PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	89Zirconium-labelled girentuximab (89Zr-TLX250) PET in Urothelial Cancer Patients (ZiPUP) – Protocol for a phase I trial of a novel staging modality for urothelial carcinoma.
AUTHORS	89Zirconium-labelled girentuximab (89Zr-TLX250) PET in Urothelial Cancer Patients (ZiPUP) – Protocol for a phase I trial of a novel staging modality for urothelial carcinoma.

VERSION 1 – REVIEW

REVIEWER	Utomo, Sri Airlangga University, Radiology
REVIEW RETURNED	29-Jan-2022

GENERAL COMMENTS	Dear Author, Your manuscript title: "89Zirconium-labelled girentuximab (89Zr-TLX250) PET in Urothelial Cancer Patients (ZiPUP) – A phase I trial of a novel staging modality for urothelial carcinoma". This is a good manuscript, but for proofing as a staging modality for urothelial carcinoma should perform the statistic analysis.

REVIEWER	Zettlitz, Kirstin City of Hope National Medical Center, Immunology and Theranostics
REVIEW RETURNED	31-Jan-2022

GENERAL COMMENTS	The study protocol “89Zirconium-labelled girentuximab (89Zr-TLX250) PET in Urothelial Cancer Patients (ZiPUP) - A phase I trial of a novel staging modality for urothelial carcinoma” by Al-Zubaidi et al. describes a phase I study for ImmunoPET imaging of urothelial cancer using an zirconium-89 labeled anti-CAIX antibody. The study’s objective and rational are properly described, the study protocol is clearly written. The design and methodology are clearly explained and understandable. Minor: Page 8, line 46: Assuming the authors mean Mega-Bequerel, please capitalize MBq, 37 MBq = 1 mCi. Could the authors include a reference and rationale for the chosen protein dose (10 mg) and imaging time points. Hekman et al, 2018, “89Zr-girentuximab in renal cell carcinoma” used 5 mg/37MBq.

REVIEWER	Ferreira, Clara University Hospital of Coventry and Warwickshire, Nuclear Medicine
REVIEW RETURNED	09-Feb-2022

GENERAL COMMENTS	Dear authors, Thank you very much for submitting your article to BMJ Open, it was a pleasure to review it. In the following points, you can find my doubts, questions and recommendations: On page 2: - I understand that in the title displayed on page 2, you underlined the letters in order for the reader to understand why the name "ZiPUP" is being used. Everything is correct for the "PUP" part, but I think that you need to highlight "Zi" in order to have everything correct and to make sure that your readers do not have any doubts; - On line 27 you mention "CT of chest-abdomen-pelvis", but normally this expression appears has thorax-abdomen-pelvis, which lead to the short name CT-TAP; - The three sentences in the start of the introduction part in the abstract are very short and they can easily be fused together – maybe this way you can add more extra words in another place that you might need; - On line 49, you mention "(…) pre-operative staging of bladder or other urothelial carcinoma (…)" – I think that you mean bladder cancer and other urothelial cancers; this way, I think that you should use the word "carcinomas" instead of just "carcinoma", otherwise it reads as if the carcinoma is only related with the urothelial part and not the bladder. Or maybe you can just use the word "carcinomas" in the next line and save some words. - On the line 54/55, you mentioned "(…) tolerability, and sensitivity and specificity" – the "and" just before sensitivity does not make sense considering that the next parameter will be the last one, so you need to present it just before specificity. On page 3: - On the line 18, you wrote "(…) urothelial cancer and bladder cancer (…)" – please delete the word "cancer" after "urothelial" and the expression "bladder cancer" should be substituted by "bladder cancers". - On the line 21, you mentioned "(…) potentiality to therapeutic or 'theranostic." I am really confused about this sentence: first of all, Zr-89 cannot be used directly for therapy because it decays by electron capture and by emitting β+ particles or do you mean that it can be associated to another radiopharmaceutical in order to create a theranostic pair? The way that is written, people are going to understand that 89Zr can be used as a therapeutic agent, which is definitely not true. If your intention is to mention that other therapy radiopharmaceutical can be used in order to make a theranostic pair, then it is important to indicate which radiopharmaceutical. If what you want to mention is that the result of the scan can be used for the therapeutic part, then it needs to be worded in a different way. - The first keyword that you mention is Zirconium, but there are different Zr isotopes that are radioactive; this way, I think you should mention the mass number in order to avoid any kind of confusion.

