PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Chronic Wounds in a Multi-Ethnic Asian Population. A Cost of Illness Study.
AUTHORS	Graves, Nicholas; Ganesan, Ganga; Tan, Kelvin; Goh, Orlanda; Ho, Jackie; Chong, Tze; Bishnoi, Priya; Carmody, David; Yuh, Ang Shin; Ng, Yi Zhen; Lo, Zhiwen; Enming, Yong; Abu Bakar Aloweni, Fazila; Zifei, Wang; Harding, Keith

VERSION 1 – REVIEW

REVIEWER	Padraig Dixon Oxford University
REVIEW RETURNED	09-Aug-2022

GENERAL COMMENTS	This paper estimates the cost of illness associated with chronic wounds in Singapore. Cost of illness studies are generally challenged by a circularity issue – the fact that the costs associated with a particular condition are high is not, in itself, an argument for more or less spending to address the economic consequences associated with the condition of interest. The paper instead correctly notes that the estimates produced could be used to model cost effectiveness of specific interventions relating chronic wounds. However, there are two significant limitations that challenge this objective. The first is that the "model" at the core of the paper is not well described. There is discussion of various data sources, and Table 1 contains parameters for modelling the cost of illness but it is not at all obvious how or what the model is doing. The perspective of the analysis is not described, which complicates interpretations of remarks made subsequently about productivity costs. Are the parameters correlated or are they independent draws from independent distributions? Presumably many of these parameters must be correlated in truth but are they modelled as such? How were the distributions parameterised? “Model evaluation was completed by combining the stated parameters to estimate…” – How was this combination given effect? I’m not clear why QALYs should feature in a cost of illness study. I struggle to interpret the QALY figures in Table 2, which is entitled “Annual cost outcomes for incident cases” despite containing these QALY data. For example, of 16,752 incident cases, what does a figure of 537 “QALYS arterial” mean? Is that associated with a per-person QALY of 0.03 for incident chronic wounds? Is that figure incremental, and if so to what? If not, how should it be interpreted? The second issue is the difficulty of understanding how costs were attributed to wounds, rather than the comorbid conditions with which

	they are associated. This is an essential part of such a model to avoid double- and over-counting. The paper reports identifying care episodes with occurrences of various wounds reported in ICD codes. The paper states "The statistical model generated a coefficient for 'wound type' expressed as a rate ratio, that showed the amount of increase in length of stay associated with the presence of wound, given that other factors that predicted length of stay had been accounted for. This rate ratio was used to moderate the mean length of stay for the entire sample and an excess length of stay associated with the wound was estimated, see Appendix 6." The detail provided here isn't sufficient to establish that no overcounting was made, or whether it was solely excess length of stay that was used to attribute costs to wounds. This type of attribution is also conditional on the covariates used in the model, which aren't reported, assumes all such relevant factors have been included, and therefore that the marginal effect of the wound coding is the sole reason for excess hospital stays. As drafted, it is not clear if wound type or the presence of wound were used to inform the rate ratio. Writing down the formal model would help with the interpretation of these steps. Other comments: I am not convinced by the references reporting costs associated with wounds. For example, the estimate in Armstrong et al is – at best – speculation based on the proportion of direct care costs associated with lower extremity complications associated diabetes "Direct costs of care for diabetes in general was $237 billion in 2017. This is compared to $80 billion for cancer in 2015. As up to one-third of the direct costs of care for diabetes may be attributed to the lower extremity, these are also readily comparable." Other references cited include a protocol for a systematic review (Jarbrink et al) rather than primary research – the actual 3% figure quoted in Jarbrink et al is in turn cited in an inaccessible source (your reference 5 – Posnett and Franks) There are two primary generalised linear models (GLMs) estimated. The link and family functions are presented without justification – absent other considerations, these would usually be chosen based on specification tests. No rationale is offered for the different parameterisations (gamma versus Poisson link) Finally, how would the final estimates be used in a cost-effectiveness analysis?

REVIEWER	Anil Gumber Sheffield Hallam University, Centre for Health and Social Care Research
REVIEW RETURNED	05-Oct-2022

GENERAL COMMENTS	An important topic on the cost of wounds is covered by the authors. The title is confusing that this is not a cost of illness study as the information has not been collected from the patients on out-of-pocket expenditure in accessing healthcare and treatment of wounds. The study uses only the cost data from the secondary sources (provider perspective). The perspective to undertake cost of illness study is not defined adequately including the conceptual framework to account for various types of direct and indirect costs. There is no account for previous studies on cost undertaken in

