PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The costs of switching to low global-warming potential inhalers. An economic and carbon footprint analysis of NHS prescription data in England.
AUTHORS	Wilkinson, Alexander JK; Braggins, Rory; Steinbach, Ingeborg; Smith, James

VERSION 1 – REVIEW

REVIEWER	Duncan Keeley General practitioner Thame OX9 3JF UK
REVIEW RETURNED	12-Feb-2019

GENERAL COMMENTS	This is an important and thorough analysis of the potential NHS costs and GWP reduction impact of increasing the proportion of inhaled treatments delivered by dry powder as opposed to metered dose inhalers. Costs would fall if switching took place to the lowest cost alternatives but would rise substantially if current prescribing patterns within the DPI options were maintained. It is an important article which should be published but could be improved. It provides data which is hard to obtain and is very useful for prescribers, prescribing advisers and policymakers in considering the carbon footprint and cost implications of changes in prescribing practice whether at an organisational level or at the level of clinicians discussing treatment choices with patients. I have not checked the all the individual inhaler costings and can not vouch for the prescribing volume based calculations of cost changes , but the data seem entirely plausible within such understanding I do have of relative drug costs, There is nothing to indicate to me that the calculations have not been done in a thorough and competent manner. The article is well written and easy to read. The article will provide important background information for an active and significant policy debate. Several key issues are highlighted - including the widely varying carbon footprint of different versions of therapeutically equivalent MDIs.

	In that context the authors mention the alcohol that allows lower propellant volumes. This is an issue that may concern some patients - and it might be worth providing a guide to the (minuscule) quantities of alcohol in each inhaler. The authors, in providing a wide range of options for helping practitioners consider how to reduce the overall GWP of respiratory treatments, do not - for this reader - adequately discuss some important issues, The first of these is the importance of using spacers to reduce inhaler technique errors and increase clinical effectiveness of treatment in those patients who do for whatever reason use MDIs. This is an area of enormous practical importance - and potential for waste reduction, which has been under appreciated for many years - due among other things to the fact that wider knowledge of this would substantially reduce inhaler waste and hence the volume of inhalers sold. Metered dose inhaler will continue to be used in any plausible scenario of change and maximising the effectiveness with which they are used will contribute significantly to reducing the overall GWP of treatments. The second is the need for adequate time with properly trained health professionals to correctly explain effective inhaler technique and self management to patients - and the need for better online educational back up resources . Inadequate patient education is a powerful driver of poor outcomes and treatment waste. The extraordinarily high residual content of returned inhalers which the authors report - and might more clearly highlight - bear testimony to this. Increased workload pressure in primary care and inadequate investment in training - particularly of the nurses to whom much respiratory care is delegated - are having (in the view of this reviewer) a major adverse effect on treatment effectiveness and hence on waste avoidance. A greater role is envisioned for pharmacists in this area - but the adequacy of pharmacists training in practical respiratory care is highly variable . The third issue is to acknowledge the patients and situations in which MDIs will have an important continuing role - for young children and some elderly patients in whom MDI spacer is the only effective treatment option, and in patients prone to exacerbations- in whom the MDI /spacer combination is vital for the most effective self management. For this latter group one option which would preserve this benefit while changing to DPIs for routine therapy would be to have an emergency treatment pack with MDI and spacer for use in emergencies only. The availability of this option would increase health professionals confidence in transitioning patients from MDI to DPI for routine treatment. (The difficulties of needing to use different inhaler types are overemphasised - especially if MDI is used with spacer - and can be handled well given adequate time and expertise for the teaching, which is needed for effective use of any inhaler.) The authors may well feel that these areas are outside their remit in this paper. But the article is an important contribution to an important debate, and I would suggest the editors let them have the space if they are prepared to include a brief consideration of any or all of these issues, so as to allow the most comprehensive possible discussion of the ways in which the GWP of respiratory treatments can be reduced.

