Health Research Authority
Skipton House
80 London Road
London
SE1 6LH

15-Dec-2017

EudraCT number: 2017-002329-39
Sponsor reference number: MRC RE06

Dear Colleague,

RE: Renal Adjuvant MultiPle Arm Randomised Trial (RAMPART): An international investigator-led phase III Multi-Arm, Multi-Stage (MAMS), multi-centre, randomised controlled platform trial of adjuvant therapy in patients with resected primary renal cell carcinoma (RCC) at high or intermediate risk of relapse

I am writing in response to the HRA Initial Outcome Letter (dated 03-Nov-17) and REC Provisional Opinion Letter (dated 16-Nov-17). In this letter we address each of the points that have been raised by the HRA and REC and we describe our proposed amendments for your consideration.

I would also like to take this opportunity to update you on the progress of our MHRA application. We have now received a Clinical Trial Authorisation Letter (dated 24-Nov-17), however this was only issued after we addressed several minor medical and pharmaceutical points in the Protocol and CTA.

We would like to streamline our application to the HRA and avoid having to submit the updated Protocol as an amendment. While we address all points raised in the Provisional Opinion Letter, we would like the revised Protocol to be considered as part of this HRA assessment.

I have attached here the revised Protocol in 'clean' and 'tracked changes' versions, the cover letter to the MHRA and Notice of Acceptance Letter. Additionally I have attached copies of the updated Participant Information Sheets which have been updated to reflect the HRA and REC recommendations. A list of additional supporting documentation is presented at the end of this cover letter.

REC Comments

1) Changes to the Participant Information Sheet (PIS)

a) Please state clearly how many study visits there will be, and what each of the visits will involve for each of the study groups. The PIS should also state clearly how many additional clinical interventions will be involved in this study that are not part of the participant's routine care. The table titled Visit Plan (page 10 of the PIS) should be re-formatted accordingly to reflect clearly what the clinical interventions are for each study arm (including how many of which are additional to routine care) and how many study visits are required.

Section 4 of the RAMPART PIS has been updated to clarify the total number of visits per arm, the number of procedures required and how that compares to routine care. The Visit Plan table has

been re-designed so that the trial arms are detailed separately and the procedures that are additional to routine care are highlighted.

b) The PIS should state clearly that the participant's study data will be exported outside the EEA and that it will be anonymised to protect the participant's identity.

Section 10 of the RAMPART PIS has been updated as suggested. A sentence has been added to further clarify that any data exported will be anonymised to protect the participant's identity.

c) In Table 2 – Side Effects, section 11 of the PIS (page 11) please revise the table to state clearly the severity of the side effects. The Committee stated that some of the side effects may require hospitalisation and that this needs to be stated clearly in the PIS.

The majority of the side effects listed in Table 2 have the potential to cause hospitalisation depending on their severity, which will likely differ between patients. Rather than updating the table, we felt it more appropriate to state that some of the side effects may cause hospitalisation, but also remind participants to contact their nurse or doctor if they have any concerns.

d) Please state clearly that the participant will be asked to complete a number of questionnaires as part of the study protocol. The PIS should state what these questionnaires will be and how long they will take to complete.

A new section (section 9) has been added to provide a brief explanation of the Patient Reported Outcomes and Quality of Life and Health Economics sub-studies. The RAMPART PIS now clearly details the number of questionnaires and their timings. There is also a note to make it clear that these are optional sub-studies.

2) Written assurance

a) The Committee requested written assurance that the participant's personal study data will be anonymised and that their study data will be anonymised prior to exporting outside of the EEA.

I can confirm that all data exported outside of the EEA will be anonymised before transfer. Section 10 has been updated as noted above to make this clear.

3) Written clarification

a) It was noted in the PIS, under the heading Why am I being invited to take part? (page 2 of the PIS) that 'the doctor treating you believe that there is a risk that the cancer may return'. The Committee queried whether the doctor's treating the patient will inform them of this fact.

The main justification for conducting RAMPART is to prevent or delay the patient's cancer from returning. We feel that it is important that the risks are discussed with the participant. This sentence not only helps to explain why we are conducting the research, but also ensures that conversation takes place.

HRA Comments

1) NHS organisations

IRAS A72 indicates 70 UK sites will host the research, however IRAS Part C lists only 47 host organisations; please clarify and confirm additional sites, if applicable

The number indicated in A72 is the total number of sites we envisage coming on board during the course of the trial whereas Part C lists the sites that we have a confirmed expression of interest from and have been assessed for feasibility. Any new centres (outside the 47 currently listed in Part C) will be added via substantial amendment.

2) Newly obtained human tissue for research purposes

IRAS Part B Section 5 states one blood sample will be collected at baseline from each participant after consent; IRAS A19 indicates that blood samples will be collected up to 18 times over the duration of the study – please clarify. Additionally, it was noted from the Participant Information Sheet that a urine sample will also be collected. Details of this sample is not included in IRAS Part B Section 5, however, it was noted that IRAS A19 indicates this is for pregnancy testing only – please confirm and provide details if any other testing will be done on these samples, where and how long will these samples be stored, if applicable

The blood samples listed in A19 are safety blood samples to be collected for haematology and biochemistry tests in order ensure patient is well enough for the treatment to be administered; and to monitor toxicity. This is reflected in the Schedule of Events. The blood sample detailed in Part B Section 5 is the only one to be collected purely for translational research purposes. The urine sample mentioned in the PIS is indeed for pregnancy testing only; therefore it is not listed in Part B Section 5 as it is not for translational research.

