PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cost-utility and budget impact analyses of the use of NEPA for chemotherapy-induced nausea and vomiting prophylaxis in Italy
AUTHORS	Restelli, Umberto; Saibene, Gabriella; Nardulli, Patrizia; Di Turi, Roberta; Bonizzoni, Erminio; Scolari, Francesca; Perrone, Tania; Croce, Davide; Celio, Luigi

VERSION 1 - REVIEW

REVIEWER	Matti Aapro Genolier Cancer Center Switzerland I know the senior author. Dr Celio and have published with him
REVIEW RETURNED	15-Feb-2017

GENERAL COMMENTS	Introduction: the study cited ref 14 had more than 114 patients. It deals only with apr/palo This reviewer does not understand where the numbers for the other variables come from: for side-effects references aregiven but for efficacy, ? Please indicate that for you HEC is cisplatin and MEC comprises of AC, carbo and others. Page 11: lung not lungs Please qualify your conclusions as pertinent only with the limitations of the moedls used

REVIEWER	de Las Peñas, Ramon Department of Medical Oncology Consorcio Hospital Provincial Castellón Spain
REVIEW RETURNED	26-Feb-2017

GENERAL COMMENTS	The authors should list the references in the order they appear in the text. On page 5, lines 48-56, the authors refer to a statistical model for analysis of successive cycles. The bibliographic reference (16) is not clearly justified with the text. For this part of the text it would be convenient to participate of a specialist statistician as a reviewer.

REVIEWER	Karthaus, Meinolf Klinikum Neuperlach, Department Hematology/Oncology and Palliative Care, Germany

	Advisory Board for HELSINN, MSD, TESARO
REVIEW RETURNED	06-Mar-2017

GENERAL COMMENTS	CINV is a major threat for patients if not protected. Incomplete protection may result in subsequent costs for treatment of complications. A combination of 5-HT3-RA together with NK1-RA-antagonists is standard of care. This combination shows a complete protection of acute and delayed vomiting in up to more than 80% of patients receiving HEC and MEC. The fixed combination with NEPA has recently been approved for HEC and MEC with anthracyclin/cyclophosphamide data. The costs of antiemetic drugs and rescue medication and add-on treatments (unscheduled visits, emergency room admissions, outpatient activities and hospitalisations) for patients not having a complete protection are presented. The estimated costs for the management of adverse events came from interview with a Key Opinion Leader referring to the Department of Medical Oncology. The authors present the data in context of the Italian National Health Service. The discussion should be more careful. It should be discussed: Palonosetron has already lost its patent and aprepitant will loose its patent in the near future. This might have an influence on the budget of cancer and supportive care and should be included in the discussion. The frequency of since severe CINV differs in Europe between countries. This might have an impact on rescue treatment costs. Further direct costs of the aquisition of drugs by hospital pharmacies differs considerably to the outpatient situation in a lot of countries. Therefore cross-country comparisons should be made with caution. The authors could include the Paper of Turini et al (Drugs in Context 2015).

REVIEWER	Karam Diaby Florida A&M University, USA
REVIEW RETURNED	15-Apr-2017

GENERAL COMMENTS	Review of the manuscript: Cost-utility and budget impact analyses of the use of NEPA for chemotherapy-induced nausea and vomiting prophylaxis in Italy I would like to praise the authors for their efforts in putting together this manuscript. The topic is of interest and relevant. That being said, I have had difficulties understanding some sections of the paper, which limited my ability to fully assess the value of their manuscript. My specific comments are below: Abstract The abstract is a good reflection of what the authors present in the main text of the paper. Page 3, line 6: I don't understand why the model used by the authors would not allow for probabilistic sensitivity analysis? How about deterministic sensitivity analysis? Introduction This section provides a good background on the topic presented in this paper. Please see my comments below. Page 4, line 4: This statement needs referencing.

