PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Clinical evaluation of pharmacists' interventions on multidisciplinary lung transplant outpatients' management: results of a 7-year observational study
AUTHORS	Duwez, Marion; Chanoine, Sébastien; Lepelley, Marion; Vo, Ha; Pluchart, Hélène; Mazet, Roseline; Allenet, Benoit; Pison, Christophe; Briault, Amandine; Saint-Raymond, Christelle; Camara, Boubou; Claustre, Johanna; Bedouch, Pierrick

VERSION 1 – REVIEW

REVIEWER	Gregory Peterson University of Tasmania, Australia
REVIEW RETURNED	27-Jun-2020

GENERAL COMMENTS	Thank you for the submission. However, I am unsure if the manuscript has sufficient novelty, importance and scientific rigour for publication in BMJ Open. It is a retrospective analysis, without a control group and real clinical outcomes; in effect, it is primarily around processes rather than evaluating outcomes in a robust manner. It covers a relatively small sample of LT recipients (157) over a 7-year period. The data are also now very old (5 years since last data collection). The data needs to be presented in terms of proportion of patients e.g. what percentage of LT recipients over the study period had DRPs and PIs? It is very difficult to interpret as is. The focus should be on the patient (e.g. as a unit of measurement). Simply listing numbers of DRPs and PIs is not very useful, without any indication of the number (and %) of patients affected. There is insufficient detail of the panel assessment e.g. was it an expert committee fully independent of the study? What was the inter-rater agreement? In the discussion, it is stated that "…clinical impact of accepted PIs was positive in 98.9% of cases and none had negative clinical impact." How was this assessed? It was not reported in the methods and results. Were patients followed to determine actual clinical outcomes? Perhaps more importantly, what were the clinical outcomes from the PIs that were not accepted?

REVIEWER	Jonathan Penm The University of Sydney
REVIEW RETURNED	15-Jul-2020

GENERAL COMMENTS	Thank you for the opportunity to review this article. I believe it is an important piece of work regarding the development of clinical pharmacy services in lung transplant patients. The authors have done a great job and I only have a few minor comments that may strengthen this paper:

	1. I noted that there is another paper investigating clinical pharmacy services in an outpatient lung transplantation. I believe this should be referenced in the introduction and results compared with in the discussion (with an explanation on why the results are similar/different) - Harrison JJ, Wang J, Cervenko J, Jackson L, Munyal D, Hamandi B, Chernenko S, Dorosz J, Chaparro C, Singer LG. Pilot study of a pharmaceutical care intervention in an outpatient lung transplant clinic. Clinical transplantation. 2012 Mar;26(2):E149-57. 2. For the website observatory, Act-IP, was recording DRPs and PIs for lung transplant patients mandatory or voluntary? Voluntary reporting can lead to bias as interventions not accepted/considered minor may not be entered. 3. Design in abstract states “prospective cohort study” while the manuscript methods state “A retrospective observational study”. Please clarify. As there was no control group, I assume this was not a cohort study. 4. You state “All patients gave written informed consent to use their data for research.” How was consent obtained e.g who ask them and was this asked for all LT recipients in Grenoble University Hospital over the 7-year period. If so, how many did not consent? 5. Can you provide the inter-rate agreement between expert committee members that blindly evaluated each accepted PI? 6. Authors should consider doing some statistical analysis in the paper to support their conclusions. e.g. Types of PIs for each group of clinical impact (major, moderate and minor) could be compared using a Chi-square test, to statistically show the difference in types of PIs that cause major clinical impact to minor ones.

REVIEWER	Tamasine Grimes Trinity College Dublin Ireland
REVIEW RETURNED	20-Jul-2020

GENERAL COMMENTS	Thank you for the opportunity to review this manuscript describing the clinical impact of pharmaceutical interventions which had been recorded at a single lung transplant outpatient clinic over a 7 year period. The paper add to the existing evidence base describing the range and complexity of medication-related problems experienced by this population. This descriptive paper is generally well written, with few minor typographical errors. Minor points which could be addressed to enhance the rigour of the study and the reporting include: Abstract - suggest revise the conclusion. The data described provide evidence of the pharmacist contribution and it's clinical impact but do not provide evidence that pharmacists optimise therapeutic outcomes. Methods - further detail on the CLEO tool and how/by whom it was applied would be useful. Reference 18 seems incomplete and the reader cannot gain further insight from the detail provided.