	A few points of detail: p 4 L 29 - the 100 year GWP potential ? This metric will be unfamiliar to readers - perhaps explain. p8 Inhaler recycling - dismal performance currently, but are the authors able to compute how much use it would be if more inhalers were recycled. Recycling is often more about feeling good than about making a significant impact on waste reduction and climate impact. Are inhaler recycling schemes going to be worth it? p8 line 54 : What could be done to accelerate the development of low GWP propellants and their therapeutic testing? Is this worthy of additional investment ? p8 line 55 Would you care to speculate? The lowest waste option in the long run might be a re-fillable canister MDI containing a low GWP propellant that goes in a re-usable and simple plastic housing. (the issue of plastic waste tends to go unconsidered in this debate) Consider having a box with bullet point action HPs could take to reduce the overall GWP of respiratory treatments. References are comprehensive and up to date. It was a pleasure to read this paper.

REVIEWER	Jerome Baddley NHS England and Public health England Sustainable Development Unit
REVIEW RETURNED	25-Feb-2019

GENERAL COMMENTS	Line 5 Pg 4: Could benefit from a greater discussion of Net Ingredient Cost as a measure of actual cost to the NHS, or a comparator cost between treatments. Line 37 Pg 3: It may be woth expanding where the EAC took evidence from to reach its target. eg…after taking oral evidence from the SDU, GSK and Mexichem and written evidence from Chiese and Dr Duncan Keeley. Pg 3 line 12: Currently MDIs contribute an estimated 3.5% of the carbon footprint of the National Health Service in the UK. This was true at time of writing and the evidence presented to the EAC, however since this date the NHS footprint has been recalculated. In the Natural resopurces footprint the emissions from inhalers, calculated from NAEI data are 0.85Mt and NHS footprint 21.54Mt, so now 4%. https://www.sduhealth.org.uk/policy-strategy/reporting/natural-resource-footprint-2018.aspx Pg3 line 37: 'In January 2019 the NHS long term plan proposed pharmacists facilitate switching patients to low GWP inhalers and claimed this could reduce the carbon footprint of the NHS by 4%.' This is not a wholly accurate characterisation of the LTP commitment. Firstly the 4% LTP commitment refers to a 50% reduction in the carbon emissions from inhalers in 10 years. To meet a 10 year

	carbon saving in-line with the Climate Change Act targets for 2030 the NHS has to cut its total footprint by around 10.6Mt. Inhalers represent 0.85Mt of the current NHS carbon footprint. 50% of 0.85Mt is 0.425Mt. This 0.425Mt is 4% of 10.6Mt. The paper should note that a cross sector working group to build this evidence base and address the challenge laid down by the EAC was set up and 1st chaired by the SDU in July 2018 (ToR published in October 2018). The group has met 3 times since, and has developed an outline set of measures underpinning the 4% LTP commitment. https://networks.sustainablehealthcare.org.uk/networks/sustainable-respiratory-care/expert-working-group-reducing-climate-change-impact-inhalers The LTP mentions inhalers in 2 places. • On LTP Pg 120 the 4% reduction from 'A shift to lower carbon inhalers' is mentioned as part of 'the challenge to deliver the Climate Change Act target'. • on LTP pg 67 relating to pharmacists and medicines reviews to 'support patients to reduce the use of short acting bronchodilator inhalers and 'switch to dry powder inhalers where clinically appropriate, which use significantly less fluorinated gases than traditional metered dose inhalers' The mention on pg67 is only part of the overall mixture of measures required to deliver the commitment on Pg120. The structure of the measures that would be required to deliver a 50% cut had been developed with the working group and used as part of the LTP evidence base. It includes DPI, better prescribing, lower volume MDI, alternative propellants, a shift away from HFA227 and canister recycling. This work provides some valuable evidence to justify that mix of options. Pg3 Line 42: Goulet B, Olson L, Mayer B. A Comparative Life Cycle Assessment between a Metered Dose Inhaler and Electric Nebulizer. Sustainability 2017; 9: 1725 states 96% in-use phase not 98%. Is the 98% from another study? https://pdfs.semanticscholar.org/2982/99c8517465fad7d5 0883fb80f273d16b8e4b.pdf . Pg4 Line 43: Patient and public involvement, 'eighty six percent of patients agreed that both cost and carbon footprint are important factors' It may be good to qualify this statement with context about the other factors that are considered more important. It would be useful to show the context in terms of a hierarchy. This would still make the point that environmental considerations are important, but not to over emphasise the relative importance related to areas such as 'ease of use' Pg 6 line 26: 2 words have been run together Pg 8 Line 40: GSK were involved in this study. Was this an industry/GSK funded study? It may be worth highlighting this if so. Pg 8 Line 28: The NICE Shared Decision Aid has been in development for about 12 months commissioned from NICE by the SDU and is due to be published in March 2019. This should be cited. Pg8 Line 23: 'The UK government's DEFRA report incorrectly assumes that all inhalers contain 12g of propellant'. There is no reference provided. It is also likely that any DEFRA report would

