PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Multicenter randomized controlled trial of balloon pulmonary angioplasty and riociguat in patients with chronic thromboembolic pulmonary hypertension: Protocol for the MR BPA study
AUTHORS	Kawakami, Takashi; Matsubara, Hiromi; Abe, Kohtaro; Kataoka, Masaharu; Kohsaka, Shun; Sato, Yasunori; Shinke, Toshiro; Fukuda, Keiichi

VERSION 1 – REVIEW

REVIEWER	Coghlan JG Royal Free Hospital London UK
REVIEW RETURNED	21-Jan-2019

GENERAL COMMENTS	This is a descriptive paper of a study that is underway. The study started in 2016, so it is quite late to attempt to publish the study proposal., however as the study appears to be still recruiting this may be acceptable. The claim is made that this is the first randomised study of BPA v Riociguat, however as the funders of this study are well aware there is a competing parallel study (RACE; NCT02634203) started at the same time (Jan 15th 2016), so not even mentioning this larger trial seems odd. Secondly it is unclear why this study is not registered with Clinicaltrials.gov. The open label nature of the trial creates a bias, in that the BPA operators are incentivised to continue pursuing a very low mPAP even if this is not in the clinical interest of the patient. This is not an intention to treat trial (those stopping riociguat will be treated as drop-outs), Whether a similar approach might be taken to BPA candidates (continuing the study is deemed a risk to the patients health) is unclear. Consenting procedures in the trial manual appear more robust than described in the paper (page 7 line 60). While there is clarity on how operable patients are defined, there is a lack of clarity that inoperability does not indicate suitability for BPA. Thus there appears to be no second step where the suitability of the candidate for BPA is assessed - generally only around 1/3 inoperable patients have sufficient targets for BPA in our population. The frequency of CT scanning seems unnecessary. The baseline data on which the mPAP is defined creates another risk. As catheters performed prior to screening are acceptable, it should be clear that the same baseline catheter will be used for both groups. If the Riociguat patients were assessed on a catheter performed some weeks/months before inclusion, while the BPA patietns - will by definition have a baseline catheter at the time of

	first treatment - there is the potential that an increase in mPAP between the first and second timepoints biases in favour of the BPA group. I think it is reasonable to publish this, but there should be clarity on what this study will add to the knowledge base in light of the RACE trial, and slightly greater clarity on how biases will be minimised given that this is an open label trial with much greater knowledge of how close one is to achieving the primary endpoint in those undergoing BPA.

REVIEWER	Dr. C. B. Wiedenroth Department of Thoracic Surgery Kerckhoff-Klinik Bad Nauheim, Germany
REVIEW RETURNED	10-Feb-2019

GENERAL COMMENTS	The reviewer thanks the editor for the opportunity to review the manuscript entitled “Multicenter randomized comparative trial of balloon pulmonary angioplasty and riociguat in patients with chronic thromboembolic pulmonary hypertension: Rationale and design of the MR BPA study”, giving the chance to proactively comment on an important trial in the field of chronic thromboembolic pulmonary hypertension (CTEPH). Pulmonary endarterectomy (PEA) surgery is the goldstandard treatment for CTEPH patients. However, around 1/3 of all patients are not operable, usually because of a peripheral localization of pulmonary arterial lesions. For these inoperable cases, the optimal treatment concept is still a matter of debate: riociguat is approved in this indication and recommended by current guidelines. The evidence is strong with existing randomized, controlled trials. On the other hand, balloon pulmonary angioplasty (BPA) has evolved in the last couple of years as an interventional treatment for inoperable CTEPH patients, but the evidence is less strong: controlled trials are outstanding, most studies are single center experiences and long-term data are scarce. This evidence led to a cautious recommendation by the guidelines. However, there is yet one study comparing initial medical therapy with riociguat and BPA on top, showing distinct further improvements after interventional treatment. The presented study hits an important and quite actual topic, but the reviewer is wondering, whether change of the mean pulmonary artery pressure is an appropriate primary endpoint. Another major concern is the assessment of operability, which is a key question in the treatment of CTEPH. Even today, it remains extremely difficult to define the borderline of what is amenable for surgery, and what distribution pattern of pulmonary artery lesions cannot be reached by surgery. In the end, it remains a question of the surgeons experience. Therefore, more than 20 PEAs per year and more than 40 PEAs in the last 3 years seems to be a debatable level of expertise. The introduction and discussion are somewhat confusing and the whole manuscript would improve by editing by a native speaker. Minor comments with regard to the manuscript: Introduction, page 5 line 5: “intractable” seems to be an inappropriate description of CTEPH.

