Author's response to reviews

Title: The Cost of Anal Cancer in England: Retrospective hospital data analysis and cohort model

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Dear Sir/Madam,

Please consider the re-submission of the enclosed research paper following peer review - The cost of anal cancer in England: retrospective hospital data analysis and Markov model. Responses to the consolidated peer review comments can be found on the following pages.

Competing Interests:

SK and SC are employees of Sanofi Pasteur MSD. MT and ST are employees of Pharmerit Ltd, which has received funding from Sanofi Pasteur MSD. KN and SO'D have received honoraria for attended advisory boards run by Sanofi Pasteur MSD.

Yours sincerely,

Michael Tempest

Research Consultant
Major Compulsory Revisions

1. The manuscript may benefit from a more clearly described sensitivity analysis and additional sensitivity analyses. For instance, the rising cost of treatment for chemotherapeutics has been seen with other cancer types with the introduction of biological agents, but the sensitivity analysis in the manuscript only compares no inflation and constant inflation. Both these scenarios are likely underestimates.

Response - addition of text: ‘A one-way sensitivity analysis was also performed for the following key inputs: type of admission for primary treatment, cost of staging and primary treatment, monthly costs of palliative care, intensity of follow-up, proportion of patients undergoing salvage surgery, proportion of patients presenting with advanced disease, cost of follow-up interventions and the proportion of patients receiving chemoradiotherapy.’

2. An incorrect assumption has been made that the treatment for squamous and adenocarcinomas are the same ~20% of the included cases will be adenocarcinoma and therefore will proceed to resection but there are no primary surgical costs in the costing analysis. This could be dealt with in a sensitivity analysis or as part of the model.

Response - Due to a lack of data on survival for patients with adenocarcinoma post resection the authors felt it was not possible to include this within the model. The manuscript has been amended to include this information and to make clear that the focus of the cohort model is anal cancer that is squamous in nature.

3. By not including pre-treatment colostomy or post-treatment surgical salvage procedures for squamous cancer there is a large omission. The authors do note that it makes their estimate conservative, however, when coupled with no mention of the primary surgical resections for adenocarcinomas at all, it seems more inaccurate that conservative...

Response - Both pre-treatment colostomy and post-treatment surgical salvage are included in the model. The text has been amended to make this clear.

4. The study question doesn’t specify the perspective from which the study was conducted. This is relevant for the identification of costs as these will depend on the perspective (i.e. societal, healthcare sector, patient, etc.). However, we might infer the authors considered the healthcare sector’s perspective as most cancers are treated and diagnosed at hospitals. In addition, I would also suggest explicitly mentioning the unit of measurement of costs and the year (i.e. 2011 British pounds) to better define the question of this study.

Response - addition of text: ‘all costs were considered from a direct healthcare perspective in GBP (2011 prices).’

5. As mentioned by the authors, the aim is to estimate the average 10-year cost of treating anal cancer. Costs may need to be adjusted for differential timing when measured. Future costs (i.e. from year 1 to year 10) should be discounted in order to represent the present value. If no discount rate was to be considered in this study, arguments should be stated supporting this decision.

The aim of our approach was to estimate realised costs as opposed to modelling an investment decision, therefore discounting was deemed to be inappropriate. Should the costs be used in a future economic evaluation then discounting could be applied to reflect the positive time preference of the relevant decision maker as well as interest rates.
Minor Essential Revisions

1. The data analysis is a case series (non-comparative) study design; however, this is never mentioned in the manuscript.

Response - addition of text: "Firstly, a retrospective (non-comparative) case series was performed using data extracted from the Hospital Episode Statistics (HES) database."

2. The assumption that adverse events of treatment are detected by HES activity data where anal cancer is the first or second diagnosis code is optimistic... Neutropenic Sepsis or radiation Proctitis may not have anal cancer coded in the first or second diagnosis codes and therefore this should be noted in the limitations.

Response - addition of text: "Nonetheless, restricting the presence of an ICD-10 code up to the tertiary and secondary diagnoses fields for inpatient and outpatients, respectively may have introduced some selection bias, for example by excluding adverse treatment events such as neutropenic sepsis and radiation proctitis. However, relaxing the this restriction may have introduced costs completely unrelated to anal cancer."

