Study Protocol

~~Randomised~~Randomised, single blind, standard controlled, equivalence clinical trial to evaluate the comparative efficacy of *Eladikasaya* versus Tranexamic acid tablet in the management of Asrigdara. (Heavy Menstrual Bleeding) – A clinical trial protocol

Abstract:

Introduction: Excessive menstrual bleeding is a problem in reproductive age group females, reported as a 1 in 20 lifetime chance of consulting a physician for excessive and prolonged menstrual bleeding. Ayurvedic literature describes excessive menstrual bleeding as Asrigdara (HMB). Eladikasaya is one of the treatment modalities for HMB given in classics and hence chosen for the current clinical trial.

Method: We planned a prospective, randomized, single-blind, parallel-group, standard controlled, and equivalence trial on the patients with HMB (blood loss > 80 ml) for the last two cycles or more. EladiKasaya 50 ml with honey and sharkara thrice a day will be given from day 1 to day-7 for 3 consecutive menstrual cycles to Group A and Tablet Tranexamic acid 500mg thrice a day to Group B. Primary outcome measures are menstrual blood loss improvement, reduction in pain assessed by visual analog scale, and change in Haemoglobin concentration. The secondary outcome measure is improvement in quality of life. All adverse drug reactions will be monitored and reported to Ayush Suraksha, pharmacovigilance center, Maharashtra. Following sample size calculation 46 patients will be recruited in each group to demonstrate equivalence with 80% power. The duration of study will be 2 years. The study is approved through Institutional Ethics Committee dated 18/06/2022,MGACHRC/IEC/June-2022/506. Participant recruitment shall be started after getting registered with the Clinical Trial Registry of India.

Results- Current manuscript is a clinical protocol, hence results are yet to derive from the study. Results will be presented in conferences and shall be attempted to publish in indexed/peer-reviewed medical journals.

Conclusion - Conclusion shall be drawn after completion of the clinical study.

Keywords: *Eladikasaya; Asrigdara; Tablet Tranxemic acid; Heavy menstrual bleeding*

Comment [A1]: This work need to be discussed with an experienced researcher as there is significant gaps in the proposal.

I would also suggest to share with a proficient English speaker as there is lots of grammatical errors and unclear sentences.

Comment [A2]: This title is too complex. Please write in simple terms and with fewer words. Keep to a maximum of 20 words.

Comment [A3]: Re-write. Confusing

Comment [A4]: Keep it simple. What is the study design in few words please?

Introduction:

The human reproductive system is a complex system and disease related to reproductive system seriously affects the physical and psychological health of individual specially women. National Health Portal of Govt. of India reports Heavy Menstrual Bleeding (HMB) occur in 9 to 14% of women between menarche and menopause[1]. Normal menstruation denotes the healthy state of the female reproductive system, but if the menstrual cycle becomes abnormal with excessive and/or prolonged bleeding associated with deranged frequency is indicative of some underlying pathology[2].

Ayurveda classics refers the HMB as*Asrigdara*, characterized as cyclical or a-cyclical, excessive and prolonged menstrual bleeding with bodyache[3]. It is considered under *pitta avrittaapanavayuvikara and raktapradoshajavikara*[4,5].Excessive menstrual bleeding may cause anemia and dysmenorrhea and impacts social, economic and psychological health of a woman[6]. Prolonged and excessive menstrual bleeding without endometrial, uterine and endocrinal pathology have been poorly understood[7]. In conventional medicine, Tranexamic acid (Anti-fibrinolytic drug) is the treatment of choice for the HMB [8],with some noticeable side effects. Hence the study is planned to explore Ayurveda medicine for HMB treatment. Fundamental principles of *Ayurveda*, like *Vataharackikitsa (pacify vata), Kapha-Pitta Shamaka (pacifier), Deepana-Pachana (digestive), RaktaShodhaka (blood purifier)* and *RaktaStambhaka (hemostatic)* are found to be effective in relieving uterine disorder[9].*Eladikasaya* is one such combination for HMB management.[10]*Eladikasaya* consist of *Ela (Elettaria cardamomum), Samanga (Mimosa pudica), Shalmali (Salmaliamalabarica), Haritaki (Terminalia chebula)* and *Maghdhika (Piper longum)*. It also helps to manage associated symptoms like anemia, pain and weakness.