	Singapore. No attempt is made to smoothen the cost data and at many places we need to provide both mean and median cost by types of wound. The rate ratio word is used which can't be used together or need to explain why they have coined this term. They have mentioned and over emphasised productivity losses but one needs to understand that majority of wounds especially leg ulcers occurs to elderly people (out-of-workforce). Some tables are too lengthy, these needs to be provide by type of ulcers as columns. Discussion needs strengthening, at some places sweeping statements are given without the support of evidence. The authors need to clarify clearly their objectives and what/how this study contributes to current evidence/knowledge. We (Klonizakis; Gumber et al.) have undertaken a couple of studies on Venous Leg Ulcers with focus on the direct and indirect costs of treatment in the UK which would help the authors to sharpen their paper's objectives and perspectives The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1. Dr. Padraig Dixon, Oxford University Comments to the Author:

This paper estimates the cost of illness associated with chronic wounds in Singapore.
Cost of illness studies are generally challenged by a circularity issue – the fact that the costs associated with a particular condition are high is not, in itself, an argument for more or less spending to address the economic consequences associated with the condition of interest. The paper instead correctly notes that the estimates produced could be used to model cost effectiveness of specific interventions relating chronic wounds. However, there are two significant limitations that challenge this objective.

The first is that the "model" at the core of the paper is not well described. There is discussion of various data sources, and Table 1 contains parameters for modelling the cost of illness but it is not at all obvious how or what the model is doing. Response 1. We have prepared a diagram - Figure 1 - that shows how the various parameters we specify are used to update the outcomes. We have also added material to the methods section under a new heading of ‘Data, Parameters and Assumptions’. The model is separated into four parts, each described separately, to make the methods used easier to follow. We believe the workings of the model are now quite well described.

The perspective of the analysis is not described, which complicates interpretations of remarks made subsequently about productivity costs. Response 2. The analysis includes the costs incurred by health services. And the losses to health benefits are estimated by QALYs, and valued in money terms. It is not a ‘societal’ perspective as we have no data on private out of pocket costs, but we do review this omission in the Discussion section. We have added sentences in the ‘Scope of the Analyses’ section in the Methods.

Are the parameters correlated or are they independent draws from independent distributions? Response 3. The results arise from independent draws from independent distributions.

Presumably many of these parameters must be correlated in truth but are they modelled as such? Response 4. We agree there is likely to be correlation between parameters. This issue is resolved by the Monte Carlo simulations we perform with a Probabilistic Sensitivity Analysis. Ades et al (1) suggests “Probabilistic methods correctly propagate correlation automatically, providing meaningful sensitivity analysis, and correct computation of expected costs and benefits in non-linear or even multilinear models, regardless of parameter correlation”. We have updated the methods section to

describe the Probabilistic Sensitivity Analysis completely, and we discuss the issue of potentially correlated parameters in the Discussion section.

How were the distributions parameterised? Response 5. The relationship between parameters is shown in Figure 1 and the details of each parameter are included in Table 1, 2, 3 & 4.

“Model evaluation was completed by combining the stated parameters to estimate…” – How was this combination given effect? Response 6. See Responses 1 & 4.

I’m not clear why QALYs should feature in a cost of illness study. Response 7. Our understanding of COI studies is that they should represent the “potential benefits of a health care intervention if it had eradicated the illness. In this vein, the COI studies generally include some metric of 'health loss' and try to measure the resource costs incurred in treating the related diseases (2)” We believe that QALYS are a useful measure of the ‘health loss’ and so are a useful outcome to report for a COI study.

I struggle to interpret the QALY figures in Table 2, which is entitled “Annual cost outcomes for incident cases” despite containing these QALY data. For example, of 16,752 incident cases, what does a figure of 537 “QALYS arterial” mean? Is that associated with a per-person QALY of 0.03 for incident chronic wounds? Is that figure incremental, and if so to what? If not, how should it be interpreted? Response 8. We report 2,206 arterial incident cases of arterial insufficiency ulcers per year. From these new cases there are 544 QALYS lost in a year. On average this is 0.25 QALYS lost per person per year, this reflects a large burden of lost health. These findings arise from the low valuations of the health states associated with arterial insufficiency ulcers, see Table 2: baseline = 0.44; month 1 = 0.52; month 3 = 0.54; month 6 =
0.58. These are incremental QALYS losses from new cases of arterial insufficiency ulcers.

The second issue is the difficulty of understanding how costs were attributed to wounds, rather than the comorbid conditions with which they are associated. This is an essential part of such a model to avoid double- and over-counting. Response 9. With respect to QALY outcomes we acknowledge this is a weakness of the study and include this text in the Discussion “We assumed that the observed decrement between the population norms for health utility and the estimates from the wound registry were wholly attributable to the presence of a wound. These QALY estimates did not adjust for the other health conditions that patients may have, and as such may overstate the QALY losses.” For the remaining cost outcomes, we adjust for factors that would explain variation by using GLM regression models with a gamma link function. Results reported in Appendices 6, 6a and 8.

