Author’s response to reviews

Title: BIOLAP: Biological versus synthetic mesh in laparo-endoscopic inguinal hernia repair: Study protocol for a randomized multicenter, self-controlled clinical trial

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Author’s response to reviews:

Dear Dr. Hakkim,

Thank you for giving us the opportunity to submit a revised draft of our manuscript titled BIOLAP: Biological versus synthetic mesh in laparo-endoscopic inguinal hernia repair: Study protocol for a randomized multicenter, self-controlled clinical trial (TRLS-D-18-00370) to Trials. We highly appreciate the time and effort that you and the reviewers have dedicated to providing valuable feedback on our manuscript. We have been able to incorporate changes to reflect most of the suggestions provided by the reviewers. We have highlighted the changes within the manuscript.

Here is a point-by-point response to the reviewers’ comments and concerns.
Dear Prof. Dr. med. Kallinowski,

We thank you for your critical analysis and comprehensive, well-reasoned remarks.

Comment 1: The proposal describes a test of two procedures already in clinical use. The liberal use of the terminology "biological versus synthetic mesh" has to be sharpened. As it stands in Ins 167 - 169, the biological mesh should be a perforated, non-cross-linked, acellular, collagenous matrix. The synthetic mesh should be large-pored, lightweight and made of polypropylene, polyester or polyvinylidene fluoride. There are a variety of meshes in this description and this reviewer envisionages the danger of a non-standardized application process. Since many more synthetic or biological meshes are on the market, care should be taken to avoid the liberal use of "synthetic or biological" as a description of the specific meshes used. Rather, the names and trade marks of the meshes selected should be stated and the presumed number of each individual mesh to be implanted should be precalculated in order to assess the power of the trial as well as the number needed to treat to reach both end points named - superior in pain and not inferior in recurrence. It is assumed that both end points need different numbers needed to treat to reach a conclusion.

• You are pointing out one of the questions we discussed repeatedly in our team when writing the study protocol. We finally agreed not to give a product list, but to limit the number of used meshes by the listed criteria – as we aim to conduct a comparison of mesh types, not products. The study protocol underwent full external peer review and was approved by the German Research foundation as a comparing trial of mesh types, not products.

As we compare two material types and not several specific products only one NNT is needed for each endpoint. As described under “Statistical analysis and power-calculation” the NNT to evaluate for superiority in chronic pain is 131, but 451 to test for non-inferiority of recurrence rate which makes 451 the total NNT for the BIOLAP protocol.

Comment 2: The liberal use of glue for fixation opens another door for the interpretation of the data and potentially alters the number needed to treat for each hernia mesh. In the Guidelines ref. 17. it is proposed to use fixation of hernia meshes with a small overlap or those bridging large hernia sizes Since both endpoints might be influenced by Fixation, this technical aspect should be standardized.
As stated under “Intervention”, we demand participating centers to operate in accordance to IEHS-guidelines. This includes using fixation especially in size three hernias and to choose sufficiently large, overlapping meshes as you are correctly pointing out. During the study group meetings several participating centers agreed with you on the need to stress the usage of fixation for size three hernias, so we added a consent to our requirements. We edited the “Intervention” paragraph accordingly and also stressed that if fixation is used, both meshes have to be fixated even if the other side is of smaller hernia size.

The usage of fixation is an intensively discussed topic in between the participating centers with strong arguments for and against a more standardized implementation. It isn’t possible to reach consent on the exact indications for mesh fixation in between more a dozen high volume hernia centers, which we must agree with you would have been a bonus for further statistical analysis. We do not research the effect of fixation on recurrence or pain though. Due to the study design there will be an exact equal number of fixated (or unfixated) biological and synthetic meshes allowing a good comparability of both mesh types.

Comment 3: The technical procedures during surgery may be crucial as stated above. Therefore, an objective assessment of the operative results, e.g. a photo of the placed mesh with a scale, to document the final mesh: defect area ratio, the overlap or the area for fixation or other should be used rather than the subjective description of the surgeon.

In principle we do not see any need for additional proof of operative accomplishments other than the usual intra-hospital documentation and the CRF signed by the surgeon. All documentation, digital and paper based, gets periodically and in detail checked by our monitoring and compared for mistakes and contradictions. Furthermore if a surgeon commits technical variations those will concern as well a biological mesh as a synthetic mesh (as he/she is required to handle both sides equally) and therefore will be equalized by randomization.