	Methods - clarify whether there was any opportunity to follow patients longitudinally in this register over the 7 years. Results - more information about the volume of patients, relative to other activity in this hospital, would be helpful. 152 outpatient visits over a 7 year period does not seem like a lot, albeit that lung transplantation is not a common intervention. Greater clarity about the proportion of patients who received a PI would be useful. Discussion - the data presented in this study describe the recorded PIs only, and not overall pharmacist activity. There is absence of data to support the claims about the positive impact of the pharmacist on patient care. However, such an investigation could be suggested for future work. Minor point: Page 4, line 40 - should the impact here be "life saving" rather than "lethal". Surely the impact is the avoidance of a potentially lethal scenario? Supplementary reporting - The STROBE checklist for observational studies may be useful here.

VERSION 1 – AUTHOR RESPONSE

Comments from Reviewer: 1
Gregory Peterson
University of Tasmania, Australia

Comment a) Thank you for the submission. However, I am unsure if the manuscript has sufficient novelty, importance and scientific rigour for publication in BMJ Open. It is a retrospective analysis, without a control group and real clinical outcomes; in effect, it is primarily around processes rather than evaluating outcomes in a robust manner.
Response: We recognize that our study design did not allow us to obtain robust results, particularly due to the lack of control group. However, we conducted an observational study over a long period (7 years) on the specific population of lung transplant recipients to assess the clinical impact of pharmaceutical interventions on outpatients' management from a validated tool already used in the literature.

Comment b) It covers a relatively small sample of LT recipients (157) over a 7-year period.
Response: We recognize that our study was carried out on a small sample size. However, lung transplantation represents 6% of the global transplantation activity in France according to the French Biomedicine Agency (Please find data here: https://www.agence-biomedecine.fr/IMG/pdf/cp_presentation-activite-greffes-annee-2019.pdf). In 2015, 345 lung transplantations were performed (vs. 1,355 liver transplantations and 3,486 kidney transplantations) in about ten French lung transplantation centers. Here, we studied clinical pharmacist's activities on 157 lung transplant outpatients followed in our lung transplantation center.

Comment c) The data are also now very old (5 years since last data collection).
Response: Indeed, data were collected prospectively over a long period, between 2009 and 2015. Then, data were extracted from the Act-IP© website and managed to ensure their quality. Each pharmacists' intervention was assessed by an independent expert

committee (a pharmacovigilance expert, a pulmonologist, and a clinical pharmacist) during a face-to-face meeting, to determine its clinical impact. All these steps took a long time, which explains that the data seem to be old.

Comment d) The data needs to be presented in terms of proportion of patients e.g. what percentage of LT recipients over the study period had DRPs and PIs? It is very difficult to interpret as is. The focus should be on the patient (e.g. as a unit of measurement). Simply listing numbers of DRPs and PIs is not very useful, without any indication of the number (and %) of patients affected.
Response: Pharmacists' interventions (PIs) were prospectively recorded on the anonymized Act-IP© database which is the national documentation system of PIs used commonly in France. This database allowed us to know the total number of interventions over the study period. As these interventions were recorded anonymously, it is not possible to present data in terms of proportion of patients. However we also used the data from the hospital transplant register over the same period to improve patient characterization independently. We recognize that is one of the study limitations and we have added this point in the Discussion section (page 18): "Our data could not be presented in terms of patient proportion as all the PIs were recorded anonymously in the Act-IP© database."