Methods-

The protocol is developed to study the comparative efficacy of *Eladikasaya* and tablet Tranexamic acid among enrolled participants falling under inclusion criteria.Study results and inferences will be disseminated among public and academicians through publication and IEC.

Study design

This will be a prospective, randomized, single blind, parallel group, standard controlled, single centre study on patients having menstrual blood loss more than 80 ml from two or more cycles with an equivalence design. The trial will be conducted at MGACH&RC,Salod(H), Wardha. Eligible search at *Prasuti tantra* and*striroga* OPD and IPD will be made. Such patients will be contacted personally and will seek consent after describing complete information about study. They will be enrolled and randomized to either of the two study groups (*Eladikasaya* or Tablet Tranexamic acid). Enrolled subjects will be evaluated for clinical, and laboratory measures as per Clinical research Form (CRF). Ayurveda evaluation will also be done through CRF. Assessment criteria is shown in table 1, 2.

All the participants will be monitored for amount of blood loss through pictorial blood assessment chart, pain through visual analog scale, haemoglobin level, drug safety, Quality of life (QoL) by menorrhagia impact questionnaire and occurrence of any adverse event. The final data analysis will be carried out after successfully completing the study of said number of patients at end of 2 years.

Recruitment, screening, consent

Comment [A5]: This is too short. You should write on the epidemiology of the disease, problem statement and justification/objective of your study.

Comment [A6]: This methodology is certainly very insufficient and does not provide enough information to allow me picture the research you intend to conduct. I should be able to reproduce your work by just reading your methodology

Comment [A7]: Write in full

Comment [A8]: You need to write more on the medications you are using. You should write more about their pharmacology, side effects and risk profile.

Comment [A9]: ?

Comment [A10]: How would the participants be selected/randomised?

Patients with heavy menstrual bleeding (>80ml), assessed through PBAC, for at least 2 or more consecutive cycles will be included in the study. 92 participants will part in study. An information sheet will be provided to participants detailing complete study protocol, and participant's rights. Head to head discussion for all queries would be invited. Voluntary decision shall not be further persuaded. After full satisfaction, consent form signature shall be obtained. Participants cleared inclusion and written consent will be randomized and enrolled.

Comment [A11]: Write in words if starting a statement with numbers. How did you calculate the sample size?

Eligibility

Inclusion criteria

Patients with heavy menstrual bleeding (>80ml) for at least 2 or more consecutive cycles with 24-35days interval; Age group of 18 to 45years; Patients willing to comply with study protocol requirements will be registered.

Comment [A12]: How would you estimate the blood loss per period?

Exclusion criteria

Patients with any diagnosed uterine organic pathology, hypertension, diabetes mellitus, congestive cardiac failure; Coagulopathy; Liver dysfunction; Thyroid dysfunction; malignancy; abortion in last three months; active genital tuberculosis; uterine polyp or erosion; Intrauterine contraceptive device in utero, pelvic endometriosis; Haemoglobin< 8 gm/dl would be the exclusion criteria.

Withdrawal criteria –

Any enrolled participant not willing to continue the protocol with or without any reason or if the patient discontinues the trial drug for more than 03 days at a time, she will be withdrawn from the study with proper data recordings to be analyzed at the end of the proposed trial.

Randomization

Comment [A13]: Is your design per intention to treat or per protocol? Why?

The participants eligible for enrolment will be randomized in a 1:1 ratio to *Eladikasaya* group or Tablet Tranexamic acid group, in accordance of a pre- specified randomization scheme using a computerized system.

Monitoring

Participant will be clinically evaluated on all subsequent visits by clinician / researcher till the completion of the visits. Regular telephonic contact will also be maintained for instruction and reminders once in 2 weeks till the study completes.

Compliance

Participants will be encouraged to remain adhered to treatment protocol and instructions given as per protocol. Medication logs will be maintained for both the groups. Morisky medication adherence scale will be adopted to evaluate medical compliance[11]. Regular telephonic contact will also be maintained for instruction and reminders.

Trial intervention

The study includes two groups *as EladiKasaya* and Tab tranexamic acid. The Tranexamic acid is the treatment of choice for HMB. Thus, Tablet Tranexamic acid group will serve as a control to ascertain the equivalent effects offered by *Eladikasaya*. Posology and other instruction for both the group is given table 3.