	assume an average of 12g propellant, which I believe is the benchmark used by the NAEI in estimation. The author should clarify this basis of this challenge. Pg8 line 51: 'Transition to a novel propellant(s) would likely take a decade' This may well be true, but is this just supposition or is there a basis in evidence? Maybe the evidence of the CFC transition?

REVIEWER	Jacob Simmering Carver College of Medicine University of Iowa
REVIEW RETURNED	03-Jun-2019

GENERAL COMMENTS	Wilkinson and colleagues present an intriguing analysis of the potential costs, savings and averted greenhouse gas emissions by switching from MDI to DPI by the NHS in the UK. Specifically, the paper considers a situation in which the change from MDI to DPI is done without brand whole the second considers the situation in which the change is to the cheapest alternative DPI. The authors found an increase of 12.7 million pounds per year per 10% of MDI switched to DPI within the same brand and a decrease of 8.2 million pounds per year per 10% which switched to the cheapest brand. As a non-clinician, I am not able to assess the validity of the MDI to DPI pairings. The methods for computing the cost savings for outpatient switching seems reasonable to me. The numbers and cost of the prescriptions originate with the NHS which should provide accurate numbers for both values. The greenhouse gas values are less certain – many had to be estimated from estimates derived from patents or the literature for the amount of propellant which has some ambiguities. For instance, the patent for one inhaler said it contains 18.2g of HFA134a while the FDA report for the same drug but different brand has a net weight of 12g. However, I believe the estimated mass of propellant are reasonable and cover most sources. I see no problems with the results as they are reported but would consider a revision. I would recommend moving the text describing how much GWP the different classes of medication have based on literature and patent review to the method's section. Same with some of the cost discussion for each of the classes. Then focus in the results section more directly on the effects of the change and less on how they values were parameterized. Minor Comments Introduction: Page 3/Line 32: GWP has not been defined earlier in the paper – I take it as global warming potential but that should be made clear. Results: Page 6/Line 3: "We didn't change these inhalers in our model" should probably have the contraction replaced with "did not." Page 6/Line 25: "with a small volume Salamol inhalerfound the weight" – these seems to be an omitted space between inhaler and found.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Duncan Keeley

Institution and Country: General practitioner Thame OX9 3JF, UK

In that context the authors mention the alcohol that allows lower propellant volumes. This is an issue that may concern some patients - and it might be worth providing a guide to the (minuscule) quantities of alcohol in each inhaler.

We felt including information on the quantities of alcohol was beyond the scope of this article and is available elsewhere, but would be happy to do this work if the editor feels it is needed here.

The authors, in providing a wide range of options for helping practitioners consider how to reduce the overall GWP of respiratory treatments, do not - for this reader - adequately discuss some important issues,

The first of these is the importance of using spacers to reduce inhaler technique errors and increase clinical effectiveness of treatment in those patients who do for whatever reason use MDIs. This is an area of enormous practical importance - and potential for waste reduction, which has been under appreciated for many years - due among other things to the fact that wider knowledge of this would substantially reduce inhaler waste and hence the volume of inhalers sold. Metered dose inhaler will continue to be used in any plausible scenario of change and maximising the effectiveness with which they are used will contribute significantly to reducing the overall GWP of treatments.

