Author's response to reviews

Title: Development of a clinical trial to determine whether watchful waiting is an acceptable alternative to surgical repair for patients with oligosymptomatic incisional hernia

Authors:

Johannes C Lauscher (johannes.lauscher@charite.de)
Peter Martus (peter.martus@charite.de)
Andrea Stroux (andrea.stroux@charite.de)
Jens Neudecker (jens.neudecker@charite.de)
Uwe Behrens (uwe.behrens@charite.de)
Jörg-Peter Ritz (joerg-peter.ritz@helios.kliniken.de)
Heinz J Buhr (heinz.buhr@charite.de)

Version: 3 Date: 15 November 2011

Author's response to reviews: see over
Cover Letter

**Title:** Development of a clinical trial to determine whether watchful waiting is an acceptable alternative to surgical repair for patients with oligosymptomatic incisional hernia

Dear Ladies and Sirs,

Please find our revised version of the manuscript MS: 3982640935922752 entitled “Development of a clinical trial to determine whether watchful waiting is an acceptable alternative to surgical repair for patients with oligosymptomatic incisional hernia”.

First we want to thank the reviewer for the comments that helped us to substantially revise and improve our manuscript. According to the reviewer`s suggestions we amended the manuscript (see below).

Due to the fact that many incisional hernia repairs are performed laparoscopically (IPOM), we will also include laparoscopic repair in the analysis. We have altered the study protocol. The revised protocol and patient information is already accepted by the local ethics committee. We have changed the corresponding passages in this manuscript and highlighted these changes in red.

In the following, we give a point-by-point response to the reviewer`s concerns. We have highlighted all changes in the revised manuscript in red.

The following changes have been included:

**Reviewer #1.**
1. Done.
2. We have toned down the wording of the manuscript (P 4, p 4, l 1; P 14, p 2, l 1) and provided details of the literature search on page 7, p 3, l 1.
3. The term “incidence” was abolished and the sentence was rewritten (P 5, p 1, l 1).
4. Done.
5. “Recent nationwide” was replaced by “2009 Danish”.
6. A definition of “incarceration” is provided (P 5, p 3, l 2).
7. There is a statistical significance. The publication showing this significance is cited [5].
8. Done.
9. Done.
10. Done.
11. Done.
12. Done.
13. The passage was rewritten (P 7, p 5, l 2).

[0.5] is a small difference on the SPS. In the Fitzgibbons’ trial dealing with watchful waiting vs. repair in inguinal hernias; the baseline pain level was 10.3±14.9 in the surgical repair group and 10.4±14.9 in the watchful waiting group [Fitzgibbons et al, JAMA 2006]. The software used for sample size calculation was nQuery6.0.
14. To our knowledge, a power of 80 % is not unusual for an inferiority trial. A reference to justify this choice is: Garbe E, Röhmel J, Gundert-Remy U. Clinical and statistical issues in therapeutic equivalence trials. Eur J Clin Pharmacol. 1993; 45:1–7. This reference is added in the manuscript [18].
15. We agree to the reviewer’s calculation. Hence, we will write an amendment in the study protocol to randomize 6 more patients. The flowchart was modified according to CONSORT guidelines with the numbers of the current calculation (P 9, p 1, l 3; figure 1) and an additional reference [23] was added. If appropriate, the LOCF method will be used for missing data.
16. We added a description of the collection of the costs in the manuscript (P 8 p 2, l1).
17. Done.
18. Since testing is performed in a hierarchical setting, no multiplicity adjustment is needed for S1 and S2. All further results will be analyzed in an exploratory manner. Tests for the two main hypotheses will be one-sided.
19. Done.
20. Measurement properties of the SPS are given in P 7, p 4, l 7. The SPS consist of 4 questions with visual analog scales. The outcome measures of the questionnaires are now documented with references to the German versions and measurement properties (P 8, p 4, l 4).
21. Done.
22. The acute incarceration is a diagnosis based on history taking and physical examination. Signs of the acute incarceration are strong pain and an irreducible hernia. Additional signs may be symptoms of a bowel obstruction like vomiting and no passing of stools. This acute incarceration can be diagnosed by a certified surgeon without special diagnostic procedures. Fitzgibbons et al. documented 2 events of acute incarceration in their trial about watchful waiting in inguinal hernia. We added Fitzgibbons’ reference in the manuscript (P 9, p 2, l 2).
23. Done.
24. We applied the CONSORT format in figure 1.

25. The functionality of the electronic random tool was shown in several randomized trials. These data is saved. The validation of the random tool is not yet published. In an addendum, we send you the test data of the AWARE trial (AWARE_Testdaten_.zip).

26. Since sample size calculation is based on a patient spectrum comparable to our study population, stratification will rather lead to lower variances within the strata.

27. Controlling for potential confounders will be performed by using multiple statistical models adjusting for these variables. Additional subgroup analyses considering hernia size, operation method and study center are planned (see appendix “statistical analysis”).

28. Done.

29. The measures are defined and references are provided (P 11, p 3 and P12, p 1).

30. All analyses will be ITT as well as as-treated. The software will be SPSS. We included the SAP as an appendix (see appendix “statistical analysis”).

31. The date of registration in ClinicalTrials is given (P13, p 2, I 2).

32. The source document of the eCRF (50_SourceDokumentation.pdf) and the test data of the random tool (AWARE_Testdaten_.zip) were added.

33. Done.

34. Done (P 13, p 6, l 4).

35. Done.

36. The 16 centers are listed in the revised manuscript (P 13, p 3, l 2). A list of abbreviations was created (P 18). All authors of the cited references are now published.

37. Added P 13 R 2: Website accessed on October 20, 2011.

38. Done.

39. Done.

40. Done.

41. Done.

42. Done.

43. Done.

44. Done.

45. The erratum in 2005;201(5):826 is about a missing attribution and has no relevance for the SPS.

46. Done.
We hope that this substantial revision of our manuscript now adds sufficient new information to allow publication in “Trials”.

Yours sincerely,

Johannes Lauscher