	- You mention the word “theranostic” in the keywords instead of “PET theranostic” – the definition of both are different. - On the line 46, you mention “mBq: MegaBecquerels” – there are two mistakes in here: first, if you are referring to MegaBecquerel you should used “M” instead of “m” otherwise mBq means milliBecquerel; secondly, physic units do not have plural so “Becquerels” does not exist, it is only “Becquerel”. On page 4: - The first two sentences of the section “Urothelial cancer” are very short and they can also be fused into just one sentence very easily. - On the line 6/7, you mention “(…) 90 percent (…)” – it should be presented as 90%. - The first part of the Urothelial cancer, from lines 3 to 7, needs to be reviewed. It seems like you just wrote very simple sentences and somehow you are expecting them to make sense to the readers, but you have to think about the best way to transmitting information to them. I know that is not easy to do, but you should put some effort into it. - On the line 18, you mention “(…) of the chest, abdomen (…)” – please use the word “thorax” instead of “chest”, just like indicated for page 2. - On the line 32, you mention “18F-fluorodeoxyglucose (FDG) (…)” – the same long name should be indicated in the keywords. - On line 41, you indicate the subtitle “Carbonic anhydrase (CAIX)”, but the long definition indicated previously is “Carbonic anhydrase IX” and you seem to mention all the long terms in the titles in the introduction. - On the line 45, the last word of the sentence should be “cancers” instead of just “cancer” considering that you identify different types of cancers. - On the lines 47/48, you mention the sensitivity, specificity and the AUC for the detection of urothelial bladder cancer: different authors present different numbers according with the characteristics of what they are studying; this way, it is good to mention the author, other than in just the reference, but actually mention it in the actual document itself and please add some specific characteristics of the research if they exist. - On the line 51, you mentioned predictive numbers: are those specifically about urothelial cancers? It is worth mention that considering that the positive and negative predictive values change according with what you are testing it for. Once again, mention the authors is also important – are they your numbers? – considering that you do not present any references. - On the lines 54/55, you mention that CAIX works in different ways for the different types of urothelial tumours – then how do you justify the numbers presented in the previous paragraph? It is extremely important to mention authors and the specific situation where these numbers come from. Otherwise, the reader will feel really confused when they go from the second to the third paragraph. - On the line 57, you mention that CAIX can be used as a prognostic value – this situation should be further explored and more data are needed. It might be worth to quote some authors and reference them. On page 5: - On the line 3/4 (sentence that starts in the last page; the very last one), you indicate that it is a “strong rationale for investigating the potential (…)” – needs part needs further