Whilst some of the authors may personally agree with this statement, and we recognise that there is good evidence for in-vitro benefits of spacers, there is a severe lack of scientific evidence to support the use of spacers in the real world. There is conflicting evidence that spacers improve inhaler technique, as we acknowledge in the manuscript already. For example: Systematic Review of Errors in Inhaler Use Sanchis, Joaquin et al.CHEST, Volume 150, Issue 2, 394 – 406 wherein the authors comment specifically "We had expected that adding holding chambers would reduce MDI errors substantially, but we saw no evidence that this is the case".

We are not aware of any studies showing waste reduction from spacers. The evidence they improve asthma control is also lacking and we'd agree with this recent review that "Further research is necessary to define more precisely the clinical benefits of the use of spacers/VHCs in the real world, which will in turn allow estimation of their cost effectiveness." - Spacer devices for inhaled therapy: why use them, and how? Walter Vincken, Mark L. Levy, Jane Scullion, Omar S. Usmani, P.N. Richard Dekhuijzen, Chris J. Corrigan
ERJ Open Research Apr 2018, 4 (2) 00065-2018;

We'd be happy to corrected on this point if there are any references we are unaware of.

The second is the need for adequate time with properly trained health professionals to correctly explain effective inhaler technique and self management to patients - and the need for better online educational back up resources . Inadequate patient education is a powerful driver of poor outcomes and treatment waste. The extraordinarily high residual content of returned inhalers which the authors report - and might more clearly highlight - bear testimony to this. Increased workload pressure in primary care and inadequate investment in training - particularly of the nurses to whom much respiratory care is delegated - are having (in the view of this reviewer) a major adverse effect on

treatment effectiveness and hence on waste avoidance. A greater role is envisioned for pharmacists in this area - but the adequacy of pharmacists training in practical respiratory care is highly variable .

This is an excellent point and we've added the following to the discussion.

This also highlights the importance of explaining to patients the number of doses their inhaler contains as part of inhaler technique training. (6th paragraph of discussion) Whatever inhalers are used, adequate patient training and assessment of inhaler technique will be essential for efficient and effective inhaler use. (8th paragraph of discussion)

The third issue is to acknowledge the patients and situations in which MDIs will have an important continuing role - for young children and some elderly patients in whom MDI spacer is the only effective treatment option, and in patients prone to exacerbations- in whom the MDI /spacer combination is vital for the most effective self management. For this latter group one option which would preserve this benefit while changing to DPIs for routine therapy would be to have an emergency treatment pack with MDI and spacer for use in emergencies only. The availability of this option would increase health professionals confidence in transitioning patients from MDI to DPI for routine treatment. (The difficulties of needing to use different inhaler types are overemphasised - especially if MDI is used with spacer - and can be handled well given adequate time and expertise for the teaching, which is needed for effective use of any inhaler.)

Another excellent point which was made in the literature after this manuscript was submitted. We have added A recent proposal suggests a reliever MDI + spacer could be kept separately in an emergency pack in case of exacerbations. (8th paragraph of discussion)

The authors may well feel that these areas are outside their remit in this paper. But the article is an important contribution to an important debate, and I would suggest the editors let them have the space if they are prepared to include a brief consideration of any or all of these issues, so as to allow the most comprehensive possible discussion of the ways in which the GWP of respiratory treatments can be reduced.

A few points of detail:

p 4 L 29 - the 100 year GWP potential ? This metric will be unfamiliar to readers - perhaps explain.

We have added an explanation of this. Global Warming Potential (GWP) is a measure of how much heat a greenhouse gas traps in the atmosphere over a specific time, relative to carbon dioxide. For the purposes of this article, we used GWP values of HFAs for the 100-year time horizon as reported in the IPCC Fifth Assessment Report.10

p8 Inhaler recycling - dismal performance currently, but are the authors able to compute how much use it would be if more inhalers were recycled. Recycling is often more about feeling good than about making a significant impact on waste reduction and climate impact. Are inhaler recycling schemes going to be worth it?