3) Participant Information Sheets and Informed Consent Forms (PIS/ICF) – inclusion of IRAS reference

We recommend that the IRAS reference is present on the PIS and ICF documents so that participants have a single reference for the study, please consider including this into your PIS and ICF

A sentence has been added in section 10 of the RAMPART PIS to provide the IRAS Project ID and explain that it is a single reference for the study. However we do not feel it is necessary to add this information to the ICF.

4) Participant Information Sheet (PIS) – compliance with Data Protection Act (DPA)

The use of participant data has been partially described in the PIS, however to meet HRA assessment criteria and standards and to comply with the DPA, the PIS must also be clear about what will happen to data, including after the study. It was noted that personal data will be required for follow-up and stored with research data for 25 years. Please include the data retention period into the PIS.

A sentence has been added in section 10 of the RAMPART PIS to clarify that the participant's data will be retained for 25 years after the completion of the study, as per UK law.

5) Participant Information Sheet and Informed Consent Form (PIS/ICF) – compliance with Human Tissue Act (HTA)

The PIS should be clear about how human biological material will be used, who it will be shared with, how and when and what will happen to it including after the study. Information in the PIS

currently only states that samples cannot be traced back to the participant. Please include more detail into the PIS so that participants will be informed on how samples (whether newly obtained or existing) will be used and where (location) samples will be transferred to and what will happen to samples during and after the study. It was noted that the ICF includes a clause stating that samples and data might be sent outside of the EU; this is not stated in the IRAS application. It is understood that Cambridge is the central labs location for the processing and analysis of samples – please clarify and update the PIS and ICF accordingly.

Section 8 of the RAMPART PIS has been updated to provide the following additional information about the how the samples will be used and where they will be stored:

> *Your samples will be sent to a central lab at Cambridge University where they will be stored for at least the duration of the study. The samples may be tested to help understand factors that may cause kidney cancer or affect the way the cancer responds to immunotherapy treatments.*
>
> *The samples (or data generated from them) may be shared with other universities and, NHS hospitals (to store your samples once collected) or commercial collaborators, possibly from outside the EEA and who might be using specialised testing methods. Proposals for the use of the samples collected in this study will be assessed on a case-by-case basis by an independent trial oversight committee.*

At present there are no plans for the samples detailed in this application to leave the EU. However, the Trial Management Group and Trial Steering Committee will consider external applications for the use of the samples (or data generated from them), so it is possible in future.

6) Participant Information Sheet (PIS) – continued provision of intervention for participants

IRAS A25 states participants who present with disease progression will be able to access first line therapies as recommended by NICE. There currently is no information in the PIS about this or the post-study care arrangements. The PIS includes information what happens a year on into the study and what happens if the participant decides to stop and withdraw from the study. It is recommended that arrangements for care after research has ended is included into the PIS and should be consistent to information provided in the IRAS application.

As there are a number of potential options available, which are likely to change over time, we felt it would not be appropriate to make reference to any specific treatment. A new question (what if my cancer comes back?) has been added to section 4 with the following guidance:

> *If a CT scan shows that your cancer has come back you will need to stop any treatment you are receiving as part of the study. You and your doctor will discuss options for further treatment with you.*

7) Sub-studies

The main ICF includes clauses for participants to participate in 2 separate sub-studies – no information if provided of these sub-studies in the main PIS, please consider a separate information

sheet for these sub-studies to provide more information to participants about what participating in these will entail.

A new section (section 9) has been added to the RAMPAT PIS to provide a brief explanation of the Patient Reported Outcomes and Quality of Life and Health Economics sub-studies. The RAMPART PIS now clearly details the number of questionnaires and their timings. There is also a note to make it clear that these are optional sub-studies.

8) Pregnant Partner Consent Form

No accompanying pregnant partner information sheet has been submitted for this consent form; please provide

The Pregnant Partner Consent Form has been provided along with this submission.

9) MHRA CTA

Please provide notice of acceptance, if/when available

The MHRA notice of acceptance, dated 24-Nov-2017, has been provided along with this submission.

I would like to thank you for considering amendments described above. We welcome the opportunity to respond to any further clarification or questions you may have.

Kind regards

Dr Angela Meade

On behalf of the RAMPART Trial Development Group

MRC Clinical Trials Unit at UCL
90 High Holborn
2nd Floor
London WC1V 6LJ
E-mail: mrcctu.rampart@ucl.ac.uk

Table 1. Enclosed documentation

Document	Version	Date
Protocol	1.0	2017-11-22
Participant Information Sheet (clean)	1.0	2017-12-15
Participant Information Sheet (tracked)	1.0	2017-12-15
Pregnant Partner Information Sheet	1.0	2017-12-15
MHRA Clinical Trials Authorisation	1.0	2017-11-24
MHRA Cover Letter Re-Submission	1.0	2017-11-22
MHRA Grounds for Non-Acceptance Letter	1.0	2017-11-08
MHRA Cover Letter	1.0	2017-10-13