	development; it is important to explain why CAIX does not work in the same way for all types of urothelial tumours, but you still think that it is worth checking it. - The section “Carbonic Anhydrase (CAIX)”, it needs further reviewing considering the mixed information which is on there, you need to word it in a different way and make it understandable for everyone. - On the lines 9/10, you present the title of the subsection and it appears mentioned “(…) Zirconum-89-girentuximab (…)” – previously you always present the mass number as superscript, it is important to change it here for the same one, please. None of them are wrong, but once you choose a way to present it, you should keep it until the end. - On the lines 12/13, you indicate the definition of theranostic, mentioning “(…) using isotope-labelled monoclonal antibodies.” – monoclonal antibodies can definitely be used in theranostic, but they are one of the options that you can use, not the only one. With the way that this definition is presented, it seems that using monoclonal antibodies is the only option, which is definitely not true. If you perform a quick search about theranostic, you will check that there are many more options and all of them are valid. - On the line 13/14, you mention that “many ligand-target combinations have been studies (…)” – this sentence could easily be fused with the previous sentence and provide the correct information from the beginning. - On the line 15, you mention the radiopharmaceutical 177Lu-PSMA-617 – once again you need to decide in the position of the mass number; it makes literally no sense in presenting in different ways and it seems like you are trying to go through all of them. Please, stick to one. - On the lines 19/20, you mention that 89Zr can be used as a “suitable ligand” considering this “intrinsic chemical properties” – which ones? Youi have to remember that some people are going to read this and they do not belong to the nuclear medicine area. If you mention something in your paper, whatever it is, it needs to be justified; you cannot just write random things and think that the readers are going to understand. - On the line 20, you mention between parentheses “initially designates as TLX-250” – well, all the other ones have been identified previously as well in the abbreviation section; why do not to mention “initially designated as” in here instead of just “TLX-250”? - On the lines 25/26, you mention that 89Zr-immuno-PET can also be used in breast cancer – it is important to include a brief description of this. Very brief, considering that this one is not the focus of your paper. - On the sentence commencing on line 28, you mention that girentuximab has been used in several clinical trials – which ones? If there are many, mention only the most relevant ones. - The fourth paragraph of the last introduction subsection contains two sentences and they can easily be merged together. - On the lines 56/57, you mention the types of tumours to which the radiopharmaceutical is being tested in this clinical trial – you mean all of these types of cancers? Or did you narrow it down in any way – any specific types of cancers, (T1, T2…)? On page 6: - In you first point in the inclusion criteria, it will be good to add “years old”.

	- In the second point of the inclusion criteria, you mentioned "Able to provide informed consent" – was there any procedure followed for this? What did you use to say that some patients are not able to provide informed consent? Is there any sheet to fill in these kinds of situations? - In the sixth point of the exclusion criteria, you mentioned "(…) non-malignant disease that may interfere with the objective of the study." – Such as? - On the line 59, you mention the need for a 12-lead ECG – is there any specific reason for it? In which way can the radiopharmaceutical affect the heart and/or lungs? On page 7: - On the line 44, you need to use 89Zr considering it was the abbreviation that you gave to it previously. - On the line 50, you mention "NCI-CTCAE v 5.0" – you need to present the full term considering that it is the first time that this term appears. - On the line 53, it would be better to present "Imaging Time (5 ± 2 days)" – the way that you present it is not good to the eye and it causes reading to be difficult. - On the line 58, you present the definition for MDT, but this definition is not indicated in the abbreviation section previously. - In the imaging section, it is important to describe the patient positioning, what to do just before the scan (if anything; for example, FDG patients need to empty their bladder just before going into the scan, I know that the radiopharmaceutical being texted is mostly excreted via hepatobiliary, but you still need to include, even if nothing is needed), do you check anything in the imaging before letting the patient go?, what are your acquisition and reconstruction methods? (these two can affect the visual analysis and the SUV calculations very intensively), ?is it given as a manual injection or do you guys use an automatic injector?. This is the part that needs most of the work; what you have at the moment is so minimal and does not give a full explanation of what is needed. If in the future, you have someone reading this paper because they want to reproduce this experiment, from what you present in this section, it would be impossible. On page 8: - On the line 8, you indicate the full term for NCI-CTC v 5.0, it should be mentioned before considering that the term appears before it. Also, it needs to be included in the abbreviation section. - On the lines 53/54, you need a comma between "English" and "an". - On the line 56, you need to include a full stop at the end of the sentence. On the page 9: - On the line 9, you mention "therapeutic or 'theranostic'" and you mention it throughout the all paper and I waited for the end to check if you were going into detail with this, but you never did. I think you mean 'PET theranostic' and not just "theranostic", if you mean the latter you need to explain it very well considering the 89Zr radioactive decay. You may need to clarify both terms before taking a decision of these. - In the data sharing statement, you mention deidentification of the patient, how do you do it? It is important to mention it. You also mention statistical analysis plan, do you think that it is important to discuss it generally in this paper, just like you did with the other parts of the study? What will be included in the clinical study report? Is there any specific model that should be followed according with this study or according with your organisation?