The paper reports identifying care episodes with occurrences of various wounds reported in ICD codes. The paper states "The statistical model generated a coefficient for ‘wound type’ expressed as a rate ratio, that showed the amount of increase in length of stay associated with the presence of wound, given that other factors that predicted length of stay had been accounted for. This rate ratio was used to moderate the mean length of stay for the entire sample and an excess length of stay associated with the wound was estimated, see Appendix 6." The detail provided here isn't sufficient to establish that no over counting was made, or whether it was solely excess length of stay that was used to attribute costs to wounds. This type of attribution is also conditional on the covariates used in the model, which aren't reported, assumes all such relevant factors have been included, and therefore that the marginal effect of the wound coding is the sole reason for excess hospital stays. As drafted, it is not clear if wound type or the presence of wound were used to inform the rate ratio.
Writing down the formal model would help with the interpretation of these steps.
Response 9. We have included the full set of results in Appendix 6a that show coefficients for all the variables included in the regression model. Factors such as Race, Age, Gender,

Myocardial infarction, Cancer, Liver disease, peptic ulcer disease, Peripheral vascular disease, Renal disease, COPD, Dementia, Diabetes, Heart Failure, Hyperlipidaemia, Lymphoproliferative disease, Major Depression, Parkinson's, Schizophrenia and Stroke all play a role in explaining variation in the observed length of stay. We fitted the best models to the available data, but acknowledge there may be important covariates missing. We would suggest the results from our models are plausible as they are similar to other published estimates reported in the Discussion. We have added a section to the discussion in response to the reviewer's feedback. If the reviewer also wishes us to include the full set of results for the Poisson model for use of poly-clinic services, CHAS and ED then we are able to include these as well.

Other comments:
I am not convinced by the references reporting costs associated with wounds. For example, the estimate in Armstrong et al is – at best – speculation based on the proportion of direct care costs associated with lower extremity complications associated diabetes "Direct costs of care for diabetes in general was $237 billion in 2017. This is compared to $80 billion for cancer in 2015. As up to one-third of the direct costs of care for diabetes may be attributed to the lower extremity, these are also readily comparable." Response 10. We agree the estimates reported in this paper might not reliable and have removed it from the manuscript.

Other references cited include a protocol for a systematic review (Jarbrink et al) rather than primary research. – the actual 3% figure quoted in Jarbrink et al is in turn cited in an inaccessible source (your reference 5 – Posnett and Franks). Response 11. We have referenced the correct systematic review now (Jarbrink & Olssen) and have correctly referenced the Posnett and Franks paper.

There are two primary generalised linear models (GLMs) estimated. The link and family functions are presented without justification – absent other considerations, these would usually be chosen based on specification tests. No rationale is offered for the different parameterisations (gamma versus Poisson link) Response 12. Regarding the 'count data' considered in the Primary Care and ED costs section, we have added this text. "A parsimonious generalised linear model with a log link Poisson function was used for all regressions. The Poisson distribution was chosen over the negative binomial distribution based on fitting the model then doing model checks with diagnostic plots and relevant statistics." Regarding the 'lengths of stay' considered in the Inpatient Acute Sector Costs section, we highlight this justification made for using a Gamma distribution link function…"A parsimonious multivariable generalised linear model (GLM) with a gamma link function was used to accommodate the skew typical of lengths of stay data (3)."

Finally, how would the final estimates be used in a cost-effectiveness analysis? Response 10. We provide estimates of the 'gross costs' and 'health benefits' foregone from tolerating a range of choric wounds. This information would be useful for other analysts who wish to model the expected change to 'total costs' and 'health benefits' arising from a programme/intervention that reduces the risks and durations of chronic wounds in an Asian population. Most of the data we use and newly collected from Singaporeans and are

contemporary. Too often we see modelling studies harvesting data from old and irrelevant studies and generalising inappropriately.

Reviewer: 2
Dr. Anil Gumber, Sheffield Hallam University Comments to the Author:

An important topic on the cost of wounds is covered by the authors. The title is confusing that this is not a cost of illness study as the information has not been collected from the patients on out-of-pocket

expenditure in accessing healthcare and treatment of wounds. Response 11. We disagree that this is ‘not a COI study’. We acknowledge that out-of-pocket expenditures are omitted and discuss this caveat in the paper. We respectfully suggest that the health services costs and losses to health benefits, which we do include, are likely to represent a large share of the total costs. We expect out-of-pocket expenditures to be a small share of the total cost burden.