Comment 4: The technique used for the follow-up might be crucial for the results as well. The manuscript gives in ln 53/160 "a clinical follow-up visit" and "an assessment of endpoints". The structure of the visit and the methodology for the assessment of endpoints was not found by this reviewer in the text. A phone call or a structured clinical assessment will have different recall and outcomes. The decription in ln 57-59/ 162-3 pg. 6 reads: "If a hernia recurrence is suspected, a verification with ultra sound, MR or CT-scan must be performed." The level of suspicion will be different in an interview on the phone performed by a technician and in a clinical examination by an experienced surgeon.

Thank you for pointing this out, we changed the paragraph under “Design/ setting/ participants” accordingly.
Comments from Reviewer 2

Dear Prof. Dr. Köckerling,

We thank you for your support of our manuscript.

Comments from Reviewer 3

Dear Dr. Zwaans,

Thank you for your thorough review, we gratefully integrated almost all recommendations in the manuscript and hope we can answer your annotations equally profoundly.

Comments Section 1: Background

• We revised the manuscript according to all your suggestions.

Comments Section 2: Methods/Design:

1. Why is the time point of six months chosen as a primary outcome for pain?

• As chronic groin pain is defined as persisting pain AFTER 3 month (cf. “Nerve management and chronic pain after open inguinal hernia repair: a prospective two phase study“, Reinpold WM, Nehls J, Eggert A, Ann Surg. 2011 Jul; 254(1):163-8.) we chose the first follow-up after this time span to test for the primary endpoint of pain.

2. Are data on other pain syndromes (e.g. headache, (lower) back pain etc) also collected?

• We explicitly ask for pain in the inguinal area only and do not collect further data on other pain syndromes.
3. How is the sequence generation determined and allocation concealment secured? Who is called for the randomization and how is this randomization performed (by computer, by person)? Is block randomization performed (e.g. by centre)?

• Thank you for your detailed question. We included a separate paragraph to elaborate randomization and allocation.

4. Is the type of hernia also documented, as this may influence the chances on a recurrence?

• It is documented using EHS-classification; we edited the paragraph “Intervention” to include this information.

5. I assume pain as an outcome measure is a quantitative measure on the level of an individual patient instead of a qualitative (binary) outcome measure (yes/no), as the VAS scale is used to quantify pain. Consequentially, the primary outcome measure is not the incidence but for example, the mean or median pain intensity in the group?

• In fact we use the pain intensity measured by VAS as primary endpoint. Therefore, we changed ‘incidence’ to ‘intensity’ in line 228. However, since many patients are expected not to have pain at all, the incidence is also an interesting question of this trial, but this will be evaluated as a secondary endpoint.

6. If you will use pain as a continuous outcome measure (quantitative) you will use the paired t-test or the Wilcoxon signed ranks test? If so, please adapt the sentence of page 7, line 188.

• We will be using Wilcoxon signed rank test, we added the information to the paragraph.

7. Please clarify the second paragraph in the 'Statistical analysis and power calculation' section. Do you have any literature or references to assume that the standard deviation of pain at different end points is different? I understand that pain at later follow-up points may be lower, but this does not automatically mean that the standard deviation is different.

• Our institute (IFOM) together with the surgical department of the Cologne-Merheim Medical Center performed multiple studies (randomized as well as observational) since the 1990s when the laparoscopic cholecystectomy was introduced in Germany. We developed a Chronic Pain Prevention Screener and published several clinical reports. Routine VAS or NRS (Numeric Rating Scale) documentation has been implemented in the hospital since the mid 1990s. So there
is plenty of experience in handling VAS data as well as developing study protocols with pain as an endpoint. The trial statistician has published 14 articles (as co-author) dealing with pain (title word).

In the present study the primary outcome parameter is pain measured with VAS. In order to reach a SD of 1.5 or 2.0 you need a considerable number of patients with pain values above 5 which is often used as a threshold for pain medication. This is not the case here. Pain at follow-up after hernia surgery is almost always less severe than VAS 5. Thus it is only theoretically possible to reach a SD of 2.0 when pain values were less than 5 (for example if half of the patients would have zero pain while the others have 4 points). The assumptions that we made for sample size calculation were thus rather realistic. The assumption of SD 1.5 is furthermore a conservative one.