	Introduction, first paragraph: The initial paragraph of the introduction is not really conclusive. Please reconsider wording. The references are insufficient, especially ref. 3 describes a very complex situation and cannot be used to underline, that PEA surgery is the goldstandard treatment for CTEPH patients. Introduction, page 5, lines 42 to 45: The reviewer thinks, that riociguat is the treatment of inoperable CTEPH. BPA may be considered in patients with target lesions for BPA. Said that, the statement should be: “the two treatment modalities for inoperable CTEPH are targeted medication with riociguat and BPA.” Introduction, page 5, lines 51 to 54: This is not correct. There is some data with regard to the results of medical treatment with riociguat and BPA in a sequential concept: “Sequential treatment with riociguat and balloon pulmonary angioplasty for patients with inoperable chronic thromboembolic pulmonary hypertension.” - Pulm Circ. 2018 You may introduce that study and use it for your discussion – it may strengthen your concept. Discussion: The text seems quite similar to the introduction. It is not conclusive and should be re-written.

VERSION 1 – AUTHOR RESPONSE

Responses to reviewer 1

The claim is made that this is the first randomised study of BPA v Riociguat, however as the funders of this study are well aware there is a competing parallel study (RACE; NCT02634203) started at the same time (Jan 15th 2016), so not even mentioning this larger trial seems odd.

We added the information of RACE study in the Introduction and Discussion sections.

Secondly it is unclear why this study is not registered with Clinicaltrials.gov.

Since this study is conducted in Japan, this study has been registered on University Hospital Medical Information Network Clinical Trial Registry (UMIN-CTR) according to the relevant regal regulations in Japan. UMIN-CTR is a non-profit trial registration in Japan that meets the requirements of the International Committee of Medical Journal Editors (ICMJE).

The open label nature of the trial creates a bias, in that the BPA operators are incentivised to continue pursuing a very low mPAP even if this is not in the clinical interest of the patient.

BPA is performed based on preoperative right heart catheterization and pulmonary angiography. This explanation is added in the study design section.
This is one of the limitations in this study. We added this limitation in the Discussion.
However, our protocol defines that BPA should be completed within 4 months. We think that this procedure is quite similar to that under real-world situation in Japan.

This is not an intention to treat trial (those stopping riociguat will be treated as drop-outs), Whether a similar approach might be taken to BPA candidates (continuing the study is deemed a risk to the patients health) is unclear.

If the lesions of pulmonary artery are not suitable for BPA treatment, BPA may not be performed. However, at least in the collaborative institutions in this study, almost no PEA-inoperable patients are unsuitable for BPA, because they are the expert BPA centers in Japan.

Consenting procedures in the trial manual appear more robust than described in the paper (page 7 line 60). While there is clarity on how operable patients are defined, there is a lack of clarity that inoperability does not indicate suitability for BPA. Thus there appears to be no second step where the suitability of the candidate for BPA is assessed - generally only around 1/3 inoperable patients have sufficient targets for BPA in our population.

If the lesions of pulmonary artery are not suitable for BPA treatment, BPA may not be performed. However, at least in the collaborative institutions in this study, almost no PEA-inoperable patients are unsuitable for BPA, because they are the expert BPA centers in Japan.

The frequency of CT scanning seems unnecessary.

For evaluating the presence/absence and extent of postoperative pulmonary injury, this study will perform chest CT scan after BPA.
As you know, the pulmonary injury was a big problem on BPA. We intend to assess the frequency and severity of the pulmonary injury after BPA in this study.

The baseline data on which the mPAP is defined creates another risk. As catheters performed prior to screening are acceptable, it should be clear that the same baseline catheter will be used for both groups. If the Riociguat patients were assessed on a catheter performed some weeks/months before inclusion, while the BPA patietns - will by definition have a baseline catheter at the time of first treatment - there is the potential that an increase in mPAP between the first and second timepoints biases in favour of the BPA group.