The study uses only the cost data from the secondary sources (provider perspective). Response 12. We harvest data from a range of sources, including primary and contemporary data from the Singapore national wound care registry. We aimed to use the best information available and include uncertainties in the data. We include health utilities to show the burden of health loss and so out perspective extends beyond just the ‘provider’.

The perspective to undertake cost of illness study is not defined adequately including the conceptual framework to account for various types of direct and indirect costs. Response 13. See Response 2. We have made an explicit statement about the ‘Perspective’ in the methods section.

There is no account for previous studies on cost undertaken in Singapore. Response 14. We found two studies reporting costs of chronic wounds in Singapore and have included these in the Discussion.

No attempt is made to smoothen the cost data and at many places we need to provide both mean and median cost by types of wound. Response 15. We conducted a multi parameter probabilistic sensitivity analysis. This is an appropriate way of propagating forward uncertainties in parameters to reported outcomes (1), including cost outcomes.

The rate ratio word is used which can't be used together or need to explain why they have coined this term. Response 16. It is common to report a quantity from a GLM as a transformed coefficient such as an odds ratio (OR) or an incidence rate ratio (IRR). The magnitude of the odds ratio or an incidence rate ratio is often presented as representing the strength of association between a predictor and an outcome. We chose to report the incidence rate ratio in this analysis. For a complete treatment of this issue, see this preprint paper:
file:///C:/Users/gmsgnic/Downloads/PAB_GLM%20Interpret_Manuscript_Unblinded.pdf

They have mentioned and over emphasised productivity losses but one needs to understand that majority of wounds especially leg ulcers occurs to elderly people (out-of-workforce).
Response 17. We assume that a year of life (quality adjusted) is still valuable even if the person is not economically active or formally employed. We are uncomfortable with the notion that people who are not in the workforce do not perform valuable tasks.

Some tables are too lengthy; these needs to be provide by type of ulcers as columns. Response 18. We have replaced the long table with four smaller ones to complement the model structure shown in Figure 1.

Discussion needs strengthening, at some places sweeping statements are given without the support of evidence. The authors need to clarify clearly their objectives and what/how this study contributes to current evidence/knowledge. Response 19. We are happy to improve the Discussion section.

We (Klonizakis; Gumber et al.) have undertaken a couple of studies on Venous Leg Ulcers with focus on the direct and indirect costs of treatment in the UK which would help the authors to sharpen their paper's objectives and perspectives. Response 20. Thank you for the suggestions, we found five papers and used them to improve out work

VERSION 2 – REVIEW

REVIEWER	Anil Gumber Sheffield Hallam University, Centre for Health and Social Care Research
REVIEW RETURNED	28-Feb-2023

GENERAL COMMENTS	Authors have not provided the detailed response to reviewers. They have not included suggestions I recommended earlier. They have not computed Mean and Median costs per person or by per hospital contact. The total cost does not mean much to researcher unless compared with other competing disease groups. The statem in the abstract Conclusion is the costs are large; BUT how we can say that unless compared with other competing disease group or as percentage of GDP, Health Budget, etc.

VERSION 2 – AUTHOR RESPONSE

Reviewer 2.

Authors have not provided the detailed response to reviewers. They have not included suggestions I recommended earlier. They have not computed Mean and Median costs per person or by per hospital contact.

Response 1. We apologise for this oversight. Table 7 has been updated to reflect the cost outcomes for the average individual. We report the mean (min:max) to be consistent with the rest of the results; also, the correct value for decision making is the mean. We have added the median value to the boxplots in Figure 2. This is appropriate as they show the distribution is skewed. The costs per hospital contact are available from Table 1; we report he excess stay per admission and the cost per bed day.

The total cost does not mean much to researcher unless compared with other competing disease groups. The statement in the abstract Conclusion is the costs are large; BUT how we can say that unless compared with other competing disease group or as percentage of GDP, Health Budget, etc.

Response 2. This text is reported in the Discussion section. This give some sense of the scale and importance of these costs. Text has ben added to show the costs in terms of the proportion of GDP.

“These findings suggest the costs of chronic wounds to Singapore are large and account for approximately 0.07% of GDP. The cost burden accounts for 3.14% of the 2019 Government Health Expenditure on services [26] and 2.3% of total economy-wide expenditure on services. Our estimates roughly align with those from other countries. In Australia 2% of the total national health expenditure is used for chronic wounds and in the UK 3% of the national health expenditure is taken up [27]. Two percent of the European health budget [28] is for care of chronic wounds and for Scandinavian countries the costs were found to be 2 to 4% of the total health care expenditure [6].”