Good point. We believe it is effective and have expanded this section of the discussion as below. This means that a significant proportion of the propellant could be captured, and that the carbon footprint of MDIs roughly halved if they were all recycled. (6th paragraph of discussion)

p8 line 54 : What could be done to accelerate the development of low GWP propellants and their therapeutic testing? Is this worthy of additional investment ?

We feel this is outside the scope of this paper and the expertise of the authors.

p8 line 55 Would you care to speculate?

Not quite sure what this refers to. p8 lines 53-55 are “Transition to a novel propellant(s) would likely take a decade, although this may be cost-effective from a worldwide perspective, especially in developing countries”

Consider having a box with bullet point action HPs could take to reduce the overall GWP of respiratory treatments.

We have added a box with action points, and would be interested in the editors’ opinion as to whether this warrants inclusion. We’ve added the line within the text Where recycling is not available, incinerating MDIs with medicines waste is an effective strategy; this causes thermal degradation of the HFA into chemicals with far smaller global warming potential.50 as this is an important action HPs could take where recycling facilities are not available, that was not included in the previous draft.

References are comprehensive and up to date.

It was a pleasure to read this paper.

Thank you!

Reviewer: 2
Reviewer Name: Jerome Baddley

Institution and Country: NHS England and Public health England Sustainable Development Unit

Please state any competing interests or state ‘None declared’: None

Please leave your comments for the authors below
Line 5 Pg 4: Could benefit from a greater discussion of Net Ingredient Cost as a measure of actual cost to the NHS, or a comparator cost between treatments.

The cost data is used here as a comparator as in reality prices are in constant flux. We’ve made this clearer in the manuscript. In reality costs are in flux and subject to market pressures, but our analysis allows comparison between treatments at a specific time point. (discussion paragraph 4)

Line 37 Pg 3: It may be woth expanding where the EAC took evidence from to reach its target. eg…after taking oral evidence from the SDU, GSK and Mexichem and written evidence from Chiese and Dr Duncan Keeley.

We felt this was probably unnecessary as this information is clearly available within the EAC report if readers wish to find it.

Pg 3 line 12: Currently MDIs contribute an estimated 3.5% of the carbon footprint of the National Health Service in the UK. This was true at time of writing and the evidence presented to the EAC, however since this date the NHS footprint has been recalculated. In the Natural resopurces footprint the emissions from inhalers, calculated from NAEI data are 0.85Mt and NHS footprint 21.54Mt, so now 4%. https://www.sduhealth.org.uk/policy-strategy/reporting/natural-resource-footprint-2018.aspx

Many thanks for this. We have updated the data and reference accordingly.

Pg3 line 37: ‘In January 2019 the NHS long term plan proposed pharmacists facilitate switching patients to low GWP inhalers and claimed this could reduce the carbon footprint of the NHS by 4%.’ This is not a wholly accurate characterisation of the LTP commitment.
Firstly the 4% LTP commitment refers to a 50% reduction in the carbon emissions from inhalers in 10 years. To meet a 10 year carbon saving in-line with the Climate Change Act targets for 2030 the NHS has to cut its total footprint by around 10.6Mt. Inhalers represent 0.85Mt of the current NHS carbon footprint. 50% of 0.85Mt is 0.425Mt. This 0.425Mt is 4% of 10.6Mt.

Thanks. We’ve adjusted to clarify.