Comment [A14]: This is not exactly correct. Rephrase

Formulation preparation, distribution, and follow-up

Eladikasaya ingredients and their used part are shown in Figure1[12-28]. All herbs will be phenotypically validated by taxonomist/*Dravyaguna* expert. Further HPTLC fingerprinting will also be done for *EladiKasaya. Eladikasaya* will be prepared and packed at institute pharmacy. It will be stored at an optimum temperature till further use. All instruction regarding Kasaya preparation and uses will be demonstrated with a video to participants and the video will also be sent to them with the help of social media. Drug shall be distributed through Patient Department of institute by researcher. Follow-up shall be done as per table 1 for physical and clinical signs evaluation till completion of study protocol.

Clinical outcomes

Primary outcome measures

Primary outcome will be measured through reduction of blood loss calculated by Pictorial Blood Assessment Chart[29] and reduction of pain by Visual Analog Scale and improvement in haemoglobin level.

Secondary outcome measures

Researcher will evaluate safety of given medication/instructions through occurrence of adverse drug reaction and QoL assessment usingmenorrhagia impact questionnaire[30].

Adverse Events

All adverse events during the study will be recorded, monitored as per ICH-GCP (2016), managed at site or referred as per referral protocol, and reported to the nearest AYUSH Pharmacovigilance Centre. All withdrawal cases will also be evaluated for safety. Severe ADR will be reported to IEC within 48 hours of cognizance. ADR rescue will be done on case to case basis and will be reported to IEC. Participants will be permitted to take rescue medication as and when required for seasonal illness or other health issues, the same will be recorded in the CRF.

Statistical analysis

Sample size, power and Analysis

The sample size is calculated based on the objective to study the efficacy of *Eladikasaya* versus tablet tranexamic acid in the management of HMB. As it is a standard control, equivalence clinical trial to confirm that these two interventions are indistinguishable from each other. The sample size was calculated with 80% power. The calculated sample size for the study is 46 per arms. Statistical analysis will be performed using SPSS. The result will be drawn as mean ± SD.The statistical level of significance will be set at 0.05.

Record retention

All data related to current study will be retained electronically and physically by scholar for at least 5 years from the completion of study or as per DMIMS policy. Data disposal shall also be made as per CTRI guidelines or DMIMS guidelines.

Discussion

Comment [A15]: Elaborate more on the extent o the statistical analysis to be conducted. Be more specific

Comment [A16]: Who will be blinded and how would you achieve this?

HMB is a major health care problem, and the only conventionally available treatment is tranexamic acid. It hinders the routine activities of females of reproductive age group and hampers QoL. Such cases are also not uncommon in routine *Stri Roga* Outpatient department. *Ayurveda* advocates a specific principal and herbs to be adopted for *Asrigdara* management. Hence a study is planned to compare the efficacy of *Eladikasaya*, with Tranxemic acid as the first-choice treatment for excessive and prolonged menstrual bleeding. *Eladikasaya* has the properties of *deepana-pachana(digestive), vatanulomana (carminative), kapha-pitta shamaka(pacifier), raktastambhaka(hemostatic) and raktavardhaka(heamatinic)* suitable for *Asrigdara*management. Considering the concerns about thromboembolic events in patients undergoing anti-fibrinolytic therapy, the *Eladikasaya* could be a new safe alternative for Heavy menstrual bleeding patients. The final discussion of the study will be written on the basis of results found.

Strengths and limitations of this study

Novel Randomized standard-controlled study of *Eladikasaya* will provide the results status and comparative result. If *Eladikasaya* shows reduction in blood loss in heavy menstrual bleeding similar to standard drug, it will give the best parallel modality for the management of heavy uterine bleeding. Anti-haemolytic markers assessment has not been done in current study. A fix drug and *anupana* (vehicle) has prescribed irrespective of seasonal, geographical and individual *prakriti* variation.

Ethics statement

Ethical approval was obtained through the institutional ethics committee of Mahatma Gandhi Ayurvedic College Hospital and Research Centre, DMIMS, Wardha, as per the reference number MGACHRC/IEC/Oct-2022/585, Dated 07/10/2022.

Conflict of Interest - Nil

Table 1-Assessment schedule of the clinical protocol.