8. You can only state that data are not normally distributed if calculated by, for example, skewness and kurtosis. Please analyze the data for its distribution before choosing the appropriate statistical test.

- Using parametric statistics like t-test etc. would not necessarily require a normal distribution. However, the converse is true: IF the data were normally distributed, THEN parametric testing would be optimal. But simulation studies have shown that even in distributions that deviate somewhat from the Gaussian one, the parametric tests would work quite well. Therefore, it is recommended to have an ‘approximate normal distribution’ when using t-tests. However, we changed the respective word in the text (line 258) from symmetrically to normally distributed.

9. Why do you expect the biological mesh to have a lower recurrence rate? Based on what data c.q. theory?

- We don’t expect biological meshes to have a lower recurrence rate as stated in our hypothesis. Köckerling et al. reported in their 2015 review of literature an equivalent recurrence rate (see “Background”), which is why we test recurrence for non-inferiority of biological meshes. We elaborated the according paragraph to add more detail.

10. Perhaps you can consider to perform a subanalysis for different types of meshes (i.e. different types of biological meshes and different types of synthetic meshes) and for endoscopic (TEP) versus laparoscopic (TAPP) repair. Previous studies have shown differences in recurrence rates and adverse events of different types of meshes.
• Thank you for the suggestion. We are considering various subanalysis, also for mesh types, even tough we must point out the trial was not designed for a statistically pure comparison of several mesh types/products - with the NNT stratified for just a comparison of the two material types.

11. Page 6 line 155: please remove the word main (main exclusion criteria)
• The mentioned exclusion criteria are only the main ones, we included a list of all inclusion and exclusion criteria in the manuscript.

Comments Section 3: Discussion
1. Please discuss some of the assumptions in the method section with up-to-date literature.
• We included more references concerning the statistical design of self-control and searched for comparable trials with VAS analysis.

2. Page 10 line 257/258: Please add a reference to the statement that 30% of patients suffer from bilateral herniae
• We included the reference for the statement.

Comments from Reviewer 4

Dear PD Dr. Reim,

Thank you for your detailed comments and thoughtful questions. We revised the manuscript according to your suggestions.

Comment 1: Are there any other secondary endpoints, which were not mentioned in the manuscript?
• There are no other secondary endpoints than local pain at other follow-up points in time, complications due to surgery (e.g. infection, mesh dislocation), hematoma, seroma, patient satisfaction and recurrence rates at other points of time, local foreign body sensation and somatosensory alterations.

Comment 2: Please discuss in more detail why two primary endpoints were chosen, which is possibly difficult to interprete when finally analyzing the data.

• Thank you for pointing this out. We felt the need to compare both chronic pain and recurrence rate as they are the most challenging problems in hernia surgery. Only analyzing chronic pain rate as primary endpoint would not have been sufficient to evaluate possible benefits of biological meshes – of what use would a lower pain rate be for patients if they suffer from significant more frequent recurrence? We revised the discussion of endpoints to be more detailed.

Comment 3: Please discuss the study design more extensively in the light of current evidence. Why is open repair ruled out for example?

• We decided to limit the trial to laparo-endoscopic procedures as this reflects the strong recommendation of this year’s HerniaSurge Group Guidelines for treatment of bilateral primary inguinal hernias. In TEP and TAPP the mesh is placed in the same topographic anatomical plane. TEP and TAPP, other than open repairs, share similar recurrence rates, (overall) complications risks as well as a similar acute and chronic pain incidence (https://doi.org/10.1007/s10029-017-1668-x). The paragraph was edited accordingly.

Comment 4: Please indicate that no commercial sponsoring is taking place. It is almost ruled out due to the fact that the study is sponsored by German Research Society. However, a company’s financial interest is not negligible in this case.

• We added the paragraph “funding” accordingly.

Comment 5: Please provide the Ethics Board Statement. Is there an official clearance from authorities? Due to the randomized design it is conceivable that the study will fall under medicinal devices legislation even if there is a CE mark.

• The Ethical approval was and is added to the submission. As stated in the “Declarations” section and according to the German medical devices act the trial is classified as an exception to
clinical investigations according to section 23b, due to the fact that the investigational device is CE-marked and will only be used within intended purpose. Therefore there is no need for authority approval.

Comment 6: Please describe how surgical quality is ensured. Even if only certified hernia centers are allowed to participate the study, surgical differences might play a certain role.