Comment e) There is insufficient detail of the panel assessment e.g. was it an expert committee fully independent of the study?
Response: The expert committee belonged to Grenoble University Hospital but was independent of the study. Moreover each pharmacists' intervention was anonymized leading to a full independent clinical assessment. We have clarified this point in the Methodsection (page 10): "Clinical assessment was performed by an independent expert committee (a pharmacovigilance expert, a pulmonologist, and a clinical pharmacist) from Grenoble University Hospital during a face-to-face meeting. After the presentation by the meeting moderator of each accepted intervention, each expert independently and blindly evaluated the clinical impact of each of these interventions prior to discussion to reach an expert consensus".

Comment f) What was the inter-rater agreement?
Response: The objective of the assessment was to get a consensus to determine the impact of pharmacists' interventions (PIs) rather than to determine the inter-rater agreement. Consequently, we used the CLEO© tool (which is comprehensive, relatively easy and not too time consuming to use, reliable and validated in different contexts) for this face-to-face assessment. As previously described, each expert independently and blindly evaluated the clinical impact of each of these interventions prior to discussion to reach an expert consensus afterward. Therefore, we did not evaluate the inter-rater agreement but it was quite easy to obtain a consensus for each PI between the experts as they all participated for each assessment and used the CLEO© algorithm for guiding ratings (please see Reference 19, page 128, figure 25: Algorithm for rating of significance of PIs according to the CLEO tool). We have clarified this point in the Methods section (page 10): "No inter-rater agreement was measured as each PI was rated after expert consensus".

Comment g) In the discussion, it is stated that "…clinical impact of accepted PIs was positive in 98.9% of cases and none had negative clinical impact." How was this assessed? It was not reported in the methods and results.
Response: We thank the Reviewer for this comment. We recognize that this point is not clear in the manuscript. According to the CLEO© tool, positive clinical impact means that interventions had a minor, moderate or major impact, or avoids fatality. Each score was defined as follows:

- Minor: the pharmacists' intervention (PI) can improve knowledge, satisfaction, medication adherence and/or quality of life OR the PI can prevent harm that does not require monitoring/treatment;

- Moderate: the PI can prevent harm that requires further monitoring/treatment, but does not lead to or does not extend a hospital stay;
- Major: the PI can prevent harm which causes or lengthens a hospital stay OR causes permanent disability or handicap;
- Avoids fatality: the PI can prevent an accident that potentially causes the need for intensive care or death of the patient.

Conversely, an intervention can be defined to have no (i.e. the PI can have no influence on the patient regarding the clinical status, knowledge, satisfaction, patient adherence and or quality of life of the patient) or a negative (i.e. the PI can lead to adverse outcomes on clinical status, knowledge, satisfaction, patient adherence and/or quality of life of the patient) clinical impact from the CLEO© tool. If the available information does not allow to evaluate clinical impact, the PI is classified as undetermined.
We have clarified this point in the Methods section (page 10): "This tool includes a clinical dimension with several numeric levels including negative, null and positive impacts (Minor, Moderate, Major, Avoids fatality), and an open level "undetermined".

Comment h) Were patients followed to determine actual clinical outcomes?
Response: In this study, we assessed the clinical impact of pharmacists' interventions (PIs) leading to a change in therapeutic management and preventing harm that would have certainly occurred if the pharmacist had not intervened. Harm was defined as alteration of the physical and mental capacities arising from an accident or illness. Lung transplant recipients were followed by the multidisciplinary transplant team during this study so that if drug related problems had been detected a PI would have been carried out if necessary and integrated into the Act-IP© database. Unfortunately, as previously specified, it was not possible to identify all the PIs relating to the same patient due to the anonymization of the data in the database used in daily practice. Moreover, the measurement of end-point outcomes was limited by the design of this 7-year retrospective study. We also recognize that a positive intermediate outcome may not lead to a positive endpoint outcome such as avoiding death but measures of potential impacts of PIs can be validly used as a measure of quality and add-value provided by pharmacists.