	Page 5, Line 7-18: This paragraph does not fully help the authors make the case about the importance of their study or why it is needed. The lack of evidence of cost-effectiveness analysis of NEPA for chemotherapy-induced nausea and vomiting prophylaxis in the Italian setting is not sufficient to warrant a study. I believe that it is the consequences/ impact of not conducting this study that should provide a full justification as to why the authors should perform such analyses. Methods I believe this section could be restructured to improve the readability of the manuscript. I would suggest the following structure (Wording can be modified) I-Economic Evaluation 1-Overview of the model (with justification of choices) Type of economic model Population Interventions Time Horizon Outcome measures Model description 2-Model Parameters Clinical efficacy analysis Costs Utility 3- Base case results 4- Sensitivity analysis II-Budget impact analysis 1- Estimation of target population size 2- Interventions compared: Current intervention mix Vs. New intervention mix\ 3- Time horizon 4- Resource use and costs 5- Scenario analysis Results This section should be organized in light of the sub-sections of the methods. Discussion and conclusion Page 5 – line 50-57: This sentence is too long. The sentence should be rephrased and statements about what the authors did should be explained. For example, the authors mentioned the following: “The proportion of patients with a either CR or CP was used to evaluate efficacy across acute and overall phases” and then estimated CR and CP rates using GLMM. Were the authors interested in estimating proportions or rates? I think there is a difference between these variables. In addition, the specification of the GLM model needs further clarifications and choice justification regarding the link identity function and family used, the need for a mixed model since only fixed effects were used. This begs the following question: What is the added value of the GLMM in estimating rates compared to classic statistical models? Page 6- Line 32-67: Figure 1 is not clear to me. The model structure is confusing, between the acute phase (1 day), the delayed phase

	(2-5) and the overall cycle. What happens to patients that reach the incomplete response state? The estimation of transition probabilities is not clearly explained, a part from a mention of the use of linear interpolation. The authors should discuss the appropriateness of using linear interpolation in this case. In the discussion section, limitations about using this approach should be discussed. Page 10- Line 33: The authors used 10 - 20% variation range for cost and utility parameters without justifying their choices. No attempt was made to conduct probabilistic sensitivity analyses, which matters a great deal since it shows the impact of joint parameter uncertainty on the ICER. Page 11- line 3: I do not believe the BIA was conducted according the ISPOR guidelines on the implementation of BIA. A structure of the BIA was suggested earlier. Results and Discussion – Overall comments by the reviewer The results are presented according to the objectives of the paper and the methods. For the results and discussion to hold in this paper, the assumptions, structure of the economic and BIA models as well as the estimation of the transition probabilities have to be appropriate. I therefore encourage the authors to address the comments raised as part of this review. I do believe though that the manuscript could add value to the literature should the authors appropriately address the comments raised.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Matti Aapro
Institution and Country: Genolier Cancer Center, Switzerland
Competing Interests: I know the senior author. Dr Celio and have published with him

Introduction: the study cited ref 14 had more than 114 patients. It deals only with apr/palo
This reviewer does not understand where the numbers for the other variables come from: for side-effects
references are given but for efficacy, ?

We corrected the number of patients treated, being four hundred and twelve.
We apologise for the lack of clarity. The effectiveness of NEPA was derived from Gralla et al 2014 (reference 15 of the manuscript). The odds ratios used for comparators were derived from the results of the study of Gralla for APR+PALO; from Hesketh et al 2014 (reference 11 of the manuscript) for APR+ONDA and PALO (HEC population); and from Aapro et al 2014 (reference 12 of the manuscript) for PALO (MEC population).
We added this information before table 1 and in the legend of table 1:
“The transition probabilities depend on the effectiveness parameters considered per treatment in the acute phase and delayed phase (as reported in table 1 for NEPA and considering the odds ratios presented for the comparators, derived from the results of the NEPA study in HEC [11] and from the results of NEPA study in MEC [12]). The effectiveness parameters of NEPA, are based on the following clinical trials: the NEPA study in patients receiving either HEC or MEC [15] and within the sensibility analysis, the NEPA studies in HEC [11] and MEC.[12]”.

Please indicate that for you HEC is cisplatin and MEC comprises of AC, carbo and others.

