Peer-review Comments and Author Responses

Reviewer 1:

Dear Reviewer A, thank you for your valuable comments, please see the changes according to them:

1. *Abstract*

Since the abstract should stand alone abbreviations like BPI-SF should be clarified in case someone not from the field read it.

Answer: The abstract has been changed. See below:

„Secondary outcomes include Quality of Life assessed by Functional Assessment of Cancer Therapy-Breast (FACT-B), further Brief Pain Inventory-Short Form BPI-SF items, Patient Health Questionnaire-8 (PHQ-8), and Quantitative Analgesic Questionnaire (QAQ) at six and twelve weeks."

2. *The other concepts there is no need to add abbreviations near them since you are not using them again in the abstract this will help you to make the abstract shorter .*

Answer: The abstract has been changed. See below:

„The study population targets post-menopause women with stage I, luminal, unilateral, non-metastatic, receptor-positive breast cancer after breast conserving surgery (BCS) healed per primary intention……. Secondary outcomes include Quality of Life assessed by Functional Assessment of Cancer Therapy-Breast (FACT-B), further Brief Pain Inventory-Short Form BPI-SF items, Patient Health Questionnaire-8 (PHQ-8), and Quantitative Analgesic Questionnaire (QAQ) at six and twelve weeks."

3. *Regarding the dose of the curcumin I would write it like this 500mg three times daily.*

Answer: The abstract has been changed. See below:

„Daily curcumin supplementation (3 x 500 mg three times daily) for twelve weeks is planned"

4. *Introduction*

I would add a reference and sentence regarding the dose of curcumin that helps to reduce inflammation in order to support using this dose in the methods.

Answer: Thank you for your suggestion. The following sentence was added:

"Studies found Curcuma extract dosages between 1000-1500 mg divided in 2 to 3 doses to be effective for joint arthritis (Daily et al., 2016)."

5. *"Finding alternative therapies for pain relief with lower adverse effects and an affordable profile is critical for effective treatment, adherence, and patient quality of life for breast cancer survivors". I would add a reference to support this paragraph.*

Answer: Thank you for your suggestion. The references were added.

6. *"Although effective, AIs show toxicity issues especially related to musculoskeletal symptoms. AIs-induced arthralgia is observed in up to 73% of patients receiving the treatment", which reference support this ?*

Answer: The reference for the whole paragraph is the same - Henry et al, 2012, written at the end. We added it right after this particular statement as well, for clarification.

7. *Methods*

A need for a reference why you think Brazil and the United States secure geographical cultural diversity, aligned to real-world contexts ?

Answer: Thank you for your suggestion, the reference has been added:

"Brazil and United States have differences in their healthcare systems, health indicators, stage of country development, ethnical and cultural diversity that will ensure the benefits of including both countries as a reliable external validation for the trial (Coronado et al., 2020; Martins, 2018)."

8. *In the emergency unblinding you wrote 'Curcumin has a well-documented safety profile" this sentence is supported by what ? I didn't see anything regarding safety in the introduction.*

Answer: Information on safety and the reference has been added to the introduction:

"Safety profile of curcumin is well-documented (Daily et al., 2016)."

9. *Brief Pain Inventory-short form (BPI-SF) is this form comes in different languages? If not, who will translate it ?, and in how many languages it will be provided?*

Answer: Dear Reviewer the BPI-SF has already been translated to other languages rather than English. In our trial, we will be offering the validated questionnaires in English and Portuguese. These information has been added to the text:

"To measure the intensity of joint pain, the BPI-SF questionnaire will be provided in 2 languages: Portuguese and English. The BPI-SF is a pain assessment tool for use in patients with cancer and validated in Brazilian population (Ferreira et al., 2011)".

Ferreira, K. A., Teixeira, M. J., Mendonza, T. R., & Cleeland, C. S. (2011). Validation of brief pain inventory to Brazilian patients with pain. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer, 19(4), 505–511. https://doi.org/10.1007/s00520-010-0844-7)

10. Adherence

I suggest to do Plasma curcumin along with the pills count to ensure the adherence.

Answer: Dear Reviewer thank you for your valuable suggestion. Nevertheless, the plasma levels of curcuminoids are extremely low (<50ng/mL) even after an oral intake of curcuminoids up to 12 g/day, this is because the low oral bioavailability, poor absorption and rapid metabolism of these compounds (Cao et al 2013). For this reason, we decided to not measure the curcumin plasma levels as it is to less reliable to track the adherence.