The right heart catheterization is performed at the screening. The result of the right heart catheterization at the screening is used as the preoperative data for BPA. As same in the riociguat group, no additional right heart catheterization is performed in patients in the BPA group.

I think it is reasonable to publish this, but there should be clarity on what this study will add to the knowledge base in light of the RACE trial, and slightly greater clarity on how biases will be minimised given that this is an open label trial with much greater knowledge of how close one is to achieving the primary endpoint in those undergoing BPA.

First of all, as you know, this study has been started at almost the same time with the RACE trial. The RACE trial is a competing parallel study. Therefore, the aim of this study is not to ADD knowledge over the RACE trial.
We added the strengths and limitations of this study in the Discussion.

Responses to reviewer 2

The presented study hits an important and quite actual topic, but the reviewer is wondering, whether change of the mean pulmonary artery pressure is an appropriate primary endpoint.

The principal investigator and the Central Committee in this study had discussed the outcomes in this study, and had decided the mean pulmonary artery pressure as the primary endpoint in this study, as the mean pulmonary artery pressure is one of the important prognosticators of CTEPH. Other outcomes often used in CTEPH, such as 6-minute walk distance and pulmonary vascular resistance, are also measured as the secondary endpoints in this study.

Another major concern is the assessment of operability, which is a key question in the treatment of CTEPH. Even today, it remains extremely difficult to define the borderline of what is amenable for surgery, and what distribution pattern of pulmonary artery lesions cannot be reached by surgery. In the end, it remains a question of the surgeons experience. Therefore, more than 20 PEAs per year and more than 40 PEAs in the last 3 years seems to be a debatable level of expertise.

The independent physician who determines the operability of PEA in this study is the most experienced PEA surgeon in Japan, who underwent 49 PEAs in the last 3 years, and total 320 PEAs. In addition, the operability of PEA is determined under blind circumstance by the independent PEA surgeon who belongs to independent institute. This will avoid bias on the subject enrollment.

The introduction and discussion are somewhat confusing and the whole manuscript would improve by editing by a native speaker.

We revised the Introduction and the Discussion sections.
The whole manuscript have edited by a commercial expert English editing service

Introduction, page 5 line 5:
“intractable” seems to be an inappropriate description of CTEPH.

We revised the sentence as CTEPH is a complication of pulmonary embolism.

Introduction, first paragraph:
The initial paragraph of the introduction is not really conclusive. Please reconsider wording. The references are insufficient, especially ref. 3 describes a very complex situation and cannot be used to underline, that PEA surgery is the goldstandard treatment for CTEPH patients.

We revised the references for PEA.

Introduction, page 5, lines 42 to 45:
The reviewer thinks, that riociguat is the treatment of inoperable CTEPH. BPA may be considered in patients with target lesions for BPA. Said that, the statement should be:
“the two treatment modalities for inoperable CTEPH are targeted medication with riociguat and BPA.”

We revised the sentence according to the reviewer 2’s suggestion.

Introduction, page 5, lines 51 to 54:
This is not correct. There is some data with regard to the results of medical treatment with riociguat and BPA in a sequential concept: “Sequential treatment with riociguat and balloon pulmonary angioplasty for patients with inoperable chronic thromboembolic pulmonary hypertension.” - Pulm Circ. 2018
You may introduce that study and use it for your discussion – it may strengthen your concept.

We deeply appreciate the reviewer 2 for kind suggestion.
We added the reference in the Introduction and the Discussion.

Discussion:
The text seems quite similar to the introduction. It is not conclusive and should be re-written.

We re-write the Discussion.