We added further information at the end of the third paragraph of the introduction and the information required in the fourth paragraph:
“It must be pointed out that the combination of AC has historically been considered a MEC regimen but because it is commonly administered to females with breast cancer, the emetogenic risk is substantially increased due to the additional patient-related risk factors (i.e., gender and age).[2,5]” …
“More recently, a multiple-cycle extension of the phase III trial with NEPA in breast cancer patients receiving AC also showed the sustained benefit of NEPA over multiple cycles of therapy [16].”
“…of the use of NEPA in the management of the prophylaxis of CINV in the Italian context, both for HEC (cisplatin) and MEC (AC, non-AC MEC), through a cost utility analysis and a budget impact analysis.”

Page 11: lung not lungs

We modified the text as suggested.

Please qualify your conclusions as pertinent only with the limitations of the models used

We modified as suggested the last paragraph of the “Discussion and conclusions” section.

Reviewer: 2
Reviewer Name: R. de las Peñas
Institution and Country: Department of Medical Oncology, Consorcio Hospital Provincial Castellón, Spain
Competing Interests: none declared

The authors should list the references in the order they appear in the text.
On page 5, lines 48-56, the authors refer to a statistical model for analysis of successive cycles. The bibliographic reference (16) is not clearly justified with the text. For this part of the text it would be convenient to participate of a specialist statistician as a reviewer.

We listed the references in the order they appear, as suggested. In reference 20, Longo and colleagues used the same statistical approach we described to derive complete response and complete protection rates.

Reviewer: 3
Reviewer Name: Karthaus, Meinolf
Institution and Country: Klinikum Neuperlach, Department Hematology/Oncology and Palliative Care, Germany
Competing Interests: Advisory Board for HELSINN, MSD, TESARO

CINV is a major threat for patients if not protected. Incomplete protection may result in subsequent costs for treatment of complications. A combination of 5-HT3-RA together with NK1-RA-antagonists is standard of care. This combination shows a complete protection of acute and delayed vomiting in up to more than 80% of patients receiving HEC and MEC. The fixed combination with NEPA has recently been approved for HEC and MEC with anthracyclin/cyclophosphamide data.
The costs of antiemetic drugs and rescue medication and add-on treatments (unscheduled visits,

emergency room admissions, outpatient activities and hospitalisations) for patients not having a complete protection are presented. The estimated costs for the management of adverse events came from interview with a Key Opinion Leader referring to the Department of Medical Oncology.
The authors present the data in context of the Italian National Health Service. The discussion should be more careful. It should be discussed:
Palonosetron has already lost its patent and aprepitant will loose its patent in the near future. This might have an influence on the budget of cancer and supportive care and should be included in the discussion. The frequency of since severe CINV differs in Europe between countries. This might have an impact on rescue treatment costs.
Further direct costs of the aquisition of drugs by hospital pharmacies differs considerably to the outpatient situation in a lot of countries. Therefore cross-country comparisons should be made with caution. The authors could include the Paper of Turini et al (Drugs in Context 2015).

We added the following phrases in the discussions and conclusions section:
"…However, since drugs acquisition costs may vary considerably between countries, as the frequency of CINV episodes, international comparisons should be taken with caution. As an example, Turini and colleagues [46] estimated the direct medical costs of severe CINV episodes requiring hospitalization in three European countries, with an average cost of 389.0 € in Italy, 750.1 € in France and 1,016.7 € in Germany."
"Due to the expiration of the patent of PALO, generic version of this molecule might be available on the market soon. This factor would reduce the lower costs associated with the use of NEPA unless a price revision for this drug would be proposed. The sensitivity analysis results of the Cost-Utility Analysis show that up to a 63% reduction of the price of PALO, NEPA would remain dominant in all scenarios."

Reviewer: 4
Reviewer Name: Karam Diaby
Institution and Country: Florida A&M University, USA
Competing Interests: None declared.