Visit	Screening Visit	Visit 1 Enrollment & randomization (day 0)	Visit 2(8^{th} day of 1^{st}cycle of menses)	Visit 3 (8^{th} day of 2^{nd} cycle of menses)	Visit 4 (8^{th} day of 3^{rd} cycle of menses)	Visit 5 (8^{th} day of 4^{th} cycle of menses)
Consent	+					

Initial demographic details	+					
Inclusion exclusion criteria	+					
Medical history	+					
Associated Symptoms	+		+	+	+	+
Randomization		+				
Complete physical examination	+	+	+	+	+	+
Menorrhagia impact questionnaire		+				+
PBAC score	+		+	+	+	+
VAS for lower abdominal pain and low backache	+		+	+	+	+
Adverse event assessment			+	+	+	+
Completion and outcome report						+

VAS-Visual analog score, PBAC score- Pictorial blood assessment chart

Table 2: Laboratory investigations Schedule of the clinical protocol

Visit	Screening Visit	Visit 1 Enrollment & randomization (day 1)	Visit 2(8^{th} day of 1^{st}cycle of menses)	Visit 3 (8^{th} day of 2^{nd} cycle of menses)	Visit 4 (8^{th} day of 3^{rd} cycle of menses)	Visit 5 (8^{th} day of 4^{th}cycle of menses)

Complete blood count	+					+
FBS	+					
Bleeding time, clotting time	+					
Liver function test	+					
Renal function test	+					
Ultrasound pelvis	+					+

Table 3: Posology of the clinical protocol

Groups	**A**	**B**
Intervention	*Eladikasaya*	Tablet Tranxemic acid
Form, Dose & frequency	*Kasaya*, 50ml, thrice a day	Tablet,500mg, thrice a day
Anupana	Honey and sugar	Water

Duration	From day 1 of menses to day 7 for 3 consecutive cycle	From day 1 of menses to day 7 for 3 consecutive cycle
Follow ups	8^{th} day of each 3 consecutive cycle and 8^{th} day of 4^{th} cycle without intervention	8^{th} day of each 3 consecutive cycle and 8^{th} day of 4^{th} cycle without intervention