VERSION 2 – REVIEW

REVIEWER	Dr JG Coghlan Royal Free Hospital, London, UK
REVIEW RETURNED	07-Sep-2019

GENERAL COMMENTS	This paper describes the methodology of a study that is nearing completion. It is overall fair and balanced, however there are some minor issues in respect of the use of English and some areas where clarifications could help. Page 4 Line 6 This is the first randomized controlled trial to compare the efficacy and safety of BPA and riociguat in patients with inoperable CTEPH. Both this trial and the RACE trial commenced in January 2016. The Race trial has completed enrolment before this trial and will report significantly in advance, so it is difficult to state as a main point that this is the first trial. Page 6 line 8 A randomized controlled trial to compare riociguat and BPA (RACE study) is ongoing in France24, Probably more correct to state that it has completed recruitment and is in the follow up phase. Line 42 In the BPA group, the degree of pulmonary hypertension severity and the pulmonary lesion is morphologically evaluated by preoperative right heart catheterization and pulmonary angiography. The table of procedures and flow chart appear to suggest that all patients undergo pulmonary angiography. It would be difficult to

	justify all patients not being deemed suitable for BPA - otherwise we may be comparing apples with oranges. So it would be good to have clarification that all patients prior to randomisation were deemed suitable for either treatment modality. Page 11 line 12 The analyses of the primary and secondary efficacy endpoints will be performed using the full analysis set, which will include all patients who underwent randomization and received at least one dose of a study drug and had at least one assessment after baseline. This is a little unclear - all patients randomised should be analysed, as written is looks as though there may be latitude with the BPA group but not the medical arm. Should state that all patients once randomised will be evaluated if they take at least one tablet or attend for one BPA procedure (whether carried out or not). Page 8 Exclusions: Are there no exclusions for severe lung disease, severe heart/valvular disease, intolerance of anticoagulation etc? Limitations. Should be more explicit about the open-label biases in the discussion. The BPA operator is aware of the primary endpoint and incentivised to continue procedures until that is met. Second the endpoint is measured by an individual with a vested interest in the outcome - this affects both arms of the trial. Finally an additional limitation of the trial is that a non clinical endpoint has been chosen - the endpoint is haemodynamic. These may contribute to optimize treatment strategy or further to amend treatment guidelines for inoperable CTEPH. It is difficult to see how a small open label trial with a haemodynamic primary endpoint can significantly influence guidelines. There is no clear hierarchy to secondary endpoint analysis that could obviate this issue. English: Page 5 Line 54 On the other hand, riociguat is the most effective pulmonary vasodilator and have low risk of serious adverse events. Riociguat is the only licensed medical therapy for CTEPH, whether it is the most effective has never been formally demonstrated. "...and have a low... should read and has or and is associated with a. line 36 An independent experienced PEA surgeon will determine if these subjects are eligible to undergo PEA under blind circumstance.

	Inelegant use of English. There is no value in adding ...under blind circumstance. It is sufficient to state that patients deemed eligible for PEA are excluded from the trial.

REVIEWER	C Wiedenroth Kerckhoff Klinik Germany
REVIEW RETURNED	08-Jun-2019

GENERAL COMMENTS	The reviewer thanks the authors for their interesting work und is glad to re-review the manuscript. Several important changes have been made and the reviewer believes, that that the manuscript substantially improved. Nevertheless, neither the experience level of the PEA surgeon, nor the chosen primary endpoint (mean PAP) are discussed. On the other hand, the reviewer believes in the scientific merit of study, generating important information regarding the treatment of inoperable CTEPH patients. Discussion, page 13, line 10: BPA is for sure not a surgical intervention! Despite the readability is much improved, the reviewer again recommends editing by a native speaker.

VERSION 2 – AUTHOR RESPONSE

Responses to reviewer 1

1. Page 4 Line 6
This is the first randomized controlled trial to compare the efficacy and safety of BPA and riociguat in patients with inoperable CTEPH.
Both this trial and the RACE trial commenced in January 2016. The Race trial has completed enrolment before this trial and will report significantly in advance, so it is difficult to state as a main point that this is the first trial.

We have changed this sentence to “This is a randomized controlled trial comparing…”

2. Page 6 line 8
A randomized controlled trial to compare riociguat and BPA (RACE study) is ongoing in France24,
Probably more correct to state that it has completed recruitment and is in the follow up phase.

We have changed this sentence to “… (RACE study) is conducted in France”.