Cao Y et al,A high-throughput quantification method of curcuminoids and curcumin metabolites in human plasma via high-performance liquid chromatography/tandem mass spectrometry. j Chromatogr B. 2014;949:70-78. doi: 10.1016/j.jchromb.2013.12.039.)

11. Modification/discontinuation

"Curcumin is well-tolerated when taken orally. Previous human trials have reported no toxicity at daily doses up to 8000 mg. Most common adverse effects of curcumin are gastrointestinal (around 16%) such as diarrhea, constipation, abdominal distension, and others. Hepatobiliary adverse events (7%) make the second largest group of adverse effects of curcumin. Allergic skin reactions such as pitting edema and itching are uncommon. The patients need to be specifically aware of the anticlotting effects of curcumin. All of the mentioned above needs to be reported as adverse events and are reasons for the potential discontinuation of the intervention." References are needed here to support what you wrote.

Answer: The references has been added.

"Curcumin is well-tolerated when taken orally. Previous human trials have reported no toxicity at daily doses up to 8000 mg (Kanai et al., 2011). Most common adverse effects of curcumin are gastrointestinal (around 16%) such as diarrhea, constipation, abdominal distension, and others. Hepatobiliary adverse events (7%) make the second largest group of adverse effects of curcumin (Giordano & Tommonaro, 2019). Allergic skin reactions such as pitting edema and itching are uncommon. The patients need to be specifically aware of the anticlotting effects of curcumin (Lao et al., 2006)."

12. Allocation concealement

How will you ensure adequate concealment ?

Answer: The explanation has been added:

"A unique code will be generated and concealed to staff members and participants to assure allocation concealment. Only pharmaceutical staff responsible for preparing curcumin capsules, or placebo will have access to the randomization list.

13. Discussion

I would add a limitation that may be you will get different results in a multicenter study depending on each center's technique level and inclusion indication criteria, but this may be prevented through a careful selection of controlled categories.

Multi-center research may be effective when conducted on drugs, as many factors can be controlled, such as dosage, timing, and method of application. However, there are many varying components. Physicians are taught differently, they execute differently, and they choose patients differently even though they are trained under the same educational protocol.

Answer: Answer was added to the chapter:

"Moreover conducting this trial as a multicenter trial can have some limitations as well. Inclusion criteria, conducting the trial and results depends on each physician of the different centers as curcumin is a dietary supplementation and not a drug."

14. Regarding supplements it is important to mention that dietary supplements are regulated somewhat differently from drugs, as they usually do not fall within the same strict regulatory framework as pharmaceuticals, so it is important to mention this

"Standardization of the entirety of a plant extract can be difficult, however, because the exact chemical composition can also be dependent not only on the plant and plant part used, but also on growing conditions and method of preparation, including possible fractionation and/or solvents used for extraction, which can differ between products and manufacturers"

Reference : Funk JL, Schneider C. Perspective on Improving the Relevance, Rigor, and Reproducibility of Botanical Clinical Trials: Lessons Learned From Turmeric Trials. Front Nutr. 2021 Dec 3;8:782912. doi: 10.3389/fnut.2021.782912. PMID: 34926556; PMCID: PMC8678600.

Answer: Dear Reviewer thank you for you valuable suggestion. This aspect has been added to the discussion:

"Plant extracts are not subjected to medical control as drugs. Standardization of curcumin can be difficult due to its chemical composition, growing conditions, preparation methods and differences of the manufacturers (Funk & Schneider, 2021)

Reviewer 2:

15. I only have doubts about the blinding, because from what was written, it seems to be more of a triple-blinding trial and not double-blinding.

Answer: The wording has been changed:

„This protocol is a phase III, multicenter, randomized, placebo-controlled, doubletriple-blinded study"

Reviewer 3:

16. Methods:

please specify how many centers will be included in each country.

Answer: Dear Reviewer, we plan to include three centers per country. This information has been added in the text:

17. "We anticipate that patients will be primarily recruited from tertiary healthcare academic hospitals in Boston area and São Paulo, who are already enrolled in a Gynecologic-Oncology Program. We also plan to advertise this trial using flyers posted in the outpatient specialist clinics, public posting boards and in a variety of media, including internet (i.e Google Ads) and newspapers. Given that cancer-related pain is multifactorial, we have included two countries (Brazil and the United States), three centers in each country."

Merge the eligibility criteria in one single paragraph including just the most relevant criteria and avoid using enumeration. (this is just a suggestion, you could create a table with the criteria)

Answer: Dear Reviewer, as you have suggested we merge the eligibility criteria in one paragraph and remove the enumeration.