	On the page 11: - It will be good to review the scheme and try to include the change mentioned previously in this document. Also, the last two boxes have lots of text – maybe you should synthetise or increase the size of the boxes if you want to keep the same text. Otherwise, it is very difficult to read. The first ones look very good with all the text centred, so you need to keep up with that work in the last two boxes. Also, please give It a decent caption considering that "trial schema" does not mean a lot – you will make the reader think that you did not know what caption to write and you did not want to think a lot about it. Please review it. This is great research, amazing, to be honest, but you need to set up a paper as good as the research; otherwise, it does not matter if you have good research considering that you do not know how to communicate it properly. It needs major reviews, but the concept being discussed is amazing. I think that the problem is passing the information in the correct way, but keep it up with the good work, guys. It will be a pleasure to review the paper once the changes have been done. I really hope the research works and that we can use it in the clinical life! Really good, congratulations! Please do not hesitate to contact if you have any questions or doubts about the recommendations.

REVIEWER	Catalano, Onofrio A. Harvard Medical School, Radiology
REVIEW RETURNED	23-Feb-2022

GENERAL COMMENTS	Dear Authors, The manuscript just describes the study you would like to do. It might fit for submission to an ethical committee but I do not see any scientific value in this. It is even not a study. There are even zero patients canned. Zero data .

VERSION 1 – AUTHOR RESPONSE

Responds to Reviewers:
Reviewer 1: Dr Sri Utomo, Airlangga University
Thank you for your review, we really appreciate your time.
We had not clearly identified the nature of this paper as a protocol in the title which has been amended. Many in the scientific community support the value of publishing a protocol paper before the study is completed though of course opinions on this may vary.

Reviewer 2: Dr Kirstin Zettlitz, City of Hope National Medical Center
Thank you for your review, we really appreciate your time.
The comments have been actioned in the manuscript.
The choice of 10mg girentuximab is based on a previous trial which is now referenced in the manuscript for clarity.

Reviewer 3: Miss Clara Ferreira, University Hospital of Coventry and Warwickshire
Thank you for your review and comments, we really appreciate your time.

All your comments are addressed, considered and actioned as follows:

On page 2:
- I understand that in the title displayed on page 2, you underlined the letters in order for the reader to understand why the name “ZiPUP” is being used. Everything is correct for the “PUP” part, but I think that you need to highlight “Zi” in order to have everything correct and to make sure that your readers do not have any doubts;
Zi of Zirconium has been underlined to make it clearer for readers.

- On line 27 you mention “CT of chest-abdomen-pelvis”, but normally this expression appears has thorax-abdomen-pelvis, which lead to the short name CT-TAP;
Many regions in the US, Europe and Australasia use CT chest abdomen and pelvis as the preferred nomenclature.

- The three sentences in the start of the introduction part in the abstract are very short and they can easily be fused together – maybe this way you can add more extra words in another place that you might need;
-We have addressed this and changed it in the manuscript accordingly.

- On line 49, you mention “(…) pre-operative staging of bladder or other urothelial carcinoma (…)” – I think that you mean bladder cancer and other urothelial cancers; this way, I think that you should use the word “carcinomas” instead of just “carcinoma”, otherwise it reads as if the carcinoma is only related with the urothelial part and not the bladder. Or maybe you can just use the word “carcinomas” in the next line and save some words.
-We have addressed this and changed it in the manuscript accordingly.

- On the line 54/55, you mentioned “(…) tolerability, and sensitivity and specificity” – the “and” just before sensitivity does not make sense considering that the next parameter will be the last one, so you need to present it just before specificity.
-We have addressed this and changed it in the manuscript accordingly.

On page 3:
- On the line 18, you wrote “(…) urothelial cancer and bladder cancer (…)” – please delete the word “cancer” after “urothelial” and the expression “bladder cancer” should be substituted by “bladder cancers”.
-We have removed this sentence as it is not reflecting the strength of the study.

