Author's response to reviews

Title: Transarterial RAdioembolization versus ChemoEmbolization for the treatment of hepatocellular carcinoma (TRACE): study protocol for a randomized controlled trial

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Version: 2 Date: 25 May 2012

Author's response to reviews: see over
Dear professor Furberg and other Editors-in-Chief,

Thank you very much for peer reviewing our manuscript, entitled ‘Transarterial RAdioembolization versus ChemoEmbolization for the treatment of hepatocellular carcinoma (TRACE): study protocol for a randomized controlled trial’, for publication in TRIALS, article type ’study protocol’.

As requested we have responded point by point to the comments of the reviewers and integrated their suggestions into the revised manuscript (2 documents attached).

Thank you for considering the acceptance of our manuscript.

Sincerely, on behalf of all co-authors,

Maurice van den Bosch, MD, PhD
Professor of Radiology
University Medical Center Utrecht
Reviewer's report

Title: Transarterial RAdioembolization versus ChemoEmbolization for the treatment of hepatocellular carcinoma (TRACE): study protocol for a randomized controlled trial

Version: 1  Date: 4 March 2012
Reviewer: Rakesh Aggarwal

Reviewer's report:
The protocol is generally well written. I have the following suggestions:

Major Compulsory Revisions

1. Sample size calculation: All assumptions made for such calculation and the details of the software etc used for this calculation should be provided. The drop-out rate of 2% assumed for each group appears to be quite small. The authors need to recheck this part of the manuscript.

We thank the reviewer for this comment.

Even though a dropout rate of 2% is rather low, we believe it to be feasible, since follow-up time is short (median survival for both treatment arms is around 17 months). In our experience patients have a high adherence in The Netherlands, since the frequent imaging coincides with clinical follow-up by the hepatologist.

Assumptions made for the sample size calculation and information about the software used are now described in more detail (paragraph ‘Methods – Sample size calculation’, page 15):

‘A total of 140 patients will be included. Sample size calculation is performed with the help of PASS Power Analysis and Sample Size software (www.ncss.com/pass.html), using the logrank test. Defined follow-up time is 24 months. Assuming a median time to progression of 13.3 months after $^{90}$Y-RE, based on the best stratified data for intermediate stage HCC patients available in the literature [1], a clinically relevant effect size of 20% difference in time to progression (2.7 months) with a power of 90% and a two sided alpha Risk of 5%, 70 patients in each treatment arm are required. Taking a hypothetical loss to follow up of 2% into account in both treatment arms, based on earlier experience with this patient group, still gives a power of 80% when 70 patients per treatment arm are included (Alpha Risk remains 5%).
Null hypothesis:
There is no difference in time to progression (TTP) in patients with intermediate stage HCC treated with $^{90}$Y-RE or TACE-DEB.
The alternative hypothesis is two-sided ($^{90}$Y-RE could have a shorter or a longer TTP).'

Minor Essential Revisions

2. The background information on TACE refers to ‘post-embolization syndrome’.
It may help to explain what this phrase means. This may be useful to some readers who are relatively unfamiliar with this treatment modality.

We have now defined the post-embolisation syndrome in more detail for the readers (paragraph ‘Background – Transarterial chemoembolisation’, page 6): ‘This is a condition in which the patient experiences abdominal pain, fever, ileus and nausea, self-limiting hours to days after the procedure, probably due to damage of hepatocytes[2]).

3. The minimization procedure will be done using a ‘validated software’. Is this software available commercially? If yes, the name and source may be added.

The randomization program, which is also equipped to perform minimization, is developed and validated by software developers and data management experts at our center. It is not available commercially.

4. The methods for TACE state that ‘A target dose of 100-150 mg doxorubicin per patient is intended’. The factors determining the drug dose within this range (e.g. who will receive 100 mg and who will receive 150 mg) may be specified. For instance, will this be based on body weight or surface area.

This section is rephrased since it appears to be confusing. It is now described as follows (paragraph ‘Methods – Intervention – TACE, page 9/10):

‘Patients receive a maximum dose of 150 mg doxorubicin per single treatment session. The doxorubicin is loaded on 100-300 µm beads and mixed with nonionic contrast medium prior to delivery. No dose adjustment is made for bilirubin concentration or body surface area.'
Dose determination is based on previous dose escalation studies, in which DEBs loaded with doxorubicin up to 150 mg was shown to be safe and effective[3,4] and recommendations from the literature[5,6]. The DEBs are slowly injected under fluoroscopic visualization while observing the contrast flow rate; the embolisation endpoint is reached when all the DEBs are administered (maximum dose is reached), or earlier when sluggish flow is seen to avoid reflux and non-target embolisation. Total administered dose is recorded.'

5. The methods for 90Y-RE state that: ‘The required activity according to the package insert is calculated based on the target volume’. It would be useful to provide the details of this within the manuscript, so that a reader can understand this without reference to the package insert of the particular commercial product.