Comment i) Perhaps more importantly, what were the clinical outcomes from the PIs that were not accepted?
Response: The clinical impact assessment of non-accepted pharmacists' interventions (PIs) was not performed as no change in therapeutic management was deemed useful by physicians. Therefore, it was not possible to perform this kind of assessment nor clinical outcomes despite the lack of change in therapeutic management (no data are available in Act-IP© database concerning these information). In addition, the validity of the CLEO© tool is better if evaluators rate accepted PIs than refused PIs (Please see reference 19).

Comments from Reviewer: 2
Jonathan Penm
The University of Sydney

Thank you for the opportunity to review this article. I believe it is an important piece of work regarding the development of clinical pharmacy services in lung transplant patients. The authors have done a great job and I only have a few minor comments that may strengthen this paper:

Comment 1) I noted that there is another paper investigating clinical pharmacy services in an outpatient lung transplantation. I believe this should be referenced in the introduction and results

compared with in the discussion (with an explanation on why the results are similar/different) - Harrison JJ, Wang J, Cervenko J, Jackson
L, Munyal D, Hamandi B, Chernenko S, Dorosz J, Chaparro C, Singer LG. Pilot study of a pharmaceutical care intervention in an outpatient lung transplant clinic. Clinical transplantation. 2012 Mar;26(2):E149-57.
Response: We thank the Reviewer for this comment. We have included this relevant reference in the Introduction section (page 6): “However, pharmaceutical care in LT recipients is less studied than in renal or liver transplantation and the impact of clinical pharmacists’ interventions (PIs) is poorly studied in lung transplantation as only one study performed in Canada on a small sample size was reported”; and in the Discussion section (pages 14-16): “To the best of our knowledge, only one other study described pharmaceutical care intervention among LT outpatients. This Canadian study was also a retrospective single center study but performed over a short period of seven months with senior clinical pharmacists providing patient care for only one-half day per week. Indeed, 55 DRPs were detected over 50 clinic visits concerning 43 patients mostly met only one time, during the early post-transplant period (< 3 months). This study mainly discussed patient satisfaction with pharmacist care rather than the type of DRPs and the clinical impact of PIs” and “However, Harrison et al. reported that their interventions mainly involved gastrointestinal drugs without discussing this finding”.

Comment 2) For the website observatory, Act-IP, was recording DRPs and PIs for lung transplant patients mandatory or voluntary? Voluntary reporting can lead to bias as interventions not accepted/considered minor may not be entered.
Response: The recording of DRPs and PIs was mandatory. However, we cannot exclude a potential under-reporting (i.e. non-accepted PIs because of lack of pharmacist impact) leading to an underestimate of DRPs prevalence. We have clarified this point in the Discussion section (page 18): “In addition, not all identified DRPs may be recorded on the Act-IP© database although it was mandatory, which may lead to an underestimate of DRPs prevalence. This possible under-reporting could not be excluded, particularly for non-accepted PIs”.

Comment 3) Design in abstract states “prospective cohort study” while the manuscript methods state “A retrospective observational study”. Please clarify. As there was no control group, I assume this was not a cohort study.
Response: We thank the Reviewer for this comment. Pharmacists’ interventions (PIs) performed during lung transplant outpatients’ management were prospectively recorded on the Act-IP© database over the 7-year study period. In 2016, a data management was performed by a pharmacist resident to guarantee data quality. Then, PIs were retrospectively described and their impact was assessed by an expert committee during a face-to-face meeting. We have clarified this point in the Abstract section (page 4): “Design: Data were collected prospectively from a LT recipients cohort during 7 years. A multidisciplinary committee assessed retrospectively the clinical impact of accepted PIs”; in the Methods section (page 7): “A retrospective observational study was performed on the PIs recorded on Act-IP© website observatory from 1st January 2009 to 31th December 2015 and related to the 152 LT recipients followed at the 2,200-bed Grenoble University Hospital over the 7-year period”.

Comment 4) You state “All patients gave written informed consent to use their data for research.” How was consent obtained e.g who ask them and was this asked for all LT recipients in Grenoble University Hospital over the 7-year period. If so, how many did not consent?
Response: All lung transplant recipients have consistently given their consent for the use of their data for research before transplantation and study ethics approval was obtained on 28th March 2019 (CECIC Rhône-Alpes-Auvergne, Clermont-Ferrand, IRB 5891).