- On the line 21, you mentioned “(…) potentiality to therapeutic or ‘theranostic.” I am really confused about this sentence: first of all, Zr-89 cannot be used directly for therapy because it decays by electron capture and by emitting β+ particles or do you mean that it can be associated to another radiopharmaceutical in order to create a theranostic pair? The way that is written, people are going to understand that 89Zr can be used as a therapeutic agent, which is definitely not true. If your intention is to mention that other therapy radiopharmaceutical can be used in order to make a theranostic pair, then it is important to indicate which radiopharmaceutical. If what you want to mention is that the result of the scan can be used for the therapeutic part, then it needs to be worded in a different way.- The first keyword that you mention is Zirconium, but there are different Zr isotopes that are radioactive; this way, I think you should mention the mass number in order to avoid any kind of confusion.

The intention was to mention the possibility of lutetium girentuximab as a theranostic agent. However as this is a protocol paper, and the journal preferences are not to have extensive discussion we have removed any mention of future potential theranostic capabilities

- You mention the word “theranostic” in the keywords instead of “PET theranostic” – the definition of both are different.
-We removed theranostic from the key words as it is not now mentioned in the paper.

- On the line 46, you mention “mBq: MegaBecquerels” – there are two mistakes in here: first, if you are referring to MegaBecquerel you should used “M” instead of “m” otherwise mBq means milliBecquerel; secondly, physic units do not have plural so “Becquerels” does not exist, it is only “Becquerel”.
-We have addressed this and changed it in the manuscript accordingly.

On page 4:
- The first two sentences of the section “Urothelial cancer” are very short and they can also be fused into just one sentence very easily.
-We have addressed this and changed it in the manuscript accordingly.

- On the line 6/7, you mention “(…) 90 percent (…)” – it should be presented as 90%.
-We have addressed this and changed it in the manuscript accordingly.

- The first part of the Urothelial cancer, from lines 3 to 7, needs to be reviewed. It seems like you just wrote very simple sentences and somehow you are expecting them to make sense to the readers, but you have to think about the best way to transmitting information to them. I know that is not easy to do, but you should put some effort into it.
We have changed the wording in this paragraph.

- On the line 18, you mention “(…) of the chest, abdomen (…)” – please use the word “thorax” instead of “chest”, just like indicated for page 2.
Many regions in the US, Europe and Australasia use CT chest abdomen and pelvis as the preferred nomenclature.

- On the line 32, you mention “18F-fluorodeoxyglucose (FDG) (…)” – the same long name should be indicated in the keywords.
-We have addressed this and changed it in the keywords section accordingly.

- On line 41, you indicate the subtitle “Carbonic anhydrase (CAIX)”, but the long definition indicated previously is “Carbonic anhydrase IX” and you seem to mention all the long terms in the titles in the introduction.
We have addressed this and changed it in the manuscript accordingly.

- On the line 45, the last word of the sentence should be “cancers” instead of just “cancer” considering that you identify different types of cancers.
-We have addressed this and changed it in the manuscript accordingly.

- On the lines 47/48, you mention the sensitivity, specificity and the AUC for the detection of urothelial bladder cancer: different authors present different numbers according with the characteristics of what they are studying; this way, it is good to mention the author, other than in just the reference, but actually mention it in the actual document itself and please add some specific characteristics of the research if they exist.
References are usually numbered rather than named, and we followed that in our protocol.

- On the line 51, you mentioned predictive numbers: are those specifically about urothelial cancers? It is worth mention that considering that the positive and negative predictive values change according with what you are testing it for. Once again, mention the authors is also important – are they your numbers? – considering that you do not present any references.
-We have addressed this and changed it in the manuscript accordingly. We have referenced positive and negative predictive values.