As suggested by the reviewer, we added details about the activity and dose calculation to the manuscript (paragraph ‘Methods – Intervention – 90Y-RE, page 11/12):

The volume of liver lobe to be treated and corresponding liver mass is determined using CT or MRI...
...The radioactivity required to deliver the desired dose to the liver is calculated using the following formula:

\[
\text{Activity Required (GBq)} = \frac{\text{Desired Dose (Gy)} \times \text{Liver Mass (kg)}}{50}
\]

The actual liver dose (Gy) delivered to the liver after injection can be calculated using the following formula:

\[
\text{Dose (Gy)} = \frac{50 \times \text{Injected Activity (GBq)} (1 - F)}{\text{Liver Mass (kg)}}
\]

where F is the fraction of injected radioactivity localizing in the lungs, as measured by 99mTc-MAA scintigraphy.

6. The methods state that: ‘Laboratory examination will be performed on a regular basis’. It may be useful to state what all examinations will be done.

This is now described in more detail (paragraph ‘Methods-Follow-up’, page 12):
Laboratory examination (complete blood count, electrolytes, kidney function tests, liver function tests, albumin, prothrombin time / INR, alpha-fetoprotein) will be performed on a regular basis during routine visits to the outpatient clinic.

7. Some parts of treatment for Y-RE are in present tense. These should preferably be in future tense.

Above suggestion is now implemented in the manuscript.

8. Background, paragraph 1: ‘Curation is only achieved by …’ can be changed to ‘Cure is achieved only by …’.

Above suggestion is now implemented in the manuscript.

9. Page 6, line 6: The text ‘…stated in a meta-analyse of RCTs …’ can be changed to ‘…stated in a meta-analysis of RCTs …’.

Above suggestion is now implemented in the manuscript.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published
Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
I have no competing interests in relation to this manuscript
Reviewer's report

**Title:** Transarterial RAdioembolization versus ChemoEmbolization for the treatment of hepatocellular carcinoma (TRACE): study protocol for a randomized controlled trial

**Version:** 1 **Date:** 14 April 2012

**Reviewer:** Christian Gluud

**Reviewer's report:**

Seinstra and colleagues describe in a design article a trial on transarterial radioembolisation with yttrium 90 versus chemoembolisation with doxorubicin loaded microspheres for patients with unresectable, intermediate stage hepatocellular carcinoma. The authors are to be congratulated with conducting clinical research in this neglected patient group. Several aspects of their design seem to be up to date methodology. The trial has started recruiting in September 2011.

Although I am very positive towards this trial, I also see some potential caveats. The problems are

1. The control intervention TACE - recommended in all guidelines and by the TACE lobby (and it is big!) - has according to our Cochrane systematic review (Cochrane Database Syst Rev. 2011;(3):CD004787) not shown the benefits that are so extensively ascribed to TACE by self-proclaimed experts. If this is so, is it then the correct design or should the trial not have been three armed including a sham group?

We thank the reviewer for this comment. We are familiar with the recent Cochrane review and meta-analysis, which was published after the design of our study. The conclusion of the review, i.e. that there is no firm evidence to support or refute TACE in patients with unresectable HCC, is highly controversial. In the past there were major discrepancies in patients’ selection and treatment strategies. Some of the studies included in the Cochrane meta-analysis included early stage and advanced stage HCC patients, which is not consistent with the more stringent selection criteria currently applied for TACE (BCLC intermediate stage B with compensated liver disease). For this selected group of patients TACE has proven to be beneficial [7,8] and is considered as standard treatment by the BCLC criteria and according to the American Association for the Study of Liver Diseases (AASLD) guidelines[9]. We therefore think that TACE is the appropriate therapy to compare to the new intervention, i.e. Yttrium 90 radioembolisation.
2. In the background postulates about the benefit of TACE needs to be modified and referenced.

As suggested by the reviewer, the paragraph ‘Background – Transarterial chemoembolisation’, page 5/6, has been modified as follows:

‘According to the BCLC staging classification and treatment schedule, TACE can be considered the current standard treatment for patients with intermediate stage HCC with compensated liver disease, with a reported median survival of around 17 months [10-12]. Two randomised controlled trials [8,13] and two systematic reviews [7,14] demonstrated a survival benefit of TACE in this selected patient group. A more recent Cochrane review and meta-analysis concluded there is no firm evidence to support or refute TACE in patients with unresectable HCC[15]. However, this review is controversial since some studies included in the meta-analysis included patients that are no longer consistent with the more stringent selection criteria currently applied for TACE (BCLC intermediate stage B with compensated liver disease) and there are discrepancies in treatment application between the studies. The lack of standardisation accompanied with the application of conventional TACE (mostly performed with a mixture of chemotherapeutics, lipiodol and an occluding agent) is no longer an issue with the arrival of drug-eluting beads (DEBs). DEBs act as both an occluding agent as well as a drug-loaded carrier, achieving local ischemia and cytotoxic death of the tumor with one device, enabling standardization[16].’

