#### Figure 1: Modified CONSORT flow diagram







### Appendix 2

#### Table 1: PRECIS-2 scores for trial domains2

|  |  |  |  |
| --- | --- | --- | --- |
|  | Domain | Score | Rationale |
| 1 | Eligibility Criteria | 4 | Participants eligible for the trial are very similar to those who would receive TUS in usual physio care for ICLB. Regional and facility differences exist across Australia, and some physiotherapists would not require the presence of a systemic symptom as well as local symptom(s) to use TUS (e.g. blocked ducts). However, the presence of ≥1 local symptom plus ≥1 systemic symptom is what the research and experts’ opinions tell us is common to this suite of conditions. The trial excludes women ≤7 days postpartum to ensure results are not confounded by physiological engorgement. |
| 2 | Recruitment Path | 3 | Women who attend a public tertiary women’s hospital and women’s health private practices for physiotherapy treatment for their ICLB will be recruited; this is identical to usual care. However, due to feasibility additional recruitment strategies will be added, comprising of advertising campaigns to speed up recruitment. Such advertising is usually done on a smaller scale by private physiotherapy practices. |
| 3 | Setting | 4 | The public hospital and women’s health private practices are identical to usual care settings, or where women would usually go to receive TUS for ICLB treatment. Also, participant’s homes, however home visits are a usual option available for women seeking care from a private physiotherapy practice.  |
| 4 | Organisation intervention | 5 | No difference in provider expertise and organisation of care delivery to usual care; the trial physiotherapist is a women’s health physiotherapist who works at 2 of the recruitment sites and is experienced in using TUS to treat women with ICLB.  |
| 5 | Flex of experimental intervention – Delivery  | 4 | A specific TUS protocol has been established for the trial (e.g. TUS parameters and dosage), however this is reflective of the majority of Australian physiotherapist’s usual / current practice for women with ICLB.  |
| 6 | Flex of experimental intervention – Adherence  | 4 | No more than usual encouragement to adhere to the intervention will be used in the trial. Participants have full flexibility to decline further TUS treatment after day 1.  |
| 7 | Follow-up | 3 | Participants will be followed-up at day 10 for outcomes only. This is not routine usual care; however, it is common for HCP to phone/SMS patients several days post intervention to ensure complete resolution and return to successful breastfeeding if symptoms were not completely resolved at the last treatment session. The trial involves more extensive data collection at three timepoints – breast milk samples will be taken which is not part of usual care but may be if the trial shows it is a valid outcome measure? |
| 8 | Outcome | 5 | The primary outcome (size of breast hardness area) is of relevance and importance to women with ICLB and is measured in a very similar way to usual care (no cling wrap usually used). |
| 9 | Analysis  | 5 | Intention to treat with all available data. |

### Appendix 3

#### Coronavirus (COVID-19) precautions, if indicated

Participant and therapist temperature checks prior to each face-to-face treatment and follow up

Participant screening questionnaire asking about recent: fever, cough, sore throat, shortness of breath; return from overseas; and contact with COVID-19 known or suspected case(s)

Thorough cleaning of all equipment with disinfectant after every participant

Diligent hand hygiene practice

Compliance with each site’s COVID-19 specific infection control procedures