3. Line 42
In the BPA group, the degree of pulmonary hypertension severity and the pulmonary lesion is morphologically evaluated by preoperative right heart catheterization and pulmonary angiography.
The table of procedures and flow chart appear to suggest that all patients undergo pulmonary angiography. It would be difficult to justify all patients not being deemed suitable for BPA - otherwise we may be comparing apples with oranges. So it would be good to have clarification that all patients prior to randomisation were deemed suitable for either treatment modality.

If lesions of the pulmonary artery are not suitable for BPA, BPA may not be performed even for patients assigned to the BPA group. However, at least in the collaborative institutions in this study, PEA-inoperable patients are rarely considered unsuitable for BPA, because these institutes are expert centers for BPA in Japan.
We have added this explanation to the Methods and Analysis.

4. Page 11 line 12
The analyses of the primary and secondary efficacy endpoints will be performed using the full analysis set, which will include all patients who underwent randomization and received at least one dose of a study drug and had at least one assessment after baseline.
This is a little unclear - all patients randomised should be analysed, as written is looks as though there may be latitude with the BPA group but not the medical arm. Should state that all patients once randomised will be evaluated if they take at least one tablet or attend for one BPA procedure (whether carried out or not).

We have changed the explanation of this to: “the full study population, which will include all patients who were randomized into one of the intervention groups.” and “the safety analysis population, which will include all patients who were randomized into one of the intervention groups and either received at least one dose of riociguat or attended at least one BPA procedure (regardless of whether BPA was carried out or not).”

5. Page 8
Exclusions: Are there no exclusions for severe lung disease, severe heart/valvular disease, intolerance of anticoagulation etc?

Only patients with CTEPH will be included in this study, according to the inclusion criteria. Diagnosis of CTEPH is based on the diagnostic criteria of the 2012 Japanese Circulation Society guidelines, as described in the Methods and Analysis. Upon diagnosis, the investigators will perform pulmonary ventilation-perfusion scintigraphy, echocardiography (cardiac ultrasound), pulmonary function tests, right-heart catheterization, and pulmonary angiography. Patients classified as having group 1–3 pulmonary hypertension, according to the Nice Pulmonary Hypertension Classification System, will be excluded. This study will not include patients who are intolerant to anticoagulant therapy, since appropriate anticoagulant therapy for at least three months prior to consent to participate is part of the inclusion criteria.

6. Limitations.
Should be more explicit about the open-label biases in the discussion. The BPA operator is aware of the primary endpoint and incentivised to continue procedures until that is met. Second the endpoint is measured by an individual with a vested interest in the outcome - this affects both arms of the trial.

We have added these limitations to the Discussion.

7. Finally an additional limitation of the trial is that a non clinical endpoint has been chosen - the endpoint is haemodynamic.
These may contribute to optimize treatment strategy or further to amend treatment guidelines for inoperable CTEPH.
It is difficult to see how a small open label trial with a haemodynamic primary endpoint can significantly influence guidelines. There is no clear hierarchy to secondary endpoint analysis that could obviate this issue.

The primary endpoint (mean pulmonary arterial pressure) is not only a hemodynamic parameter, but also an important clinical endpoint for CTEPH treatment.
Combined with the overall results of the secondary endpoints, which are also important prognostic factors for CTEPH treatment, we believe that the results of this study can contribute to optimization of treatment strategies, or inform amendments to treatment guidelines for inoperable CTEPH.

8. English
Page 5 Line 54
On the other hand, riociguat is the most effective pulmonary vasodilator and have low risk of serious adverse events.
Riociguat is the only licensed medical therapy for CTEPH, whether it is the most effective has never been formally demonstrated. "...and have a low... should read and has or and is associated with a.

We have revised this sentence.

9. line 36
An independent experienced PEA surgeon will determine if these subjects are eligible to undergo PEA under blind circumstance.
Inelegant use of English. There is no value in adding ...under blind circumstance. It is sufficient to state that patients deemed eligible for PEA are excluded from the trial.

We have removed the phrase “under blind circumstance”.

Responses to reviewer 2

1. Nevertheless, neither the experience level of the PEA surgeon, nor the chosen primary endpoint (mean PAP) are discussed.

We have added the experience level of the PEA surgeon and the rationale for the primary endpoint to the discussion.