3. In the section on TACE the lack of firm evidence needs to be acknowledged. The design article needs to refer to updated systematic reviews on the topic or the authors need to conduct such reviews themselves. Such systematic reviews need to take into consideration both risks of systematic errors (bias), random errors (play of chance), and design errors.

As suggested by the reviewer, we have implemented the results of the Cochrane review in our manuscript (paragraph ‘Background – Transarterial chemoembolisation’, page 5). Despite the conclusion of the review, and for reasons mentioned earlier in our reply to comment 1, we do believe that the use of TACE in BCLC intermediate stage HCC with compensated liver disease (Child-Pugh A-B7) is evidence based. This conclusion is based on two randomised
controlled trials [8,13] and two systematic reviews [7,14] that demonstrated a survival benefit of TACE in this selected patient group.

4. In the yttrium 90 section, the design article needs to refer to updated systematic reviews on the topic or the authors need to conduct such reviews themselves – this goes for two comparisons: radioembolisation with yttrium 90 versus sham/placebo; radioembolisation with yttrium 90 versus TACE. Such systematic reviews need to take into consideration both risks of systematic errors (bias), random errors (play of chance), and design errors. Anything else will leave Western medicine in the mess of traditional Chinese medicine where one herbal mixture gets compared with another herbal mixture, without anyone knowing if any of the works.

There have been several publications which indicate that Yttrium 90 radioembolisation has a significant antitumor effect in HCC; most evidence comes from retrospective studies. In the manuscript we now refer to a systematic review that describes response rates and a recent review that addresses response rates and survival benefit following radioembolisation (paragraph ‘Background - Yttrium-90 radioembolisation’ page 7):

‘Several prospective and retrospective studies demonstrated the safety and efficacy of 90Y-RE treatment for unresectable HCC, all documented in a recent review[17]. An earlier structured meta-analysis describes a response rate of 78% (glass microspheres) and 89% (resin microspheres)[18].’

No systematic reviews concerning the comparison of Y90 radioembolisation versus sham/placebo have been published. In the manuscript we do describe all comparative cohort studies describing the results of chemoembolisation versus radioembolisation (paragraph ‘Study Rationale’, page 7). We designed this trial since both treatment modalities have never been prospectively compared in a randomised controlled setting.

5. The group of patients randomised to transarterial radioembolisation with yttrium 90 actually seems to get two interventions: first a meticulous work up with selective visceral catheterisation and then (if the patients qualify!) the transarterial radioembolisation with yttrium 90. This may be the ‘intervention’ package, however, it is very important to describe it clearly. Therefore, this trial actually compares meticulous visceral catheterisation work up plus transarterial radioembolisation with yttrium 90 versus chemoembolisation with doxorubicin loaded microspheres for
patients with unresectable, intermediate stage hepatocellular carcinoma! This ought to become the title of the design article and later on when the trial result is published. Moreover, the authors need to describe how they are going to treat patients with an unfavourable technetium scintigraphy. I hope they enter the intention-to-treat analysis.

We understand the reviewers concerns. We therefore put in some extra effort to explain that the $^{99m}$Tc-MAA workup procedure ought to be seen as an integral part of the Yttrium 90 radioembolisation treatment. It is of vital importance to prevent extrahepatic deposition of Y90 microspheres and the actual treatment procedure cannot be performed without the information gathered during the work-up procedure. Therefore the Yttrium 90 radioembolisation treatment strategy consists of the $^{99m}$Tc-MAA workup session and the radioembolisation session, just as the TACE treatment strategy consists of several chemoembolisation sessions.

The following has been added to the manuscript (paragraph ‘Intervention - $^{90}$Y-RE’, page 11):

‘In case a patient has an unfavorable $^{99m}$Tc scintigraphy, the $^{99m}$Tc-MAA workup procedure is repeated, if feasible, to detect the cause of the extrahepatic deposition (e.g. previously undetected patent extrahepatic vessels arising from the hepatic artery) and a solution is searched for (e.g. more selective placement of the catheter during injection). In the unlikely event no solution is found and $^{90}$Y-RE cannot be performed, the patient is treated according to best medical practice and still enters the intention-to-treat analysis in the $^{90}$Y-RE arm.’

6. The planned per protocol analyses need to be described.

The following is now stated in the manuscript (paragraph ‘Statistical analyses’, page 15): ‘Per protocol analysis will be performed including only those patients who completed the treatment protocol originally allocated.’

7. The objective of this trial ought to become to assess the benefits and harms of the two interventions – not just efficacy.