References

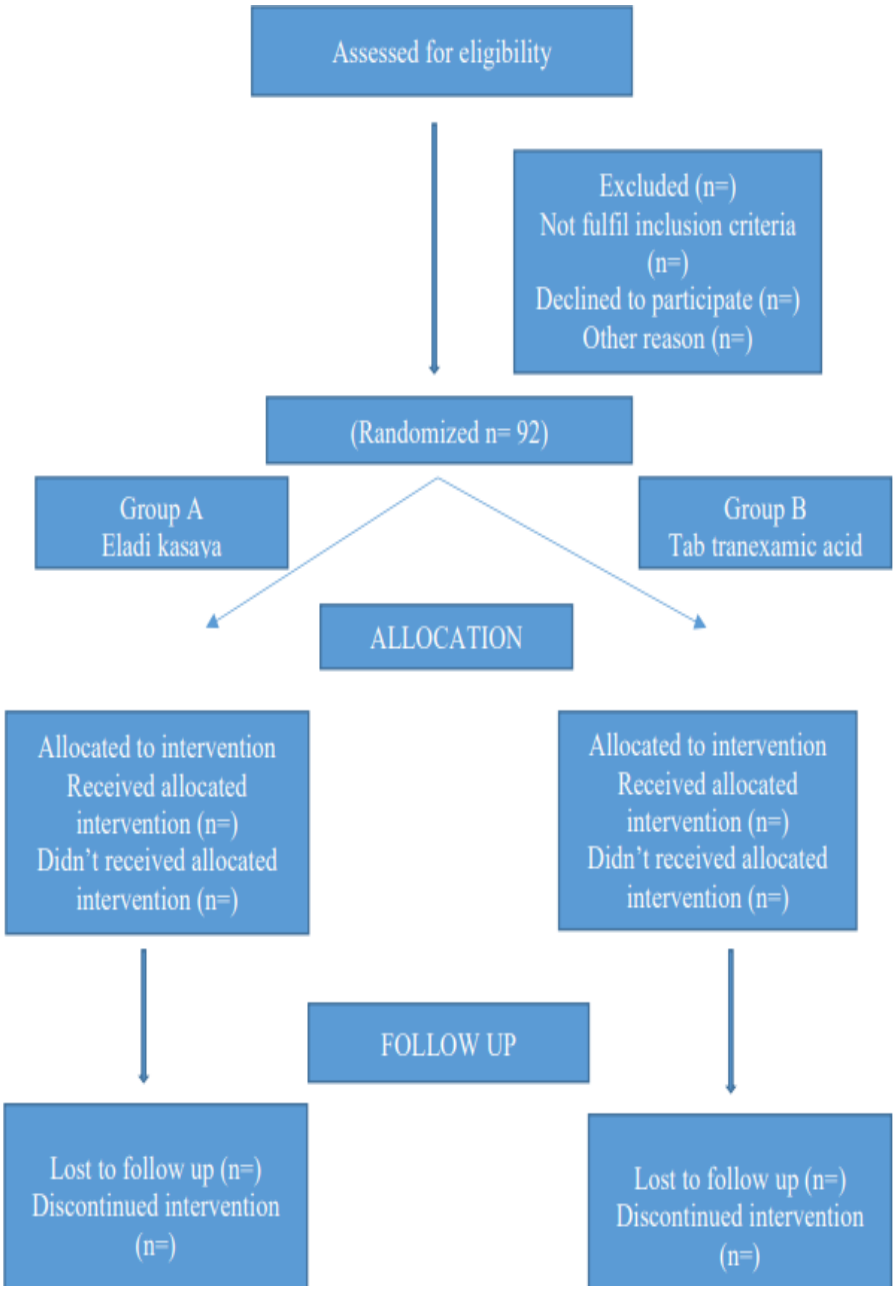
1. Available from: http://nhp.gov.in>disease>abnormal uterine bleeding. [Last accessed on 9 September 2022]
2. Hoffman BL, Schorge JO, Bradshaw KD, Halvorson LM, Schaffer JI, Corton MM. Williams Gynecology, New York,McGraw hill education; 2012.p 219-223
3. Sushruta Samhita, Sharersthana, Shukrashonitasuddhi, 2/21, Available from:http://niimh.nic.in/ebooks/esushruta [Last accessed on 9 September 2022]
4. Charak Samhita, Chikitsasthana,Vatavyadhi, 28/230Vol 2,Available from: http://niimh.nic.in/ebooks/echarak [Last accessed on 17 September 2022]
5. Sushruta Samhita, Sutra Sthana, Vyadhisamuddeshiya, 24/11, Available from: http://niimh.nic.in/ebooks/esushruta [Last accessed on 17 September 2022]
6. Wood C. Alternative treatment. Baillieres Clin ObstetGynaecol. 1995 Jun; 9(2): 373-97.
7. Dutta DC, Text book of gynecology, New Delhi, Jaypee brothers medical publishers; 2020. p 156.
8. Critchley HO, Maybin JA. Molecular and cellular causes of abnormal uterine bleeding of endometrial origin. Semin Reprod Med. 2011 Sep;29(5):400-9.
9. Charak Samhita, Chikitsasthana, Yonivyapadchikitsa, 30/86, Varanasi: Available from: http://niimh.nic.in/ebooks/echarak [Last accessed on 17 September 2022]
10. Pandey G, editor.Harita Samhita, Varanasi: Chaukhamba Sanskrit series; 2014, p. 401.
11. https://www.moriskyscale.com [Last accessed on 9 September 2022]
12. Sharma S, Sharma J, Kaur G. Therapeutic uses of Elettaria cardomum. International journal of drug formulation and research. 2011; 2(6):102-8.
13. Maurya SK, Verma NK, Verma DK. Bombax ceiba Linn: a review on its phytochemistry and pharmacology, Curr Res J Pharm Allied Sci 2018;2(3):14-23