The paper should note that a cross sector working group to build this evidence base and address the challenge laid down by the EAC was set up and 1st chaired by the SDU in July 2018 (ToR published in October 2018). The group has met 3 times since, and has developed an outline set of measures underpinning the 4% LTP commitment.
https://networks.sustainablehealthcare.org.uk/networks/sustainable-respiratory-care/expert-working-group-reducing-climate-change-impact-inhalers
The LTP mentions inhalers in 2 places.
• On LTP Pg 120 the 4% reduction from ‘A shift to lower carbon inhalers’ is mentioned as part of ‘the challenge to deliver the Climate Change Act target’.
• on LTP pg 67 relating to pharmacists and medicines reviews to ‘support patients to reduce the use of short acting bronchodilator inhalers and ‘switch to dry powder inhalers where clinically appropriate, which use significantly less fluorinated gases than traditional metered dose inhalers’
The mention on pg67 is only part of the overall mixture of measures required to deliver the commitment on Pg120. The structure of the measures that would be required to deliver a 50% cut had been developed with the working group and used as part of the LTP evidence base. It includes DPI, better prescribing, lower volume MDI, alternative propellants, a shift away from HFA227 and canister recycling. This work provides some valuable evidence to justify that mix of options.

Many thanks for this clarification. We have adjusted the manuscript to be clearer and made reference to the expert working group. In January 2019 the NHS long term plan proposed a 50% reduction in the greenhouse gas emmissions from inhalers in 10 years,10 and established an expert working group to evaluate potential strategies to achieve this.11

Pg3 Line 42: Goulet B, Olson L, Mayer B. A Comparative Life Cycle Assessment between a Metered Dose Inhaler and Electric Nebulizer. Sustainability 2017; 9: 1725 states 96% in-use phase not 98%. Is the 98% from another study?
https://pdfs.semanticscholar.org/2982/99c8517465fad7d50883fb80f273d16b8e4b.pdf .

98% is from Reduced environmental impact of a reusable soft mist inhaler
Michaela Hänsel, Thomas Bambach, Herbert Wachtel European Respiratory Journal Sep 2018, 52 (suppl 62) PA1021

In Goulet et al. 96% is released in use phase, but some propellant is also released during manufacture and as test doses in quality control checks. The amount of propellant in the inhaler in their study is 6.68g so the carbon footprint of the propellant is 6.68x1430=9,552g (they used AR4 GWP values). The total carbon footprint of the inhaler in Goulet et al is 9772g so 9552/9772=0.98 or 98%.

Having said that, I am aware that some companies capture the HFA released during test doses and GSK quote 95% on their website. We have therefore adjusted this to 95-98%.

Pg4 Line 43: Patient and public involvement, ‘eighty six percent of patients agreed that both cost and carbon footprint are important factors’ It may be good to qualify this statement with context about the other factors that are considered more important. It would be useful to show the context in terms of a hierarchy. This would still make the point that environmental considerations are important, but not to over emphasise the relative importance related to areas such as ‘ease of use’

We have amended the manuscript to reflect this . … although ease of use was considered the most important factor overall.

Pg 6 line 26: 2 words have been run together

Thanks. Corrected.

Pg 8 Line 40: GSK were involved in this study. Was this an industry/GSK funded study? It may be worth highlighting this if so.

Added …jointly funded by GSK and NHS Grampian…

Pg 8 Line 28: The NICE Shared Decision Aid has been in development for about 12 months commissioned from NICE by the SDU and is due to be published in March 2019. This should be cited.

Absolutely. It came out after we wrote initial drafts of this paper but we should have added it.
…tools, such as NICE’s recent patient decision aid for asthma inhalers are to be welcomed.45
Pg8 Line 23: ‘The UK government’s DEFRA report incorrectly assumes that all inhalers contain 12g of propellant’. There is no reference provided. It is also likely that any DEFRA report would assume an average of 12g propellant, which I believe is the benchmark used by the NAEI in estimation. The author should clarify this basis of this challenge.

Good point. We have added the reference. (36)

Pg8 line 51: ‘Transition to a novel propellant(s) would likely take a decade’ This may well be true, but is this just supposition or is there a basis in evidence? Maybe the evidence of the CFC transition?