3. Missing HES fields data were poorly commented on.

Response - addition of text: "Fields such as patient age, sex, admission and discharge methods, hospital provider codes and codes pertaining to diagnosis and operational procedures are mandatory in the grouping process from FCEs to spells of care and the derivation of the dominant and correct HRG; the prevalence of missing fields and thus erroneous coding was higher within these data years, leading to potential underestimations within the economic analysis."

4. The limitations section does not comment on the inherent bias of using a case series.

Response - addition of text: "Firstly it should be acknowledged that despite the non-comparative case-series study design, the inherent bias noted with this approach was limited in the present study. Patient records were extracted from all English hospitals based on the aforementioned ICD-10 codes only with no additional inclusion or exclusion criteria applied. Furthermore, cases were retrieved retrospectively with all information collected routinely in relevant medical records. One could argue that restricting the presence of an ICD-10 code up to the tertiary and secondary diagnoses fields for inpatient and outpatients, respectively could introduce some selection bias, however up to twenty diagnoses are available per FCE in HES and thus expanding the scope may have introduced costs completely unrelated to anal cancer."

5. There was no baseline of cost of untreated anal cancer and there were no opportunity costs of other proposed treatment options (e.g. vaccine). A comment on these would be helpful.

Response - addition of text: "Although not an incremental analysis in itself, this study provides the first attempt to estimate the cost of treating anal cancer in England. and potentially allows for better assessment of the cost-effectiveness of new treatments for anal cancer through the determination of the costs of current best available treatment."

The discussion also includes the following text: "These data are timely given the increasing number of new interventions aimed at anal cancer, including monoclonal antibodies which have been used to treat other squamous cell carcinomas, such as cetuximab (ERBITUX; ImClone Systems Inc., New
York, NY, and Bristol-Myers Squibb Co. Princeton, NJ), and vaccines against HPV (e.g. Gardasil, a quadrivalent vaccine developed and marketed in the UK by Sanofi Pasteur MSD).

6. There is no attempt to consider ancillary costs of caring at home (stoma nurses/district nurses for dressings post radiotherapy etc). Since these data are not available then it should be noted in the limitations section that there are additional potential ‘health service’ costs not included in the model.

Response – addition of text: "Finally, costs for care delivered during follow-up outside of the standard pattern of appointments, for example those related to stoma nurses, could not be included in the model due to a lack of available information."

7. The study’s main objective was to estimate de costs of anal cancer, however, to do so, the authors had to estimate the number of anal cancer cases diagnosed in England for which a retrospective review was required and performed. I would suggest considering this to explicitly be mentioned in the title of the study (i.e. Incidence and cost of anal cancer in England...). In addition, the whole manuscript talks about a Markov model and never mentions the word cohort. In fact, the word cohort is only mentioned in the title. I would suggest reformulating the title or otherwise explaining how the cohort model is actually defining the methods part of the study.

Response – addition of text: 'Cohort' has been removed from the title and replaced with Markov.

8. The methods section should better describe the anal cancer cohort considered in this study.

Response – addition of text: 'Cohort' has been removed from the title and emphasis instead placed on the retrospective nature of the hospital analysis.

9. The study doesn’t mention the software used for the data analysis.

Response – addition of text: 'HES data aggregation and pertaining descriptive statistics were conducted using SAS Enterprise Guide 4.3.'

'C costing analyses were performed in Excel 2007.'

10. As mentioned by the authors, there is data deficiency and several assumptions had to be considered. All these assumptions bring uncertainty around the final estimate so an uncertainty analysis would be adequate. This way, cost estimates could be reported within a confidence interval.

Response – The range from the sensitivity analysis has been added to the base case estimates to provide a measure of uncertainty for the reader.

11. Due to lack of information and data, the authors built a Markov model used to simulate the treatment pathway/natural history of the disease in order to obtain the final average cost. It is unclear for which year the costs are presented.

Response – addition of text: ‘all costs were considered from a direct healthcare perspective in GBP (2011 prices).’