- On the lines 54/55, you mention that CAIX works in different ways for the different types of urothelial tumours – then how do you justify the numbers presented in the previous paragraph? It is extremely important to mention authors and the specific situation where these numbers come from. Otherwise, the reader will feel really confused when they go from the second to the third paragraph.
-We have addressed this and changed it in the manuscript accordingly. References are usually numbered rather than named, and we followed that in our protocol.

- On the line 57, you mention that CAIX can be used as a prognostic value – this situation should be further explored and more data are needed. It might be worth to quote some authors and reference them.
We have removed that statement due to paucity of data.

On page 5:
- On the line 3/4 (sentence that starts in the last page; the very last one), you indicate that it is a “strong rationale for investigating the potential (…)” – needs part needs further development; it is important to explain why CAIX does not work in the same way for all types of urothelial tumours, but you still think that it is worth checking it.
It was mentioned and referenced that >70% of urothelial carcinomas express CAIX unlike normal urothelial tissue which does not express it. Which yields to use it as a urothelial carcinoma identification tool.

- The section “Carbonic Anhydrase (CAIX)”, it needs further reviewing considering the mixed information which is on there, you need to word it in a different way and make it understandable for everyone.
-We have addressed this and changed it in the manuscript accordingly.

- On the lines 9/10, you present the title of the subsection and it appears mentioned “(…) Zirconum-89-girentuximab (…)” – previously you always present the mass number as superscript, it is important to change it here for the same one, please. None of them are

wrong, but once you choose a way to present it, you should keep it until the end.
-We have addressed this and changed it in the manuscript accordingly.

- On the lines 12/13, you indicate the definition of theranostic, mentioning "(…) using isotope-labelled monoclonal antibodies." – monoclonal antibodies can definitely be used in theranostic, but they are one of the options that you can use, not the only one. With the way that this definition is presented, it seems that using monoclonal antibodies is the only option, which is definitely not true. If you perform a quick search about theranostic, you will check that there are many more options and all of them are valid.
-We have addressed this and changed it in the manuscript accordingly.

- On the line 13/14, you mention that "many ligand-target combinations have been studies (…)" – this sentence could easily be fused with the previous sentence and provide the correct information from the beginning.
-We have addressed this and changed it in the manuscript accordingly.

- On the line 15, you mention the radiopharmaceutical 177Lu-PSMA-617 – once again you need to decide in the position of the mass number; it makes literally no sense in presenting in different ways and it seems like you are trying to go through all of them. Please, stick to one.
-We have addressed this and changed it in the manuscript accordingly.

- On the lines 19/20, you mention that 89Zr can be used as a "suitable ligand" considering this "intrinsic chemical properties" – which ones? Youi have to remember that some people are going to read this and they do not belong to the nuclear medicine area. If you mention something in your paper, whatever it is, it needs to be justified; you cannot just write random things and think that the readers are going to understand.
-We have addressed this and changed it in the manuscript accordingly.

- On the line 20, you mention between parentheses "initially designates as TLX-250" – well, all the other ones have been identified previously as well in the abbreviation section; why do not to mention "initially designated as" in here instead of just "TLX-250"?
-We have addressed this and changed it in the manuscript accordingly.

-On the lines 25/26, you mention that 89Zr-immuno-PET can also be used in breast cancer it is important to include a brief description of this. Very brief, considering that this one is not the focus of your paper.
As it is not the main focus of the study, it is mentioned and referenced briefly only.

- On the sentence commencing on line 28, you mention that girentuximab has been used in several clinical trials – which ones? If there are many, mention only the most relevant ones.
-We have addressed this and removed this paragraph from the manuscript accordingly.

- The fourth paragraph of the last introduction subsection contains two sentences and they can easily be merged together.
-We have addressed this and changed it in the manuscript accordingly.

- On the lines 56/57, you mention the types of tumours to which the radiopharmaceutical is being tested in this clinical trial – you mean all of these types of cancers? Or did you narrow it down in any way – any specific types of cancers, (T1, T2…)?
We mean all these types of cancers.

On page 6:
- In you first point in the inclusion criteria, it will be good to add “years old”.
-We have addressed this and changed it in the manuscript accordingly.