As you point out, this was based mainly on what was seen with CFC transition and we have made this clearer. Transition to a novel propellant(s) would likely take at least a decade based on experience from the transition from CFCs,39

Reviewer: 3
Reviewer Name: Jacob Simmering

The methods for computing the cost savings for outpatient switching seems reasonable to me. The numbers and cost of the prescriptions originate with the NHS which should provide accurate numbers for both values. The greenhouse gas values are less certain – many had to be estimated from estimates derived from patents or the literature for the amount of propellant which has some ambiguities. For instance, the patent for one inhaler said it contains 18.2g of HFA134a while the FDA report for the same drug but different brand has a net weight of 12g. However, I believe the estimated mass of propellant are reasonable and cover most sources.

This is fair criticism and as we point out in the paper some of this information is not currently in the public domain.

I see no problems with the results as they are reported but would consider a revision. I would recommend moving the text describing how much GWP the different classes of medication have based on literature and patent review to the method's section. Same with some of the cost discussion for each of the classes. Then focus in the results section more directly on the effects of the change and less on how they values were parameterized.

I think this is a good idea and it makes the results section more readable. We have made the suggested changes in the methods and results sections. There are too many structural changes to the document to list here, but they are tracked within the word document. We've copied this summary from the abstract to the start of the carbon footprint results We found some reliever inhalers (e.g. Ventolin™) to have a carbon footprint over 25kgCO2e per inhaler, whilst others use far less HFA134a (e.g. Salamol™) with a carbon footprint of less than 10kgCO2e per inhaler. HFA227ea LABA/ICS inhalers (e.g. Flutiform™) have a carbon footprint over 36kgCO2e, compared to an equivalent HFA134a combination inhaler (e.g. Fostair™) at less than 20kgCO2e

Minor Comments
Introduction:
Page 3/Line 32: GWP has not been defined earlier in the paper – I take it as global warming potential but that should be made clear.

Thanks. This point was also made by another reviewer and we have added more details in methods. Global Warming Potential (GWP) is a measure of how much heat a greenhouse gas traps in the atmosphere over a specific time, relative to carbon dioxide. For the purposes of this article, we used GWP values of HFAs for the 100-year time horizon as reported in the IPCC Fifth Assessment Report.15

Results:
Page 6/Line 3: "We didn't change these inhalers in our model" should probably have the contraction replaced with "did not."

Thanks. Changed accordingly.

Page 6/Line 25: "with a small volume Salamol inhalerfound the weight" – these seems to be an omitted space between inhaler and found.

Thanks. Changed accordingly.

VERSION 2 – REVIEW

REVIEWER	Duncan Keeley General Practitioner Thame Oxon OX9 3JF
REVIEW RETURNED	08-Aug-2019

GENERAL COMMENTS	Thank you for the detailed attention to the various referees' comments. I apologise for the delay in re-reviewing this paper . I am happy with the responses and revisions. (Please check Column 3 in Table 2 - is it really 1,300 for every inhaler except flutiform?)

REVIEWER	Jerome Baddley NHS England and NHS Improvement
REVIEW RETURNED	27-Jul-2019

GENERAL COMMENTS	Thank to the author for addressing suggested revisions. I only have one suggested change. Table 3 on strategies while useful, may need to be caveated more heavily. Particularly, a full lifecycle analysis has not been carried out to ascertain the potential carbon savings from different disposal routes, ie recycling could actually result in greater fugitive HFA emissions and a higher carbon footprint than estimated. HFA propellants are required to be incinerated at the end of their useful life, ie recycling may just mean delayed incineration, with greater opportunity for incidental atmospheric release of gas. Over all it may be better in terms of carbon emissions to incinerate MDIs decommissioning the propellants immediately rather than recycling them. This current uncertainty should be clearly reflected and the paper should avoid stating that one route is preferable over another. In general I would say that this is an excellent, well balanced paper that adds usefully to the knowledge base in this rapidly evolving area.

VERSION 2 – AUTHOR RESPONSE

DUNCAN:

Indeed, all the other inhalers in this list use HFA134a with GWP 1,300.

JEROME:

Thanks for highlighting this. We have, as suggested, caveated both the table and the text more heavily.