18. Also, I just wanted to ask one more thing, maybe you should also record what patients include curcumin as a part of their diet to adjust for this covariate too. Many supplements contain curcumin already and many foods contain curcumin)

Answer: Dear Reviewer, thank you for your valuable comment. Indeed, it is important to record this information and adjust as covariate. Recording additional curcumin intake in diet or supplements has been added as a component to track with the pain medication/diet diary.

19. "The patient will document their intake of analgesics and curcumin intake in diet in their Pain Medication/Diet Diary, including the name, dosage date and time of each intake."

I don't think you need to add the "two-tailed test" (most studies use two tales instead of one)

Answer: Have been deleated:

„The alpha level was set at 0.05, and the calculation was conducted for 80% power and a two-tailed hypothesis test"

20. Observation: do you think it's a good idea to add the difference reported in the literature in the sample size calculation section? I suggest you change that line to the introduction section and remove that reference from the methodology.

Answer: The text has been moved to introduction and reference removed in the Method section. Please see:

„Differences in pain score due to curcumin use reported in the literature are from 0.25 to 2.8, where 0.25 was stated as not significant (Hershman et al., 2015, 2018; Martínez et al., 2019).“

„Assuming from the literature a mean BPI-WP difference in the placebo group of 1.5 and a mean BPI-WP difference in the intervention group of 2, a standard deviation of 1, and 25% dropout rate the sample size needed is 160 participants, 80 per group. We assume the difference between the placebo and intervention group of 0.5 as conservative, as the differences reported in the literature are from 0.25 to 2.8, and 0.25 was stated as not significant (Hershman et al., 2015, 2018; Martínez et al., 2019).“

21. For the statistical analysis: well done. I think it's very important that you'll adjust for covariates and avoid potential confounders. However, no need to add how you'll assess for normality. The scales are a good fit for your study and the statistical tests.

Answer: Has been removed.

22. Discussion:

“Positive outcomes can support the information already available on the analgesic efficacy of curcumin. Negative results, however, also have an important scientific impact. We will therefore be able to produce scientific evidence against the use of curcumin in this group of patients.“ do you think this paragraph is necessary? Maybe just add a short sentence explaining this.

Answer: Dear Reviewer thank you for this suggestion. The information has been added to the discussion:

“Currently, there are no published studies that have utilized curcumin as a treatment for joint pain resulting from the use of an aromatase inhibitor. Conducting such a study can provide valuable insights for managing this specific population, either confirming or refuting the null hypothesis.”

23. I suggest you remove this line:

“ The stratified block randomization will balance important covariates such as PCS and study site”

Answer: Has been removed.

24. In the introduction you already explained where curcumin comes from, so I suggest you remove it from the discussion section.

Answer: Has been removed.

25. Avoid using "could" and "also" (it's too informal)

Answer: We have avoid this words and removed them from the text.

26. I liked that in the discussion you talked about the limitations of your study and the strengths. I suggest you avoid explaining why you're doing stratified randomization. In addition, remove the part where you talk about the follow-up and increase the power of the study.

Answer: Dear Reviewer, thank you for your suggestion. We removed the suggested parts from the Discussion section. Additionally, we have discussed limitations:

"Moreover, conducting this trial as a multicenter trial can have some limitations as well. Inclusion criteria, conducting the trial and results depends on each physician of the different centers as curcumin is a dietary supplementation and not a drug."

27. You can talk more about other trials, what you expect to see, and what's different from your trial vs. The already existing evidence supporting the use of curcumin in induced AI - arthralgia. And finish it with a small conclusion.

Answer: Dear Rewiever thank you for you comment, we have added this aspects in the discussion:

"Currently, there are no published studies that have utilized curcumin as a treatment for joint pain resulting from the use of an aromatase inhibitor. Conducting such a study can provide valuable insights for managing this specific population, either confirming or refuting the null hypothesis."

28. Otherwise, I think you did a great job. I consider you don't need to explain too much about why you're doing this or that (as previously mentioned). For instance, it's okay to say "to ensure adherence... You'll do x". But mentioning you're doing stratified randomization to ensure your groups are equally comparable seems redundant. It seems your discussion talks again about the rest of the paper...
Remember, you're not discussing the methodology in your discussion but the changes you expect to see and what makes your trial a good way to answer your research question.

Answer: Dear Reviewer, thank you for your suggestion, we have removed sentences that discussed the methodology and focused on the expected findings of this study protocol.