- In the second point of the inclusion criteria, you mentioned “Able to provide informed consent” – was there any procedure followed for this? What did you use to say that some patients are not able to provide informed consent? Is there any sheet to fill in these kinds of situations?
-As this is a trial, an informed written consent is necessary for participation. Patients cannot be included if unable to provide a written consent.

- In the sixth point of the exclusion criteria, you mentioned “(…) non-malignant disease that may interfere with the objective of the study.” – Such as?
-Liver cirrhosis, advanced heart failure, end stage respiratory disease.
-We have addressed this and changed it in the manuscript accordingly.

- On the line 59, you mention the need for a 12-lead ECG – is there any specific reason for it? In which way can the radiopharmaceutical affect the heart and/or lungs?
ECG is part of initial assessment to confirm no underlying cardiac conduction defect
ECG after injection is needed to confirm no arrythmia or ischemic changes.

On page 7:
- On the line 44, you need to use 89Zr considering it was the abbreviation that you gave to it previously.
-We have addressed this and changed it in the manuscript accordingly.

- On the line 50, you mention “NCI-CTCAE v 5.0” – you need to present the full term considering that it is the first time that this term appears.
-We have addressed this and included it in the abbreviation section.

- On the line 53, it would be better to present “Imaging Time (5 ± 2 days)” – the way that you present it is not good to the eye and it causes reading to be difficult.
-We have addressed this and changed it in the manuscript accordingly.

- On the line 58, you present the definition for MDT, but this definition is not indicated in the abbreviation section previously.
-We have addressed this and changed it in the manuscript accordingly.

- In the imaging section, it is important to describe the patient positioning, what to do just before the scan (if anything; for example, FDG patients need to empty their bladder just

before going into the scan, I know that the radiopharmaceutical being texted is mostly excreted via hepatobiliary, but you still need to include, even if nothing is needed), do you check anything in the imaging before letting the patient go?, what are your acquisition and reconstruction methods? (these two can affect the visual analysis and the SUV calculations very intensively), ?is it given as a manual injection or do you guys use an automatic injector?. This is the part that needs most of the work; what you have at the moment is so minimal and does not give a full explanation of what is needed. If in the future, you have someone reading this paper because they want to reproduce this experiment, from what you present in this section, it would be impossible.
-We have addressed this and changed it in the manuscript accordingly. The scan takes 45 minutes, so emptying bladder is needed as usual.
Route of administration is usually by automatic injector as it is available in Australia, however it can be replaced with manual injection if necessary.

On page 8:
- On the line 8, you indicate the full term for NCI-CTC v 5.0, it should be mentioned before considering that the term appears before it. Also, it needs to be included in the abbreviation section.
-We have addressed this and changed it in the manuscript accordingly.

- On the lines 53/54, you need a comma between “English” and “an”.
-We have addressed this and changed it in the manuscript accordingly.

- On the line 56, you need to include a full stop at the end of the sentence.
-We have addressed this and changed it in the manuscript accordingly.

On the page 9:
- On the line 9, you mention “therapeutic or ‘theranostic’” and you mention it throughout the all paper and I waited for the end to check if you were going into detail with this, but you never did. I think you mean ‘PET theranostic’ and not just “theranostic”, if you mean the latter you need to explain it very well considering the 89Zr radioactive decay. You may need to clarify both terms before taking a decision of these.
The intention was to mention the possibility of lutetium girentuximab as a theranostic agent. However as this is a protocol paper, and the journal preferences are not to have extensive discussion we have removed any mention of future potential theranostic capabilities.

- In the data sharing statement, you mention deidentification of the patient, how do you do it? It is important to mention it. You also mention statistical analysis plan, do you think that it is important to discuss it generally in this paper, just like you did with the other parts of the study? What will be included in the clinical study report? Is there any specific model that should be followed according with this study or according with your organisation?
Deidentification means removing all identifiable details from all correspondence once data sharing is requested.
No data has been collected for statistical analysis plan, however, it is mentioned that it will be available along with the clinical study report afterwards once available. This statement is requested by the medical journal.

