12/11/18

To the Editor,

Thank you for your rapid turn-around of our edits. We have made the changes you requested to the manuscript. Please see details below.

1. We have corrected the order of references 14-16
2. We have removed the reference to Ahmed’s study. After review, we did not feel that it fit in well with references 15 and 16. Therefore, no discussion of template biopsy with mpMRI is needed.
3. We have added further discussion on the number of systematic cores to be taken. The software only proposes either 6 or 12 locations. There are no other options. We choose 12 systematic cores for the sake of thoroughness.
4. We agree with incorporating the discussion on using hydrogen peroxide solution as a “Note” in step 3.2.
5. We have spelled out PSA and discussed how PSA is obtained
6. Step 11.1: the needle streak is observed in real time on the ultrasound image
7. We agree with the adjustment of step 11.2.
8. Regarding the merger of steps 12 with 11 – we feel that it is best to keep these steps separate, since step 11 is about Needle Segmentation. We feel that discussing the number of cores to obtain from each ROI should be in its own step, since it is separate from needle segmentation.
9. We agree with removing the reference to “Hodge and Stamey’s” study from Figure 1’s legend
10. We have spelled out CaP (prosate cancer) and csCAP (clinically significant prostate cancer)
11. We have spelled our Odds Ratio and Confidence Interval
12. References included in the figures are correct
13. The Reference list has been corrected to incorporate “et al” if there are 6 or more authors

12/10/18

To the Editor:

Thank you very much for the constructive edits and comments that you provided for our manuscript titled “Use of MRI-Ultrasound Fusion to Achieve Targeted Prostate Biopsy.” We have made the following changes to our manuscript, as recommended by your team.

1. We have read through the manuscript to ensure no grammatical or spelling errors are present.
2. We have provided copyright permission for figures that are reproduced. Figure legends include appropriate citation.
3. We have provided email addresses for each author.
4. We have attached all figures as “SVG” files as well as “PDF” files
5. We have modified the long abstract to more clearly state the goal of the protocol.
6. We have removed commercial language, including “™”.
7. We have reduced the number of instances that the text refers to “Artemis” to 2. The remaining mentions of “Artemis” inform the reader of the make/model of the MRI/US fusion system that protocol is based upon.
8. We have provided an ethics statement before the numbered protocol steps.
9. We have removed personal pronouns from the manuscript.
10. We have revised the protocol to contain only action items in the imperative tense. Text that cannot be written in the imperative tense has been added as a “Note” at the end of the appropriate step. The number of “notes” have been reduced in the protocol, and are used only sparingly where we believe they are necessary for the reader’s comprehension. A few minor areas of protocol discussion have been moved to the Discussion section of the manuscript.
11. We have provided Inclusion and exclusion criteria for MRI/US fusion biopsy to the protocol.
12. We have described Steps 2.4 and 2.5 more fully.
13. We have provided instructions on the calculation of PSA density.
14. We have simplified the protocol to only contain 2-3 actions per step and a maximum of 4 sentences per step.
15. We have ensured that all highlighted text includes at least one action written in the imperative tense
16. We have provided relevant details that are required to perform each highlighted step.
17. We have added an expanded discussion of several critical steps within the Discussion section of the manuscript.
18. We have sorted the Table of materials in alphabetical order.

Edits based on Reviewers’ comments:

Reviewer #1:

1. We have replaced the term “understaging” with “undergrading,” which we agree is a more accurate description.
2. We have provided the citation by Ahmed.
3. We have provided a description of how the systematic biopsy locations are proposed by the device.
4. We have provided further detail on how the number of systematic cores is determined.

Reviewer #2:

Major comments:

1. We have provided further detail on the UCLA prostate lesion scoring system that was used prior to the development of PI-RADS v1 and PI-RADS v2. We have given descriptions of how a “grade 1” lesion differs from a “grade 2” lesion in terms of T2 imaging, dynamic contrast enhancement, and diffusion weighted imaging. This description illustrates to the reader how similar the PI-RADs and UCLA scoring systems are.
2. We have defined “targeted biopsy” as any biopsy aimed at an ROI, regardless of the final pathology.
3. We have expanded upon the definition of “combination biopsy” and have included it in the Representative Results section (a brief description was previously in the Discussion section).
4. We have added discussion of several critical steps from the Protocol to the Discussion section of the manuscript. This new section elaborates on motion compensation, and strategies to properly sample an ROI. We have kept the discussion of active surveillance based upon fusion biopsy as we believe it demonstrates the relevancy of the fusion platform in several aspects of prostate cancer management.
5. We have added a discussion of critical steps that help to maintain biopsy precision within the Discussion section. This section mainly discusses the importance of elastic and rigid registration as well as motion compensation. It is certainly true that, if the patient position changes, registration accuracy and the precision of the procedure can be somewhat reduced. However, this platform employs rigid and elastic registration that is able to compensate for minor variations in patient position. We have read the article by Cornud that incorporates Euclidian geometry, but we did not feel strongly about commenting on it for this methods paper.
6. We understand the importance of assuring TRUS probes are properly disinfected, as mentioned by the Reviewer. At UCLA, all TRUS probes are disinfected via an automated system that uses vaporized hydrogen peroxide solution. We did not add this description to the protocol since different institutions may use other disinfection methods that are equally effective. If this step is included in the final video, we will be sure to add a segment on disinfection.
7. We have removed the non-metric system measurement (inch) from the manuscript.