Discretionary Revisions

1. Would suggest that the authors make clear that Sanofi Pasteur MSD develop and market the quadrivalent HPV vaccine used in the UK.
Response - addition of text: "(e.g. Gardasil, a quadrivalent vaccine developed and marketed in the UK by Sanofi Pasteur MSD)"

2. There was no incremental analysis, but the reminder of the analysis provides sufficient detail for this to be considered.

Response - addition of text: "Although not an incremental analysis in itself, this study provides the first attempt to estimate the cost of treating anal cancer in England, and potentially allows for better assessment of the cost-effectiveness of new treatments for anal cancer through the determination of the costs of current best available treatment."

3. There is no discounting, which would be interesting to consider for the population suffering from anal cancer.

Response - As was stated above, the aim of our approach was to estimate realised costs as opposed to modelling an investment decision, therefore discounting was deemed to be inappropriate.

4. There is uncertain merit in extrapolating figures from 9 months of data up to one year. At the very least a sensitivity analysis without the extrapolation should be presented to test the assumptions made that the trends would remain the same over the remaining three months. The alternative would be to present only the existing data.

Response - Excluding the final year of data did not result in significantly different results from those presented (-2% lower costs).

5. It was a strength to consider local disease separately, however, there may be merit in considering age or region separately as well.

Response - Expanding the model to incorporate the impact of age and region on the total costs was outside of the original scope. Furthermore age-specific data required is sparse within the literature and costing components.

6. Since high-cost cancer drugs aren’t included in the costing (not included under PbR) should something be interpolated for this?

Response - Hospital prescribing data is not available in HES and high cost drugs are excluded under PbR due to wide variation price through local negotiations. Interpolation would have therefore been conducted on assumptions associated with high uncertainty. We erred on the side on a conservative estimate as opposed to potential overestimations.

7. The retrospective part of this study involved reviewing patient data. It is unclear if the authors required an ethics committee approval.

Response - addition of text: 'All patient records were anonymised and contained no sensitive fields that would enable the unmasking of a patient's true identification, thus no ethics approval was required.'

8. Strong arguments are presented supporting the research. Recent studies on the epidemiology of anal cancer show evidence regarding some possible explanations for the increased incidence of the disease (i.e. Use of HAART, change in sexual behaviour, etc.). I would suggest considering this as additional information in the background section.

Response - addition of text: 'Recent epidemiology studies have postulated the increase in anal cancer incidence is attributable to changes in sexual behaviour (i.e. a higher number of unprotected receptive anal sex partners), a likely surrogate for infection with multiple high-risk HPV strains.
Interestingly the incidence of anal cancer has dramatically increased among HIV-infected men despite antiviral therapy (e.g. during and proceeding the HAART era); it is postulated that whilst antiviral therapy may reduce competing mortality risks, it has no impact on the impact on the natural history of HPV nor the likelihood of HPV co-infection and moreover by increasing life expectancy allow for sufficient time for the accumulation of genetic mutations implicated in the development of anal cancer. Such data highlights the need for preventative strategies for anal cancer.

9. The authors clearly specify the two main objectives of the study which are to estimate the annual costs of treating anal cancer and the cost of treating a single case. However, I would suggest specifying the fact that average costs were measured (page 5, lines 1 and 2). This is in accordance to the methods described.

Response – addition of text: ‘this study reports an estimate of both the mean annual costs of treating anal cancer in England, and also the average cost of treating a single case’

10. The methods are divided into two parts. The first aims to determine the number of anal cancer cases. It is unclear if these cases correspond to incident or prevalent cases.

Response – no text added, already included in the introduction and discussion:

“Due to the short span of extracted data years, the exclusion of primary care, the inability to distinguish between initial and recurrent cases, and the lack of information pertaining to the cancer stage; a separate mathematical model was developed to simulate the treatment pathway for an anal cancer patient in order to estimate the average cost of treating a single case.” Reference to the inability to distinguish between prevalence and incidence also noted in the discussion.

11. The mean start age for males and females reported in the results section (page 9) was not shown in the tables. This could be stated at the end of the sentence (i.e. data not shown).

Response – addition of text: ‘(data not shown) added.’