On the page 11:

- It will be good to review the scheme and try to include the change mentioned previously in this document. Also, the last two boxes have lots of text – maybe you should synthetise or increase the size of the boxes if you want to keep the same text. Otherwise, it is very difficult to read. The first ones look very good with all the text centred, so you need to keep up with that work in the last two boxes. Also, please give It a decent caption considering that “trial schema” does not mean a lot – you will make the reader think that you did not know what caption to write and you did not want to think a lot about it. Please review it.
-We have addressed this and changed it in the manuscript accordingly.

Reviewer 4: Dr Onofrio A. Catalano, Harvard Medical School
Thank you for your review, we really appreciate your time.
We had not clearly identified the nature of this paper as a protocol in the title which has been amended. Many in the scientific community support the value of publishing a protocol paper before the study is completed though of course opinions on this may vary.

VERSION 2 – REVIEW

REVIEWER	Zettlitz, Kirstin City of Hope National Medical Center, Immunology and Theranostics
REVIEW RETURNED	04-Mar-2022

GENERAL COMMENTS	Congratulations on a clearly and concisely written study protocol. My comments have been fully addressed.

REVIEWER	Ferreira, Clara University Hospital of Coventry and Warwickshire, Nuclear Medicine
REVIEW RETURNED	18-Mar-2022

GENERAL COMMENTS	Thank you very much for re-submitting this scientific paper again in order to perform a new revision. Before everything, congratulations, it is a big improvement since last time. There are only some minor corrections and/or considerations - I made the comments in the word file which you have submitted.

VERSION 2 – AUTHOR RESPONSE

Reviewer Reports:

Reviewer: 2

Dr. Kirstin Zettlitz, City of Hope National Medical Center

Comments to the Author:

Congratulations on a clearly and concisely written study protocol.

My comments have been fully addressed.

Thank you very much for your review and feedback.

Reviewer: 3

Miss Clara Ferreira, University Hospital of Coventry and Warwickshire

Comments to the Author:

Dear author,

Thank you very much for re-submitting this scientific paper again in order to perform a new revision.

Before everything, congratulations, it is a big improvement since last time. There are only some minor corrections and/or considerations - I made the comments in the pdf file which you have submitted.

Thank you,

Thank your for your feedback and efforts, We are responding to the comments according to its reference as follows:

CF1) Many regions in the US, Europe and Australasia use CT chest abdomen and pelvis as the preferred nomenclature. Therefore, we are using Chest (rather than Thorax) as it is the term used here.

CF2) -We have addressed this and changed it in the manuscript accordingly.

CF3) We have addressed this and changed it in the manuscript accordingly.

CF4) Bladder cancer here is a general term including all histological subtypes, therefore it has not been changed.

CF5) In this paragraph, we are mentioning the most common subtype of bladder cancer unlike the previous sentences in (CF4).

CF6) We have maintained the sentence structure as previously; we have rephrased the second sentence for clarity.

CF7) Many regions in the US, Europe and Australasia use CT chest abdomen and pelvis as the preferred nomenclature. Therefore, we are using Chest (rather than Thorax) as it is the term used here.

CF8) We meant biopsy in general; therefore, we have addressed your comment by making it biopsy as a general term.

CF9) This cited reference used the term cancer not carcinomas; therefore, this is remains unchanged.

CF10) We have addressed this and changed it in the manuscript accordingly.

CF 11) We have addressed this and changed it in the manuscript accordingly.

CF12) We have addressed this and changed it in the manuscript accordingly.

CF13) We have addressed this and changed it in the manuscript accordingly.

CF14) It is a term that usually used to refer to days after a procedure or interventions. We believe it is clear. However, we have further clarified in the paragraph below as per your advice.

CF15) We have addressed this and changed it in the manuscript accordingly.

CF16) The figure has been uploaded to the BMJ Open portal as per instructions and guidance.