• You raised an important point here. We ensure surgical quality only by limiting participation to hernia centers. Occurring surgical differences won’t interfere with the results, as every difference in technique will affect as well one biological and one synthetic mesh side and won’t affect the comparison of the two mesh types. As guidelines stress the importance of the tailored approach we do not think it is possible to convince 20 specialized hernia centers to complete the operations in exactly the same technique. By referring to the IEHS-guidelines we try to ensure best possible comparability. We modified the “Intervention”-paragraph to be more detailed, especially about the usage of fixation, which is an intensively discussed topic during multicenter study group meetings.

Comments from Reviewer 5

Dear Dr. Hüttner,

Thank you for your structured review and helpful remarks. We modified the manuscript according to most of your suggestions and hope to meet your expectations.

Comment 1: The manuscript needs some language editing. I would recommend revision by a native speaker.

• The manuscript was revised and corrected by two native speakers.

Comment 2: I would recommend to use the term "trial" throughout instead of "study" for the current research.

• We changed the manuscript accordingly.
Comment 3: Title: I would recommend to include the word "inguinal" or "groin" in the title to clarify what types of hernia are considered within the trial. In the current form, one could not tell if the trials assess groin hernia repair or e.g. ventral hernia (by laparoscopic IPOM technique).

• Thank you for pointing this out, we modified the title to be more specific!

Comment 4: Abstract: The abstract needs some substantial rework since it reports some information that is not necessary in an abstract whereas it omits some points that should be mentioned (e.g. principal eligibility criteria, setting/what type of hospitals, randomization details etc.). Even though the current manuscript is not a report of results, I would recommend the authors to orient themselves e.g. in the CONSORT extension for abstracts of trials assessing non-pharmacological interventions, regarding what needs to be reported in the abstract and what does not need to be reported here.

• We worked over the abstract to ensure compliance with all demands of trials as well as best possible accordance with the CONSORT check list within a 350 word limitation.

Comment 5: Abstract: The last two sentences of the discussion are basically the same. Please delete one of them.

• We deleted one sentence according to your correct finding.

Comment 6: Background: I would recommend moving the first paragraph of this section to the end of the section. The background section should lead the reader towards the objective of the trial not start with the objective.

• Thank you for the suggestion. We moved the paragraph to the end of the section.

Comment 7: Background 3rd paragraph: in the description of treatment options for inguinal hernia, the authors should also mention watchful waiting, which represents a viable treatment option especially for oligosymptomatic groin hernia in men. Another option would be to revise the sentence to clarify that the authors only list the surgical treatment options e.g. "if surgical treatment is indicated/planned, patients can be treated by either primary open repair, ....".

• We agree with your finding and corrected the manuscript to state that the presented options are for already indicated surgical treatment only.

- Comment 8: Background 4th paragraph: the authors should reconsider their literature search: they state that only one study compares biological to synthetic mesh in open inguinal hernia repair. This is not true; to my knowledge there are at least 4 RCTs comparing biological mesh to synthetic mesh in open inguinal hernia repair and even a meta-analysis of these trials (Fang et al. ANZ J Surg 2015; PMID: 26183816). Furthermore, some of these trials and the meta-analysis
showed a significantly higher rate of seroma formation in the biologic mesh group. This should also be mentioned as potential disadvantage of the biological mesh group.

• We must agree in both points; we corrected the paragraph and references. Thank you for your reference suggestion, which we gladly included.

Comment 9: I would recommend to separate the combined headers (e.g. "aim of the study/primary and secondary outcomes") to e.g. "aim of the trial" next header "primary and secondary endpoints"). Furthermore, I would recommend to adapt the order of the points to the usual and widely accepted order, for example: aims, trial design, participants/eligibility criteria, randomization/operations for minimising bias such as blinding etc, interventions, outcomes, safety measures, sample size, statistical analyses...Additionally, the authors mix it up in some parts, for example mentioning some details of the randomization (telephone-based randomization) in the "Intervention"-section instead of the "Design"-section

• We separated the paragraphs "Aim of study" and “Outcomes” as suggested. We worked over the intervention section including a separate randomization and safety paragraph to adapt to your suggested order.

Comment 10: Methods: The current description of trial specific features is insufficient. How was the random sequence generated, how was allocation concealed? Were only patients blinded or also outcome assessors, statisticians etc.?