I would like to praise the authors for their efforts in putting together this manuscript. The topic is of interest and relevant. That being said, I have had difficulties understanding some sections of the paper, which limited my ability to fully assess the value of their manuscript. My specific comments are below:

Abstract
The abstract is a good reflection of what the authors present in the main text of the paper.
Page 3, line 6: I don't understand why the model used by the authors would not allow for probabilistic sensitivity analysis? How about deterministic sensitivity analysis?

The model used was adapted by the authors, but developed by an international team. Unfortunately, the model does not allow any structural modification and it did not allowed the authors to perform a probability sensitivity analysis. Therefore, we dealt with uncertainty conducting the univariate sensitivity analyses presented in the article, considering variability ranges that were considered wide enough to deal with the possible variation of each variable.

Introduction
This section provides a good background on the topic presented in this paper. Please see my comments below.
Page 4, line 4: This statement needs referencing.

We added the following reference, as suggested.
“Lorusso D, Bria E, Costantini A et al. Patients' perception of chemotherapy side effects: Expectations, doctor-patient communication and impact on quality of life - An Italian survey. Eur J Cancer Care (Engl). 2017 Mar;26(2)”

Page 5, Line 7-18: This paragraph does not fully help the authors make the case about the importance of their study or why it is needed. The lack of evidence of cost-effectiveness analysis of NEPA for chemotherapy-induced nausea and vomiting prophylaxis in the Italian setting is not sufficient to warrant a study. I believe that it is the consequences/ impact of not conducting this study that should provide a full justification as to why the authors should perform such analyses.

We added the following considerations:
“The assessment of this dimension is crucial considering the context in which National Health Services worldwide are operating, characterized by a persistent stress on national healthcare budgets (i.e. austerity measures)[18] and the need to make new and effective health technologies available to patients. Due to a lack of economic evaluation within the Italian National Health Service, and the aforementioned considerations, the analysis presented aimed at evaluating the efficiency of resources allocation and sustainability of the use of NEPA in the management of the prophylaxis of CINV in the Italian context, both for HEC (cisplatin) and MEC (AC and non-AC MEC), through a cost utility analysis and a budget impact analysis.”

Methods
I believe this section could be restructured to improve the readability of the manuscript. I would suggest the following structure (Wording can be modified)

I-Economic Evaluation
1-Overview of the model (with justification of choices)
Type of economic model
Population
Interventions
Time Horizon
Outcome measures
Model description
2-Model Parameters
Clinical efficacy analysis
Costs
Utility

3- Base case results
4- Sensitivity analysis

II-Budget impact analysis
1- Estimation of target population size
2- Interventions compared: Current intervention mix Vs. New intervention mix\
3- Time horizon
4- Resource use and costs
5- Scenario analysis

We thank the reviewer for the detailed and precise structure suggested. We reorganized the methods section accordingly. Some sub-headings were grouped, to avoid having several sub-sections consisting of a single phrase.

Results
This section should be organized in light of the sub-sections of the methods.

The results section was organized considering the results of the two main sub sections: “Cost utility analysis” and “Budget impact analysis”.

Discussion and conclusion

Page 5 – line 50-57: This sentence is too long. The sentence should be rephrased and statements about what the authors did should be explained. For example, the authors mentioned the following: “The proportion of patients with a either CR or CP was used to evaluate efficacy across acute and overall phases” and then estimated CR and CP rates using GLMM. Were the authors interested in estimating proportions or rates? I think there is a difference between these variables.

We revised the whole paragraph as suggested by the reviewer. The point raised is correct, CR and CP are expressed as proportions therefore only the term “proportion” were used in the revised text: “The proportion of patients with either CR or CP was used to evaluate efficacy across acute and overall phases. To accurately determine protection against CINV over multiple consecutive cycles, a generalized mixed linear model was used. In details, the overall proportions and proportions at each chemotherapy cycle of CR and CP, with associated two-tailed 95% confidence intervals (CI), were estimated using a model with an identity link function (non-canonical link function), binomial probability distribution and parameterized with treatment group, cycle and treatment-by-cycle interaction as fixed effects.[20] Overall CR and CP proportions were estimated directly from the generalized mixed linear model as least-square mean of the fixed effect “treatment group”. Since incomplete profiles may occur because of the physician’s decision to administer fewer than 6 cycles or because of drop-out events, the mixed model was parameterized using a full Toeplitz variance-covariance matrix. This should represent a suitable choice to take into account correlation across repeated measures (cycles) and to adjust for the potential bias caused by incomplete profiles. Computations were performed using the GLIMMIX procedure of SAS version 9.4.
The adjusted proportion estimates of achieving CINV control in each treatment arm during the acute and overall periods among patients receiving a cycle of HEC or MEC are presented in the Supplementary Material.”.

