Author's response to reviews

Title: Pancreatogastrostomy versus pancreateojejunostomy for REConstrucion after partial PANCreatoduodenectomy - A randomized controlled trial (RECOPANC)

Authors:

Ulrich F Wellner (dr.ulrich.wellner@gmail.com)
Sabine Brett (sabine.brett@uniklinik-freiburg.de)
Thomas Bruckner (bruckner@imbi.uni-heidelberg.de)
Ronald Limprecht (limprecht@imbi.uni-heidelberg.de)
Inga Rossion (inga.rossion@med.uni-heidelberg.de)
Christoph Seiler (christoph.seiler@med.uni-heidelberg.de)
Olivia Sick (olivia.sick@uniklinik-freiburg.de)
Inga Wegener (inga.wegener@med.uni-heidelberg.de)
Ulrich T Hopt (ulrich.hopt@uniklinik-freiburg.de)
Tobias Keck (tobias.keck@uniklinik-freiburg.de)

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Author's response to reviews: see over
Dear Members of the Editorial Board,
Dear Professor Goldsmith,

Hereby we submit the second revision of our manuscript.

Again, we are grateful for a professional review and include point-by-point answers to the reviewer’s comments below. We have again revised the manuscript and paid special attention to add more explanations and references to avoid uncertain points of interest.

With our second revision, we hope to meet the high standards for publication in Trials.

Sincerely yours,

Prof. Dr. med. Tobias Keck; MBA FACS FEBS
Senior Author
Reviewer’s Comments and Point-by-Point Answers

While the answers to the reviewer comments from the first review look sensible apart from the sample size expansion due to centers, the revised text looks as if nobody has read it over for sensibility. This should have been done. There are now a new set of issues that should be considered by the authors. The pages in the revised protocol have been numbered from 1 to 18.

1. Page 2, paragraph 1, line 6. Delete [have].
The desired changes were applied to the manuscript

2. P 2, p 3, l 1. Replace [significant] by [clinically important].
The desired changes were applied to the manuscript

3. P 4, p 5, l 17. Given that different centers may have different standards for determining serum amylase activity, and this could make the 3 times upper limit of normal different by center, it is more important to stratify by center and hence inflate the sample size by the number of centers to accommodate this adjustment in the analysis.

The ISGPS definition of pancreatic fistula requires the use of the threefold upper normal value of serum amylase activity as a cutoff to define fistula on day three postoperatively. The upper normal value slightly varies between different laboratories by very small amounts (e.g. 100 +/- 2 U/l). To satisfy the ISGPS definition to the very detail, the respective upper normal value for each center is used. This issue is not a matter of highly differing standards for determination of serum amylase activity; rather a maximal correctness in outcome assessment to the smallest detail is achieved. It would probably also be valid to simply define 300 U/l as the cutoff. In addition, the purpose of this cutoff is to detect EVERY pancreatic fistula, especially fistula of grade A which is “only” a laboratory diagnosis and has been shown to have no impact on treatment or health care costs [1]. The primary endpoint of this trial is therefore not grade A fistula but the clinically relevant grade B or C fistula. For those fistulae, drain amylase activity fairly exceeds 1000 U/l.

In summary, regardless of the described cutoff, every fistula constituting the primary endpoint will be detected. Minimal differences of upper normal values in serum amylase activity are completely irrelevant to the primary endpoint but still are paid consideration for assessment of one of the secondary endpoints, POPF grade A. The mention of these details has been omitted from the manuscript as it generates unnecessary confusion to the reader.

It has been demonstrated by others that hospital case number positively affects outcome in pancreatic surgery [2]. In our trial, this bias is minimized by inclusion of high-volume academic centers only. Nevertheless, the center effect is given consideration by including center as a covariate in the final analysis. It can be assumed that inclusion of relevant covariates increases the power of the trial [3], hence the sample size does not have to be increased for the number of centers. Furthermore, in a review of the literature, we were not able to find a reference to support the reviewer’s suggestion to increase the sample size for the number of centers.
The desired changes were applied to the manuscript.

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In a randomized trial of PG versus PJ performed at our institution, there was no patient lost to follow-up in n=116 patients (Wellner, Keck et al.; manuscript submitted to Annals of Surgery). A multicenter trial of PG versus PJ from France reports that out of n=149 randomized patients, no patient was lost to follow-up regarding the endpoint POPF [4]. A similarly designed multicenter trial of pancreatic left resection initiated from Germany included POPF in a mixed primary endpoint and reports none of n=352 randomized patients was lost to follow-up [5]. Accordingly, this explanation and the references were added to the manuscript.

The standard ITT principle will be applied (i.e. no “modified” approach [6, 7]). As already mentioned in the manuscript, patients not receiving a pancreatoduodenectomy (for inoperability or other operations) will be excluded. Inclusion of these cases in the analysis does not make sense as neither “control” (PJ) nor “intervention” (PG) is performed. Accordingly this explanation and the references were added to the manuscript.

Apart from the 14 plus centers, how many levels of age, levels of surgical experience, and texture of pancreatic tissue will be used in the analysis. As long as there are no interactions of these adjustments with treatment, the levels should be used to expand the sample size to accommodate these features.

Age is a continuous variable, surgical experience is an ordinal variable of three possible grades, and pancreatic texture is assessed dichotomous as hard or soft. These variables are proven to be of relevance (risk factors) to outcome (i.e. the primary endpoint) [2, 8] and are given consideration by inclusion as covariates in the final analysis. As already stated in the manuscript, it can be assumed that inclusion of covariates with proven relevance increases the power of the trial [3]. As already mentioned, in a review of the literature, we were not able to find a reference to support the reviewer’s suggestion to increase the sample size for the number of centers. An explanation and references were added to the manuscript.
9. P 6, l 4, l 9. How many of the patients are expected to have a soft pancreas? Is it possible to stratify on this fact prior to randomization? This ensures close balance in each level of this factor. This could have an impact on the subgroup analysis and whether it will be statistically significant. It is important that the interaction between pancreatic softness and treatment be also tested for to provide a valid subgroup analysis. The authors should provide a reference to the principles they are using for this subgroup analysis.

From our experience [8], about half of the patients can be expected to have a soft pancreas. This can only be assessed by direct intraoperative palpation of the pancreatic remnant, so stratification prior to randomization (which is performed preoperatively) is not possible. The subgroup analysis will include statistical testing for interaction [3] analogous to the primary endpoint analysis. Still the results of subgroup analysis will have to be interpreted with caution. An explanation and references were added to the manuscript.

The desired changes were applied to the manuscript

11. P 7, p 3, l 7. Delete [and/].
The desired changes were applied to the manuscript

12. P 7, p 5, l 3. Provide references to these guidelines.
The desired changes were applied to the manuscript

13. P 7, p 6, l 4. Is there a reference or website that describes the features of this software? If so, provide it.
The desired changes were applied to the manuscript

The desired changes were applied to the manuscript

15. P 8, p 3, l 6. Suggest deleting [appropriate]. This will not be known until after if is done!
The desired changes were applied to the manuscript

16. P 10. Both [EDC] and [ICAr] are missing from this list.
The desired changes were applied to the manuscript

17. P 16, references 20 and 23. The [square brackets] should be around the English translations of the titles and the [German titles] in square brackets as well as German titles for each of these references should be deleted
The desired changes were applied to the manuscript
References