2. Discussion, page 13, line 10:
BPA is for sure not a surgical intervention!

We have changed this sentence to state “surgical treatment”.

3. Despite the readability is much improved, the reviewer again recommends editing by a native speaker.

We have engaged a professional English editing service, and the entire manuscript has been edited for English language and grammar. We attach the certificate of English editing from the professional company.

VERSION 3 – REVIEW

REVIEWER	JG Coghan Royal Free Hospital & Royal Papworth Hospital UK
REVIEW RETURNED	12-Oct-2019

GENERAL COMMENTS	Thank you for resubmitting and taking all the points made on board. Unfortunately time has moved on and the results of the RACE trial have now been presented at the ERS, so it is difficult to avoid including a comment on the outcome of that trial and how the current study may adds to the body of knowledge already in the public domain. I think a reasonable argument could be made that the French experience in BPA was more limited than the Japanese and therefore the results of the RACE trial may reflect the lesser reduction of mPAP achieved and higher complication rate seen in less experienced centres. The following long paragraph in the methods section could be improved: "As shown subjects will undergo right-heart catheterization and pulmonary angiography before provisional enrollment. An independent experienced PEA surgeon will determine if subjects are eligible for PEA. Those who are judged to have inoperable CTEPH will be assigned into either a BPA or riociguat group via an online assignment system, and will be observed for 12 months. In the BPA group, the severity of pulmonary hypertension and morphology of the pulmonary lesion will be evaluated by preoperative right-heart catheterization and pulmonary angiography. .....If lesions of pulmonary artery are not suitable for BPA, the procedure will not be performed even if the patient is assigned to the BPA group. However, at least among the collaborative institutions included in this study, PEA-inoperable patients are very rarely considered unsuitable for BPA, because these institutes are expert BPA centers in Japan." Perhaps: As per standard practice in Japan patients are identified as having CTEPH at right heart catheterization with pulmonary angiography. Subjects willing to consider enrolment are consented prior to invasive evaluation and have their imaging reviewed by an independent experienced PEA surgeon, and if deemed technically operable are excluded from the study. Those deemed inoperable are randomized to either medical therapy (Riociguat) or BPA, irrespective of disease burden or lesion accessibility. In exclusion criteria: .....co-existing etiology of pulmonary hypertension (except for that classified as Group 4 in the Nice Pulmonary Hypertension Classification...) Already evident – leave out component in brackets. Methodology: “As a general rule, right-heart catheterization and pulmonary angiography are performed after acquiring consent and the

	possibility of definitive diagnosis of CTEPH is determined by the investigators." This is confusing – suggests that patients are approached for study entry before the diagnosis is made. If so could be clarified: Perhaps: Patients identified as possible CTEPH patients based on non-invasive imaging are pre-screened for study entry and consented prior to right heart catheterization and pulmonary angiography. Suitable patients that have undergone comprehensive evaluation including pulmonary angiography within 3 months can also be enrolled to the study. Note if the dominant approach is pre evaluation, I would expect some data on the numbers approached and the number agreeing to enrolement – given that no of patients per year having BPA in Japan averages over 300, I would want some explanation for the slow recruitment. No info on costings how data gathered and analysed, even though this is claimed as a secondary endpoint Throughout the text the future tense is used e.g. "Random assignment will be performed centrally" or The Data Center will prepare a "Procedure Manual for Data Management". Given that enrolment has now been completed, it would be more sensible to use the past tense for that which has already been done and reserve the future tense for the follow up and analysis yet to be completed. All the points I have previously made have been addressed, and therefore I am comfortable with approving the paper as is. However, believe the paper would be better received if these issues are addressed.