Comment 5) Can you provide the inter-rate agreement between expert committee members that blindly evaluated each accepted PI?

Response: We thank the Reviewer for this comment and invite him to find the reply to one of the comments from another reviewer (Reviewer 1, Comment f).
The objective of the assessment was to get a consensus to determine the impact of pharmacists' interventions (PIs) rather than to determine the inter-rater agreement. Consequently, we used the CLEO© tool (which is comprehensive, relatively easy and not too time consuming to use, reliable and validated in different contexts) for this face-to-face assessment. As previously described, each expert independently and blindly evaluated the clinical impact of each of these interventions prior to discussion to reach an expert consensus afterward. Therefore, we did not evaluate the inter-rater agreement but it was quite easy to obtain a consensus for each PI between the experts as they all participated for each assessment and used the CLEO© algorithm for guiding ratings (please see Reference 19, page 128, figure 25: Algorithm for rating of significance of PIs according to the CLEO tool). We have clarified this point in the Methods section (page 10): "No inter-rater agreement was measured as each PI was rated after expert consensus".

Comment 6) Authors should consider doing some statistical analysis in the paper to support their conclusions. e.g. Types of PIs for each group of clinical impact (major, moderate and minor) could be compared using a Chi-square test, to statistically show the difference in types of PIs that cause major clinical impact to minor ones.
Response: We thank the Reviewer for this relevant comment. We performed some statistical analysis to support our conclusions. We showed that the difference in the distributions of drug related problems (DRPs) according to the clinical impact levels is statistically significant ($p < 0.0001$).
We also performed Cochran-Armitage tests for trend to specify the association of some DRPs with clinical impact. We added these points in the Methods section (page 11): "Fisher's exact test was used to compare the distribution of DRPs according to the clinical impact levels. Cochran-Armitage test for trend was used to test the association between differet types of DRPs (drug-drug interaction, drug without indication and drug monitoring) and the clinical impact level as ordinal variable" and in the Results section (page 13): "PIs with major clinical impact were mostly related to drug-drug interactions (n=40, 39.6%, $p < 0.0001$)" and " There was a positive association between "drug-drug interactions" DRPs and the clinical impact level ($p < 0,0001$) whereas "drug without indication" and "drug monitoring" DRPs had a negative association with the clinical impact level ($p < 0,0001$)".

Comments from Reviewer: 3
Tamasine Grimes
Trinity College Dublin, Ireland

Thank you for the opportunity to review this manuscript describing the clinical impact of pharmaceutical interventions which had been recorded at a single lung transplant outpatient clinic over a 7 year period. The paper add to the existing evidence base describing the range and complexity of medication-related problems experienced by this population. This descriptive paper is generally well written, with few minor typographical errors. Minor points which could be addressed to enhance the rigour of the study and the reporting include:

Comment 1) Abstract - suggest revise the conclusion. The data described provide evidence of the pharmacist contribution and its clinical impact but do not provide evidence that pharmacists optimize therapeutic outcomes.
Response: We thank the Reviewer for this comment. In this study, the positive clinical impact of pharmacists' interventions (PIs) was clearly highlighted leading to a change in therapeutic management. We recognize that PIs could only prevent harm that would have certainly occurred if the pharmacist had not intervened and that the potential clinical impact of PIs rated through the CLEO© tool are only intermediate outcomes for proving the benefits of PIs. We have clarified the Conclusion in the Abstract section (pages 4-5): "Clinical pharmacists play a key role for detecting DRPs mostly leading to a change in therapeutic management among LT outpatients. Our study

provides a new insight to analyze the clinical impact of pharmacists' interventions in order to target PIs which have most value and contribute to patient care through interdisciplinary approach".