14. Joseph B, George J, Mohan J. Pharmacology and traditional uses of Mimosa pudica, international journal of pharmaceutical science and drug research 2013;5(2):41-44
15. Bag A, Bhattacharya SK, Chattopadhyay RR. The development of Terminalia chebula (Retz.) combretaceae in clinical research, Asian Pac J Trop Biomed 2013;3(3):244-252
16. Kumar S, Kamboj J, Suman, Sharma S. Overview for various aspects of the health benefits of Piper longum linn. Fruit. J Acupunct Meridian Stud 2011;4(2):134-140.
17. Gupta PK, Sonewane K, Rajan M, Patil NJ, Agrawal T, Banerjee ER, Chauhan NS, Kumar A. Scientific rationale of Indian AYUSH Ministry advisory for COVID-19 prevention, prophylaxis, and immunomodulation. ADV TRADIT MED (ADTM). 2021 Apr 29:1–25.
18. Kocaadam B, Şanlier N. Curcumin, an active component of turmeric (Curcuma longa), and its effects on health. Crit Rev Food Sci Nutr. 2017 Sep 2;57(13):2889-2895.
19. Cunha Neto F, Marton LT, de Marqui SV, Lima TA, Barbalho SM. Curcuminoids from *Curcuma Longa*: New adjuvants for the treatment of crohn's disease and ulcerative colitis? Crit Rev Food Sci Nutr. 2019;59(13):2136-2143.
20. Komati A, Anand A, Shaik H, Mudiam MKR, Suresh Babu K, Tiwari AK. Bombax ceiba (Linn.) calyxes ameliorate methylglyoxal-induced oxidative stress via modulation of RAGE expression: identification of active phytometabolites by GC-MS analysis. Food Funct. 2020 Jun 24;11(6):5486-5497.
21. Diab KA, El-Shenawy R, Helmy NM, El-Toumy SA. Polyphenol Content, Antioxidant, Cytotoxic, and Genotoxic Activities of Bombax ceiba Flowers in Liver Cancer Cells Huh7. Asian Pac J Cancer Prev. 2022 Apr 1;23(4):1345-1350.
22. Afshari AR, Sadeghnia HR, Mollazadeh H. A Review on Potential Mechanisms of Terminalia chebula in Alzheimer's Disease. Adv Pharmacol Sci. 2016;2016:8964849.
23. Ashokkumar K, Murugan M, Dhanya MK, Warkentin TD. Botany, traditional uses, phytochemistry and biological activities of cardamom [Elettaria cardamomum (L.) Maton] - A critical review. J Ethnopharmacol. 2020 Jan 10;246:112244.
24. Nigam M, Mishra AP, Adhikari-Devkota A, Dirar AI, Hassan MM, Adhikari A, Belwal T, Devkota HP. Fruits of Terminalia chebula Retz.: A review on traditional uses, bioactive chemical constituents and pharmacological activities. Phytother Res. 2020 Oct;34(10):2518-2533.

25. Gupta P, Tripathi A, Agrawal T, Narayan C, Singh BM, Kumar M, Kumar A. Synergistic protective effect of picrorhiza with honey in acetaminophen induced hepatic injury. Indian J Exp Biol. 2016 Aug;54(8):530-6.
26. Khan A, Akram M, Thiruvengadam M, Daniyal M, Zakki SA, Munir N, Zainab R, Heydari M, Mosavat SH, Rebezov M, Shariati MA. Anti-anxiety Properties of Selected Medicinal Plants. Curr Pharm Biotechnol. 2022;23(8):1041-1060.
27. Mandal MD, Mandal S. Honey: its medicinal property and antibacterial activity. Asian Pac J Trop Biomed. 2011 Apr;1(2):154-60.
28. Kokane DD, More RY, Kale MB, Nehete MN, Mehendale PC, Gadgoli CH. Evaluation of wound healing activity of root of Mimosa pudica. J Ethnopharmacol. 2009 Jul 15;124(2):311-5.
29. Janssen CA. Menorrhagia: the 80 mL criterion and the usefulness in clinical practice. Am J ObstetGynecol 2005;192(6):2093
30. Bushnell DM, Martin ML, Moore KA, Richter HE, Rubin A, Patrick DL. Menorrhagia Impact Questionnaire: assessing the influence of heavy menstrual bleeding on quality of life. Curr Med Res Opin. 2010 Dec;26(12):2745-55.

Figure 1- Part used and pharmacological properties of ingredients of *EladiKasaya.*

Figure 2 - Consort flow chart of the clinical protocol


Assessed for eligibility
Excluded (n=)
Not fulfil inclusion criteria (n=)
Declined to participate (n=)
Other reason (n=)
(Randomized n= 92)
Group A
Eladi kasaya
Group B
Tab tranexamic acid
ALLOCATION
Allocated to intervention
Received allocated intervention (n=)
Didn't received allocated intervention (n=)
Allocated to intervention
Received allocated intervention (n=)
Didn't received allocated intervention (n=)
FOLLOW UP
Lost to follow up (n=)
Discontinued intervention (n=)
Lost to follow up (n=)
Discontinued intervention (n=)