REVIEWER	Christoph Wiedenroth Kerckhoff Klinik Bad Nauheim Germany The reviewer reports having received speaker fees and/or consultant honoraria from Actelion, Bayer, BTG, MSD, and Pfizer.
REVIEW RETURNED	24-Nov-2019

GENERAL COMMENTS	The reviewer thanks the authors again for their interesting work und is glad to re-re-review the manuscript. The manuscript and especially the readability improved. There is only a minor comment: Discussion page 13: BPA surgeons should be BPA interventionalist or operator: "Because there is no distinct criterion for BPA in each lesion, interventionalists are aware of…" "Thus, bias for the BPA operators cannot…" "However, since this study will compare medical and interventional treatment…"

VERSION 3 – AUTHOR RESPONSE

Responses to reviewer 1

1. Unfortunately time has moved on and the results of the RACE trial have now been presented at the ERS, so it is difficult to avoid including a comment on the outcome of that trial and how the current study may adds to the body of knowledge already in the public domain.
I think a reasonable argument could be made that the French experience in BPA was more limited than the Japanese and therefore the results of the RACE trial may reflect the lesser reduction of mPAP achieved and higher complication rate seen in less experienced centres.

Although the reviewer 1 commented that the results of the RACE trial was already presented in ESR, authors did not attend the conference and did not hear the presentation. Also, the results have not been yet published elsewhere. Therefore, in this protocol article at this time, we think that the further description of the detailed RACE trial results is not necessary.
We will refer the results in the RACE trial in future result paper of this study.

2. The following long paragraph in the methods section could be improved:
"As shown subjects will undergo right-heart catheterization and pulmonary angiography before provisional enrollment. An independent experienced PEA surgeon will determine if subjects are eligible for PEA. Those who are judged to have inoperable CTEPH will be assigned into either a BPA or riociguat group via an online assignment system, and will be observed for 12 months. In the BPA group, the severity of pulmonary hypertension and morphology of the pulmonary lesion will be evaluated by preoperative right-heart catheterization and pulmonary angiography. .....If lesions of pulmonary artery are not suitable for BPA, the procedure will not be performed even if the patient is assigned to the BPA group. However, at least among the collaborative institutions included in this study, PEA-inoperable patients are very rarely considered unsuitable for BPA, because these institutes are expert BPA centers in Japan."
Perhaps: As per standard practice in Japan patients are identified as having CTEPH at right heart catheterization with pulmonary angiography. Subjects willing to consider enrolment are consented prior to invasive evaluation and have their imaging reviewed by an independent experienced PEA surgeon, and if deemed technically operable are excluded from the study. Those deemed inoperable are randomized to either medical therapy (Riociguat) or BPA, irrespective of disease burden or lesion accessibility.

We revised the paragraph according to the reviewer 1’s suggestion in the study design and setting section in page 6.

3. In exclusion criteria:
.....co-existing etiology of pulmonary hypertension
(except for that classified as Group 4 in the Nice Pulmonary Hypertension Classification...)
Already evident – leave out component in brackets.

We removed the component in the brackets according to the reviewer 1’s suggestion in the eligibility criteria section in page 8.

4. Methodology:
“As a general rule, right-heart catheterization and pulmonary angiography are performed after acquiring consent and the possibility of definitive diagnosis of CTEPH is determined by the investigators.”
This is confusing – suggests that patients are approached for study entry before the diagnosis is made. If so could be clarified:

Perhaps: Patients identified as possible CTEPH patients based on non-invasive imaging are pre-screened for study entry and consented prior to right heart catheterization and pulmonary angiography. Suitable patients that have undergone comprehensive evaluation including pulmonary angiography within 3 months can also be enrolled to the study.
Note if the dominant approach is pre evaluation, I would expect some data on the numbers approached and the number agreeing to enrolement – given that no of patients per year having BPA in Japan averages over 300, I would want some explanation for the slow recruitment.

We revised the paragraph according to the reviewer 1's suggestion the Recruitment and consent section in page 8.

5. No info on costings how data gathered and analysed, even though this is claimed as a secondary endpoint

We added the description in the Data collection section in page 9.

6. Throughout the text the future tense is used e.g. "Random assignment will be performed centrally" or The Data Center will prepare a "Procedure Manual for Data Management".
Given that enrolment has now been completed, it would be more sensible to use the past tense for that which has already been done and reserve the future tense for the follow up and analysis yet to be completed.

We revised description of the recruitment and execution in this study from the future tense to the present tense or the past tense.

Responses to reviewer 2

1. BPA surgeons should be BPA interventionalist or operator:

We revised the BPA surgeons to the BPA operators in the Discussion page 9.