Comment 2) Methods - further detail on the CLEO tool and how/by whom it was applied would be useful.
Response: The CLEO© tool is the result of a review of theoretical models of evaluation, existing tools and inputs of clinical pharmacists' practice. Indeed, the creation was based on an integrated model synthetizing six types of impacts from many evaluation models in the literature: a systematic review of existing tool for assessment of the potential significance of pharmacists' interventions (PIs) was conducted and lead to recommendations on characteristics of optimal tool to assess PIs (Please see Reference 24). From these recommendations, a new tool was developed and tested for validity, inter-rater and intra-rater reliability, and user friendliness in two studies (19).
Compared to the results of other tools in the literature, clinical dimension of CLEO© tool is reliable and valid to be used in daily practice by pharmacists and allows them an assessment of clinical and humanistic outcomes from the patient's perspective.
There are others benefits of using the CLEO© tool to assess clinical impact: many definitions and terminology used in "clinical impact" are similar to the NCC MERP Index - a famous grading system for the actual severity of medication errors – and the six-level structure of "clinical impact" was inspired from the structure of a famous tool of Hatoum et al. used most widely in the literature, which facilitated better comparison of results from our study and from other solid organ transplantation studies. To the best of our knowledge, the CLEO© tool was applied to assess PIs in a Chemotherapy Preparation Unit (33) and was also translated in a German version (34).
We have clarified this point in the Discussion section (page 17): "This CLEO© tool was used to assess the clinical impact of PIs on injectable antineoplastic prescriptions in a French Hospital Chemotherapy Preparation Unit (33) and was translated and validated in a German version (34)".

19. Thi Ha Vo. Evaluation of the potential impact of pharmacist interventions: development and validation of the CLEO multidimensional tool. Pharmaceutical sciences. Université Grenoble Alpes, 2015. English. ffNNT : 2015GREAS034ff. fftel-01315619

33. Zecchini C, Vo T-H, Chanoine S, Lepelley M, Laramas M, Lemoigne A, et al. Clinical, economic and organizational impact of pharmacist interventions on injectable antineoplastic prescriptions: a prospective observational study. BMC Health Serv Res [Internet]. déc 2020 [cité 4 oct 2020];20(1). Disponible sur: https://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-020-4963-7

34. Stämpfli D, Baumgartner P, Boeni F, Bedouch P, Lampert ML, Hersberger KE. Translation and validation of a tool to assess the impact of clinical pharmacists' interventions. Int J Clin Pharm. févr 2019;41(1):56-64

Comment 3) Reference 19 seems incomplete and the reader cannot gain further insight from the detail provided.
Response: We thank the Reviewer for this comment. Reference 19 is now clarified completely in the References section (page 22): "Vo T-H. Evaluation of the potential impact of pharmacist interventions: development and validation of the CLEO multidimensional tool. Pharmaceutical sciences. Université Grenoble Alpes, 2015. English. ffNNT : 2015GREAS034ff. fftel-01315619".

Comment 4) Methods - clarify whether there was any opportunity to follow patients longitudinally in this register over the 7 years.
Response: The Act-IP© database allows a recording of pharmacists' interventions through a one-time action in a standard form without any follow-up integrated. Thus, it was not possible to follow patients longitudinally through this official database.

We have clarified this point in the Methods section (page 9): “The pharmacist prospectively completed the anonymized online report form” and “This tool was designed to record PIs through one-time actions and does not allow to follow patients longitudinally”

Comment 5) Results - more information about the volume of patients, relative to other activity in this hospital, would be helpful. 152 outpatient visits over a 7-year period does not seem like a lot, albeit that lung transplantation is not a common intervention.
Response: We thank the Reviewer for this comment, as there is a potential misleading. This study concerns 152 lung transplant outpatients followed in the 15-bed Pneumology day hospital of the 2,200-bed Grenoble University Hospital over a 7-year period. Each of these outpatients came in the Pneumology day hospital about every one to three months for monitoring. However this day hospital treats an average of 60 outpatients per week from Monday to Friday, suffering from different pulmonary diseases (mostly cystic fibrosis, pulmonary arterial hypertension, chronic obstructive pulmonary disease, asthma or lung transplantation) and LT outpatients represent 17% of them. We have clarified this point in the Methods section (pages 8-9): “LT outpatients come in the 15-bed Pneumology day hospital about every one to three months for monitoring according to medical appreciation” and “Clinical pharmacists interview 10 LT outpatients per week on average, representing about 17% of the total number of outpatients visiting the day hospital”.