We thank the reviewer for this comment. We now describe the trial objective as follows (paragraph ‘Methods – Objective’, page 13): ‘
'The objective of this study is to compare the efficacy and safety of TACE versus $^{90}$Y-RE in patients with intermediate stage HCC.'

The primary outcome of this trial is the efficacy of both treatments (in other words: ‘the benefits’). However we also take safety (toxicities and adverse events) into account, defined as a secondary outcome (in other words: ‘the harms’). Another secondary outcome that gives some information about the benefits and harms of the treatments is Quality of Life.

8. The entry time for calculation of time to progression ought to become time at minimization.

_We thank the reviewer for this suggestion and have made the necessary adaptations to our study protocol._

9. The way toxicities and adverse events are going to be graded and analysed ought to become much better described.

_This is now described in the manuscript as follows:_

**Paragraph ‘Methods-Follow-up’, page 13:**

Adverse events and toxicities are recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE version 4.0). These criteria define adverse events on a scale from 1 to 5, corresponding to severity (grade 1: mild, grade 2: moderate, grade 3: severe, grade 4: life-threatening or disabling, grade 5: resulting in death). Toxicity is recorded only if the grade increases from baseline. Adverse events and toxicities are monitored for 6 months following the last treatment procedure.

**Paragraph ‘Methods-Statistical analyses’, page 15/16:**

Differences in proportions of patients reporting toxic / adverse events or treatment related complications will be analysed by means of chi square test.

10. The sample size calculation seems OK apart from the fact that the authors postulate a rather large intervention effect of 20%. This needs to be discussed. It also seems strange to base the calculation of the expected mean time to progression on the experimental intervention and not on the control intervention. This needs to be
discussed.

We chose a 20% difference in TTP between the two treatment arms, since this is a difference that is of importance to the patient; a smaller difference would be of less clinical relevance. Based on the estimated TTP from the literature (13.3 months for Y90-RE), this would imply a difference of 2.7 months.

We based our sample size calculation on the median time to progression after Y90 radioembolisation reported in the literature, since this provided the best stratified data for our specific patient group (HCC patients with BCLC intermediate stage B). This is now described in the manuscript as follows (paragraph ‘Methods – Sample size calculation’, page 15):

‘Assuming a median time to progression of 13.3 months after $^{90}$Y-RE, based on the best stratified data for intermediate stage HCC patients available in the literature [1], a clinically relevant effect size of 20% difference in time to progression (2.7 months) with a power of 90% and a two sided alpha Risk of 5%, 70 patients in each treatment arm are required.’

11. Why not use imputation in case there are drop outs?

If necessary we can indeed use imputation. For the analysis of continuous variables (i.e. QoL scores) we are able to deal with incomplete data by the use of mixed models.

12. In the inclusion criteria written informed consent needs to be mentioned (now it stands after the exclusion criteria). Likewise, lack of informed consent needs to become an exclusion criterium.

We thank the reviewer for this suggestion. Written informed consent is now mentioned in the inclusion criteria and lack of informed consent is now mentioned in the exclusion criteria (manuscript paragraph ‘Methods – Study participants’, page 8).

13. Is this a randomised multicentre trial or is it a single centre with several hospitals referring patients to one treatment centre? This is unclear!

It is a randomised multicentre trial with currently two hospitals participating (University Medical Centre Utrecht and Ghent University Hospital).
14. The chosen minimisation method does not take centre into account as a stratification factor. If it is a single treatment centre trial, the minimization may not be optimal in avoiding risks of selection bias. If this is a multicentre trial, then confounding by centre may be very problematic.

In this study we perform minimisation stratified by treatment centre. We have now mentioned this more prominently in the manuscript (paragraph ‘Methods – Study design’, page 9).

15. Please give reference to the validated software used for minimization.

The randomization program, which is also equipped to perform minimization, is developed and validated by software developers and data management experts at our centre. It is not available commercially.

16. Use entry or trial entry throughout in stead of baseline.

Above suggestion is now implemented in the manuscript.

17. Spelling needs to be UK English throughout.

Indeed there was some inconsistency as regards to the usage of British vs American English throughout the manuscript. We now use British spelling throughout.

18. The trial status can be described a bit more in detail. How many patients have been minimised? Can they stick to the planned conduct?

The following has been added to the manuscript (paragraph ‘Trial Status’, page 16):
‘The trial is currently including patients. The first 10 patients have been minimised and treated according to the allocated treatment arm. Up till now all patients complied to the trial protocol.’

19. When was the trial protocol registered compared to time of the inclusion of the first patient?
The trial was registered at clinicaltrial.gov at June 14th 2011 and the inclusion of the first patient took place on November 14th 2011.

20. Several of the points raised above needs to be discussed in detail (point 1,3,4,5,6,8,9,10,11,13,14,16,18,19).

See comments above.

Level of interest: An article of importance in its field
Quality of written English: Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician.
Reference List