• We added to our description of methods and included more detailed information as requested.

Comment 11: Methods: Since the trial is already recruitin, the participating centres should be stated explicitly in the methods section.

• The list of participating centers is openly published at the German Clinical Trials Register. We discussed your demand in our study group and decided to publish the final list of participating centers with the results in order to include further participating study centers.

Comment 12: Methods/Intervention: Glue fixation is left up to the discretion of the individual surgeon/Center. If glue fixation is performed, is it prespecified that it has to be performed on both sides in the individual patient? If not this may represent a relevant source of bias.

• The original test plan did not state it, but according to a consent from the first study meet, if any fixation is used, the same fixation has to be used on the other side, even if the hernia is significantly smaller. We revised the paragraph accordingly.

Comment 13: Methods: Considering the primary endpoint: Is it planned to assess whether patients are dependent of pain medication? Since the trial is self-controlled this should not have a major impact on the primary endpoint; nevertheless, it would still be interesting and relevant to
know how many patients are still dependent on pain medication due to groin pain at the individual points of time.

- It is not planned to assess dependence of pain medication as it doesn’t add information to the comparison of the biological mesh on the one side and the synthetic mesh on the other side (as pain medication influences both VAS numbers).

Comment 14: Methods: The sample size calculation for the primary pain endpoint is based on a difference of 0.5 points on the VAS scale. How clinically relevant would the authors judge a difference of 0.5 in VAS? Could you provide any literature discussing clinical relevance of the amount of change in VAS?

- Our institute (IFOM) together with the surgical department of the Cologne-Merheim Medical Center performed multiple studies (randomized as well as observational) since the 1990s when the laparoscopic cholecystectomy was introduced in Germany. We developed a Chronic Pain Prevention Screener and published several clinical reports. Routine VAS or NRS (Numeric Rating Scale) documentation has been implemented in the hospital since the mid 1990s. So there is plenty of experience in handling VAS data as well as developing study protocols with pain as an endpoint. The trial statistician has published 14 articles (as co-author) dealing with pain (title word).

A colleague has also investigated the minimal amount which is relevant for the patient. Since his publication was only in German and nearly 20 years old, we did not cite this paper. Here is the reference:


Comment 15: Methods: On the other hand I have concerns about the sample size assumptions for the recurrence endpoint. The authors set a non-inferiority margin of 3%; considering the expected frequency of 5% recurrences during 2 years of follow-up this would represent a 60% increase of recurrent hernias. As frequency of recurrences increases over time it could be possible that the gap between the two procedures would even grow over time to an even larger amount.
This assumption has been discussed several times with the clinical colleagues and the primary investigator. You could present the difference of 5% vs. 8% as a 60% increase. This is correct from the calculation. But it does not reflect that the absolute incidence of a recurrence is rather low here. The present decision has been set based on the clinical relevance. The present trial has been approved by the German Research Council (DFG) who extensively reviewed the grant application (also by a statistician). They have accepted these assumptions.

Comment 16: Methods: More detail should be provided for secondary endpoints, e.g. complications: which complications will be assessed? how are they defined?

• We changed the manuscript to be more detailed.

Comment 17: How are safety aspects managed within the current trial? Is there some kind of serious adverse reporting? Is there a DSMB or comparable board overseeing safety and conduct of the trial?

• We added a paragraph for trial safety with the demanded information.

Comment 18: The self-controlled design of the trial has several clear benefits, but one major confounding factor is not adjusted for by the current design: it is well known that several preoperative factors represent risk factors for postoperative pain such as preoperative groin pain or size of the hernia (c.f. Magnusson et al. Surgery 2014; PMID: 23973111). Patients with bilateral hernia usually do not have the same preoperative symptoms or hernia size on both sides. In fact in a lot of cases the contralateral hernia is only discovered incidentally during the preoperative work-up. Randomization cannot completely adjust for that and this fact is not considered in the analysis. Considering the worst case scenario if by chance one type of mesh will in most cases be randomized to the symptomatic side, this could substantially distort the results and limit their validity.

• In fact we realized that hernia size may have an influence on pain and other aspects like recurrence. However, since we randomize the side (right or left) it could be assumed that larger and smaller hernias were distributed approximately evenly in the sample.