Comment 6) Greater clarity about the proportion of patients who received a PI would be useful.
Response: We thank the Reviewer for this comment as it was notified by another Reviewer. Pharmacists’ interventions (PIs) were prospectively recorded on the anonymized Act-IP© database which is the national documentation system of PIs used commonly in France. This database allowed us to know the total number of interventions over the study period. As these interventions were recorded anonymously, it is not possible to present data in terms of proportion of patients. However we also used the data from the hospital transplant register over the same period to improve patient characterization independently. We recognize that is one of the study limitations and we have added this point in the Discussion section (page 18): “Our data could not be presented in terms of patient proportion as all the PIs were recorded anonymously in the Act-IP© database.”

Comment 7) Discussion - the data presented in this study describe the recorded PIs only, and not overall pharmacist activity. There is absence of data to support the claims about the positive impact of the pharmacist on patient care. However, such an investigation could be suggested for future work.
Response: Following these patients over the 7-year period relied on a multidisciplinary approach through medical visits, dietician visits, and pharmacist interviews.
Clinical pharmacists’ activities consist in optimizing patient care in the ward: attending medical rounds (i.e. validation of computerized medication orders), patient interview (patient teaching and counseling about medication and lifestyle, medication reconciliation, optimizing medication adherence) but also analyzing lab results for therapeutic drug monitoring and implementing drug protocols.
In this study, we described the recorded pharmacists’ interventions (PIs) from lung transplant outpatients’ follow-up concerning all these pharmacists’ activities in the ward. However, clinical pharmacy activities are also monthly documented separately in a local Pharmacy department database (i.e. number of computerized medication orders validated, number of medication reconciliations, number of patient education sessions, number of pharmacovigilance reporting, number of drug protocols created or updated, etc.) and we thank the Reviewer for the suggestion to investigate these data in a future work.

Comment 8) Minor point: Page 4, line 40 - should the impact here be "life saving" rather than "lethal". Surely the impact is the avoidance of a potentially lethal scenario?

Response: We thank the Reviewer for this comment. The impact is clearly the avoidance of a potentially lethal scenario so the term “lethal” was replaced by “avoids fatality” in the entire manuscript as the pharmacist’s intervention can prevent an accident. We chose “Avoids fatality” instead of “life saving” to be consistent with the CLEO© terms. We have clarified this point in the Abstract section (page 4): “The clinical impact of PIs was ”avoids fatality”, “major” and “moderate”, in 0.1%, 7.0%, and 57.9%, respectively”; in the Results section (page 14): “According to the Pareto chart, concerning PIs with major or “avoids fatality” clinical impact (n=103) related to 144 drugs” ; and in the Figure 4 Title: “Figure 4: Pareto chart of “major” and ”avoids fatality” clinical impact of accepted pharmacist’s interventions (PIs) according to ATC groups (n=103), related to 144 drugs (group A: 80% of PIs; group B: 15% of PIs; group C: 5% of PIs)”.

Comment 9) Supplementary reporting - The STROBE checklist for observational studies may be useful here.
Response: We thank the Reviewer for this comment. We have added a completed copy of STROBE checklist along with the manuscript providing some clarification throughout the manuscript. We have also clarified point 6. of STROBE checklist in the Methods section (pages 7-8): “Patients were eligible if they were lung transplanted before 1st January 2009 or between 1st January 2009 and 31th December 2015 according to our computerized hospital register of transplantation” and point 7. of STROBE checklist in the Methods section (page 8): “Overall, clinical pharmacy services are provided since 2008 by two senior and two resident pharmacists five days a week in our lung transplantation center”.