In addition, the specification of the GLM model needs further clarifications and choice justification regarding the link identity function and family used,

CR and CP are dichotomous endpoints therefore it is mandatory that the distribution family to be used is the binomial one. Moreover CR and CP are modeled and estimated as absolute risks (i.e. proportions) and risk differences therefore the proper link function must be the identity link function. In fact, using the canonical logit link function or the log link function, CR and CP would be modeled and estimated as odds ratio and relative risk respectively.

the need for a mixed model since only fixed effects were used. This begs the following question: What is the added value of the GLMM in estimating rates compared to classic statistical models?

We explained the point raised by the reviewer in the “Clinical efficacy analysis” paragraph. In other words, we employed a mixed model in order to obtain “model-based” estimates (namely parameters estimated directly from the statistical model) which have the advantage to be adjusted for the presence of missing and incomplete cycles. To accomplish this, the statistical model was parameterized with a Toeplitz variance-covariance matrix (parameterization that can be done only through a GLMM) in order to take into account correlation across repeated measures (namely cycles).

Page 6- Line 32-67: Figure 1 is not clear to me. The model structure is confusing, between the acute phase (1 day), the delayed phase (2-5) and the overall cycle. What happens to patients that reach the incomplete response state? The estimation of transition probabilities is not clearly explained, a part from a mention of the use of linear interpolation. The authors should discuss the appropriateness of using linear interpolation in this case. In the discussion section, limitations about using this approach should be discussed.

We apologise for the lack of clarity. We completed Figure 1, adding the possibility for patients in the "incomplete response" state to remain within it. The reason to use linear interpolation is that higher degree of approximations (spline or polynomial interpolations) looked much more unstable. Of course linear interpolation is, by definition, more rough than spline/polynomial interpolation but in our context this limitation looks acceptable.

Page 10- Line 33: The authors used 10 - 20% variation range for cost and utility parameters without justifying their choices. No attempt was made to conduct probabilistic sensitivity analyses, which matters a great deal since it shows the impact of joint parameter uncertainty on the ICER.

We agree with the reviewer, considering the lack of a probabilistic sensitivity analysis as a limit of the analysis. We added to the conclusion the following text:
"In conclusion, being aware of the limitations of the model and of the lack of a probabilistic sensitivity analysis, the use of NEPA for the prophylaxis of CINV within the Italian context would lead to an efficient allocation of resources both for the treatment of patient receiving HEC (being dominant compared with APR + PALO, fAPR + PALO, APR + ONDA and fAPR + ONDA) and MEC (being dominant compared with APR + PALO and fAPR + PALO)."

Page 11- line 3: I do not believe the BIA was conducted according the ISPOR guidelines on the implementation of BIA. A structure of the BIA was suggested earlier.

We followed ISPOR guidelines while structuring the BIA, in terms of considering and made explicit the perspective of the analysis, the eligible population, the technology considered and the current mix of technologies, the uptake of the new technology, the direct medical costs related to the use and to the lack of use of the technology, the time horizon, the lack of discounting, and the sensitivity analysis. However, the manuscript was not structured considering this elements in single sections.

Results and Discussion – Overall comments by the reviewer
The results are presented according to the objectives of the paper and the methods. For the results and discussion to hold in this paper, the assumptions, structure of the economic and BIA models as well as the estimation of the transition probabilities have to be appropriate. I therefore encourage the authors to address the comments raised as part of this review. I do believe though that the manuscript could add value to the literature should the authors appropriately address the comments raised.