Dear Editor

**CRF 1434 The Lymphedema Evaluation in Gynecological cancer Study (LEGS): design of a prospective, longitudinal, cohort study**

Thank you for considering the abovementioned manuscript for publication in Cancer Research Frontiers. The authors have now incorporated the revisions as suggested by the Reviewers and a list of responses to each of their comments is provided below.

We look forward to your reply.

Yours sincerely

[Signature]

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The authors provide a clearly written description of an important study. This manuscript will serve as a valuable reference citation as they publish the main findings from this study. I have only a few minor comments.

P6-7. Data collection. What do the numbers in parenthesis indicate? 95% CI. 90% CI. Please specify.

Thank you for highlighting this omission; numbers in parenthesis indicate 95% confidence intervals. Revisions have been incorporated to reflect this (pages 6-7).

p 7. Can the authors provide some guidance on the interpretation of the Bland Altman results? e.g., do these results indicate 'good', 'very good', or 'excellent' agreement?

Bland Altman results for BIS and circumference measurements indicate excellent agreement – differences in measures (within and between testers) were less than 0.5% (most cases well below <0.5%) and are clinically irrelevant. This additional information has been added to the paper (page 7, paragraph 1).

p 8. Gynecologic oncology patients who received pelvic or para-aortic lymphadenectomy may often experience swelling in the hip. This area does not seem to be addressed in the self-administered questionnaire or in the objective measurements. Can the authors comment on why this area was not included in the evaluation or whether they feel existing assessments would capture swelling in this area?

The reviewer rightly identifies that swelling in the hip has not been specifically questioned or objectively assessed, but instead is included within leg swelling assessment via BIS and self-report. That is, BIS measures incorporate the hip region. However, our measurement approach does not allow us to determine segmental leg swelling (i.e., identify area of swelling specific to the foot, lower leg, knee, upper leg or hip). Our BIS approach may be able to tease out leg versus trunk (including the pelvic region/lower abdomen) swelling. Our self-report swelling is consistent with our BIS approach and asks participants to categorize any lower body swelling as swelling of the leg or between the legs or abdomen/pelvic region.

p 9. It is not clear if BMI as a risk factor for LE was assessed at the time of surgery only or if changes in BMI over time were also measured.

Height and weight were measured pre-surgery and over time; this has now been made clear in the manuscript (page 8, paragraph 1).

p 9. It is not clear whether the treatment data abstracted was for the initial surgery only or if data for additional surgeries that occurred during the 24 month follow-up period were also abstracted. Similarly on Table 2, it would be helpful to know if any women with relapse had additional surgery, particularly additional lymph node removal.

Data pertaining to treatment (i.e., surgery, histopathology, adjuvant treatments) was collected at the 24 month follow-up, thereby providing information for the entire study period.

p 10. Participants were referred to their general practitioner for concerns in between visits. Did the authors ask the participants who did see another provider for LE related symptoms whether that provider diagnosed the participant with lymphedema? My concern is that if a patient is
diagnosed and treated for mild lymphedema in between visits to the study team, her LE (if well managed) might not be detected by BIS and circumference. Hence, this new diagnosis would not be included in the calculations of the incidence rate.

Participants were asked at each follow-up if they had received any treatment for lymphedema since the last visit and, if so, details of treatment (who provided treatment and start dates) were collected (page 9, paragraph 4). It will be important to consider this data when calculating incident lymphedema.

p 17. The authors note that AT LEAST 24 months of follow-up are needed based on the breast cancer literature. This prospective study follows women for AT MOST 24 months. Is that long enough? Is this duration of follow-up a potential limitation to be noted on P 13?

This is the first study to assess lymphedema among women diagnosed with gynecological cancer beyond 6 months post-diagnosis. The breast cancer literature demonstrates that the majority of lymphedema cases present within 24 months post-diagnosis. We suspect that this will be similar lower limb setting, and as such, this information was used to guide length of follow-up. Of note, we are planning a 6-year post-diagnosis follow up, which in turn will provide additional information about lymphedema development beyond the 24 month post-diagnosis time point.

Tables 2/4. The detailed information on histological type takes up a lot of space in the tables and wasn't particularly informative to me. I suggest deleting it.

We acknowledge that the histological data is descriptive and this in part, highlights the need for this baseline paper, as it allows us to present detail that will not be possible to present in subsequent publications. Unfortunately, since the proportion of women with different histological types differs according to the difference gynecological cancers it is not appropriate to collapse/group these variables further.

General comment. Were any of the women in the benign disease comparison group diagnosed and treated for gynecological cancer during the study period? If yes, how did the authors address this in the study design?

No, women in the benign disease comparison were not subsequently treated for gynaecological cancer during the study period.

Reviewer 2: Declination

This paper presents the authors methods for designing a prospective longitudinal cohort study of patients with gynecological cancers followed up for lymphedema. Unfortunately, the manuscript has no real "data" (there’s no report of any sort of lymphedema outcomes even though they are mentioned in the methods). As a result, the paper is really just a description of the patient information. While this is exhaustive and clearly shows a lot of work, it is not really scientifically interesting or warrant publication on its own.

This manuscript presents details of a novel area of research and is the first study worldwide to prospectively follow a cohort of women with malignant and benign gynaecological disease, with regular assessment of a range of physical and psychosocial outcomes up to 24 months post-diagnosis. Lymphoedema, our primary outcome, is an understudied chronic condition, with findings from this work able to evaluate incidence, risk factors and relationship with quality and quantity of life. A detailed account of our cohort study design and methods, including detailed description of
sample characteristics and demonstration of the generalizability of this sample to the wider gynaecological cancer cohort is fundamental to understanding the clinical relevance of subsequent findings. We would not be able to provide this important level of detail in subsequent outcome papers. Thus, while this paper does not include outcome results, it clearly documents the strengths and limitations of study design, as well as the potential generalizability of subsequent findings and will be cited in all subsequent papers (with work on 3 outcome papers already underway; total planned publications to come from the LEGS study is expected to exceed 10 in the next 3 years).

Reviewer 2: Accept

The authors performed a longitudinal, observational, cohort study prospectively evaluating the incidence and risk factors of lower-limb lymphedema after treatment for gynecological cancer and they describe the protocol of their study and the characteristics of their sample. The authors managed to successfully recruit a big number of women into LEGS protocol and overall, this represents a well-designed cohort study of good quality. They nicely discuss both the strengths and shortcomings of their study and mention the significance of such a cohort for future clinical care and further investigation.

The authors thank the Reviewer for their time taken to consider our manuscript.