An imbalance might be a relevant point when the overall sample size is small. This is not the case here. As with other measurable and non-measurable confounders we trust in the methodology of random allocation rather than to introduce additional methods.
A stratified randomization will be performed for each center. A further factor for randomization (like hernia size) might only be possible in a few large centers, and would fail in smaller hospitals.

Comment 19: SPIRIT checklist: the authors filled the checklist with "not applicable" in several places. In my opinion most of these points are applicable to the current trial (e.g. "role of the sponsor and funder", "relevant concomitant care" -> e.g. glue fixation, "unblinding options", "data collection methods", "confidentiality/data protection"...). I would request the authors to substantially revise the checklist an the manuscript considering the checklist respectively. Some points are already addressed in the text and just need to be filled in the checklist and others need to be amended to the text.

- Thank you for pointing this out. We thoroughly went through the SPIRIT checklist minding your concerns and reconsidered every point. We added information on every point possible in the manuscript, especially on the points you listed.

Comments from Reviewer 6

Dear Prof. Dr. Fortelny,

Thank you for your constructive revision and helpful annotations. We were able to implement most suggested changes:

Comment 1: the title of this paper should include anyhow the item of inguinal or groin hernia repair - since TAPP- or TEP-technique is possible the title should be changed into ...in laparo-endoscopic inguinal hernia repair

- Thank you for pointing this out, we changed the title and wording accordingly.

Comment 2: missing: Tables of inclusion and exclusion criteria

- We added a table of all inclusion and exclusion criteria.
Comment 3: What kind of hernia classification will be used - EHS? Which kind of pain assessment will be used VAS or NAR or other?

- The EHS classification and the VAS are used, we added that information to the manuscript.

Comment 4: Is there any kind of QoL-assessment included in the study?

- No, as any limitation to quality of life would most likely not be linkable to the left or right side only (and therefore the mesh type) we decided not to include any QoL questionnaire.

Comment 5: "Additional glue fixation may be used" in the biological mesh group - in which cases? In case of big size medial hernia (> 3cm) the Guidelines of the EHS and HerniaSurge recommend to use a fixation. in the protocol no statement can be found concerning this crucial part of procedure.

- We agree that our original manuscript wasn’t very detailed in that question. We revised the paragraph to be more specific. We pay special attention to accordance to the Hernia Surge Group and EHS Guidelines and ask our clinical investigators to stick to the IEHS guidelines, especially concerning fixation of size three herniae. If fixation is used, it has to be used on both sides, left and right.

Comment 6: using two different techniques (TAPP and TEP) might be a risk of bias concerning the primary endpoint of pain.

- We discussed this question intensively while designing BIOLAP. As stated in this year’s HerniaSurge guidelines (https://doi.org/10.1007/s10029-017-1668-x) “TEP and TAPP have similar …. overall complication risks, postoperative acute and chronic pain incidence and recurrence rates” (cf. Bansal et al., Surg Endosc. 2017 Mar;31(3):1478-1486). As our study focus is on the comparison of two mesh types, not the different operation techniques, we do not expect much bias to our results by allowing both techniques.

Comment 7: what kind of preop. investigation to confirm the bilateral inguinal hernia is a precondition to include the patient?

- We don’t specify how the participating centre confirms their diagnosis, as according to the up to date HerniaSurge Group “International guidelines for groin hernia management” only patient
history and clinical examination are needed for diagnostics. Further imaging is only needed if seen as indicated by the clinical investigator.

Comment 8: is there any kind of intraop. documentation of hernia, mesh placement or fixation intended?

• Documentation is done via operation report and the usual operation documentation, as well as the signed CRF. Monitoring also checks digital documentations (like scanned product numbers). We do not ask for e.g. intraoperative photography as a proof of diagnosis and procedure.

Comment 9: what kind of structured perioperative pain medication is planned to reduce the risk of bias?

• We decided against structured perioperative pain medication as systemic pain medication doesn’t influence the comparison of the biological mesh on the one side and the synthetic mesh on the other side. Systemic pain medication has to be expected to influence the VAS numbers of both mesh types equally and therefore this factor is equalized by randomization.

In addition to the above comments, all spelling and grammatical errors pointed out by the reviewers have been corrected.

We look forward to hearing from you regarding our submission and to respond to any further questions and comments you may have.

Sincerely,

C.S. Seefeldt
J. Knievel
R. Lefering
M.M. Heiss