Author’s response to reviews

Title: Impact of a change of bronchodilator medications in a hospital drug formulary on intra- and out-of-hospital drug prescriptions: interrupted time series design with comparison group.

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Version: 2 Date: 15 Apr 2020

Author’s response to reviews:

14/04/2020
Implementation Science IMPS-D-19-00607R1

Impact of a change of bronchodilator medications in a hospital drug formulary on intra- and out-of-hospital drug prescriptions: interrupted time series design with comparison group.

Thank you for considering our manuscript and for the constructive comments. We have carefully considered these comments and used them to draw up an improved version of the manuscript which explicitly addresses each in turn.

Reviewer reports:
Reviewer #1: The authors study the impact of a change of bronchodilator medications in a hospital drug formulary on intra- and out-of-hospital drug prescriptions. They use an interrupted time series design with a comparison group.

The topic is of interest.

I have some remarks:

Reviewer 1, point 1. The authors should include a table where they show some characteristics of the patients analyzed in order to see if the two groups are comparable.

Reply:
Thank you for this comment. As suggested, a new Table 1 is now included (shown below) with the demographic characteristics of the intervention and control groups, from which it will be seen that the groups are comparable in terms of age and sex.

Table 1. Intervention and control groups: demographic data

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Intervention group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>N= 445,474</td>
<td></td>
<td>N= 549,292</td>
</tr>
<tr>
<td>Age – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>0-18 yrs</td>
<td>67,347 (15.1)</td>
<td>83,157 (15.1)</td>
</tr>
<tr>
<td>19-30 yrs</td>
<td>47,669 (10.7)</td>
<td>56,328 (10.2)</td>
</tr>
<tr>
<td>31-50 yrs</td>
<td>134,660 (30.3)</td>
<td>171,673 (31.2)</td>
</tr>
<tr>
<td>51-70 yrs</td>
<td>119,066 (26.7)</td>
<td>144,879 (26.4)</td>
</tr>
<tr>
<td>&gt;70 yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>215,653 (48.4)</td>
<td>263,249 (47.9)</td>
</tr>
<tr>
<td>Women</td>
<td>229,821 (51.5)</td>
<td>286,043 (52.1)</td>
</tr>
</tbody>
</table>

Reviewer 1, point 2. The results should only be presented to one decimal place - see Abstract and Results (e.g. 173.2% rise (95%CI: 47.3%-299.0%). In table 1 the coefficients (and CI) should also just be presented by at most 3 decimal places to improve the readability.

Reply:
Thank you for this comment. As suggested, the changes have now been made to the Results section, Abstract, and corresponding table (both coefficients and CI).

Reviewer 1, point 3. The English language should be improved and also some typos: E.g. instead of "their prices with pharmaceutical laboratories" one should write "their prices with pharmaceutical companies"; e.g. Table 1: instead of expedienture - expenditure
I do not understand the following sentence: For statistical analysis purposes, we interrupted time series (ITS) analysis and constructed a segmented regression used an model with control group

Reply:
Thank you for pointing this out. The above two errors have now been corrected and the text of the manuscript revised, with the amendments highlighted in red.

Reviewer #2: Thank you very much for giving me the opportunity to review this manuscript which is very well written and very enjoyable to read. I congratulate the authors for the clarity of the information it contains.

Thank you very much! We feel that the manuscript has greatly improved thanks to your comments.

Reviewer 2, point 1. However, I do have a few small remarks which I hope will help to improve the manuscript:

My first remark is related to the study design and the limitations it might present: the authors have conducted an interrupted time series with a control group, which is a strength. Moreover, the analyses were not based on samples, but on the two populations that were comparable at first glance. Randomization would have ensured the comparability of the groups with respect to known and unknown confounding factors. Since we are not in such design here, the regression analyses are inevitably subject to residual confusion, which unfortunately is neither taken into account in the analyses nor discussed as a limitation of the study. In the analysis, for example, the authors could have
incorporated adjustment variables such as socio-demographic variables, determinants of prescribing and determinants of drug supply into the models. Or again, in the discussion, clearly mention this as a limitation of the analyses presented.

Reply:
One characteristic of these types of ITS designs is that confounding variables which are stable over time are automatically controlled for by design (and not by the analysis), with each study unit (population area) being compared in the post-intervention versus the pre-intervention period. This is the case of population characteristics, which tend to change not only gradually but over the very long term. According to Lopez Bernal et al: “One of the strengths of ITS studies is that they are generally unaffected by typical confounding variables which remain fairly constant, such as population age distribution or socioeconomic status, as these only change relatively slowly over time and are normally taken into account when modelling the underlying long-term trend” (Int J Epidemiol. 2017 Feb 1;46(1):348-355).

“[…] interrupted time series use multiple pre-intervention and post-intervention observations, thereby allowing the underlying trend to be accounted for. These have the advantage that confounding is rarely a problem, as population characteristics tend to change only gradually over time” (Int J Epidemiol. 2018 Dec 1;47(6):2082-2093.) Accordingly, potentially confounding variables ("socio-demographic variables, determinants of prescribing and determinants of drug supply") that do not vary between the pre- and post-intervention periods are automatically adjusted by design, thereby rendering it unnecessary to control for these in the statistical models.

Hence, in studies in which this methodology is used, a control is not normally required (BMJ 2015; 350 doi: https://doi.org/10.1136/bmj.h2750). Even so, the design of a model with control group helps to control for confounding caused by co-interventions or external factors that vary over time (e.g., outbreaks, climate change, seasonality or others such as the publication of guidelines, papers and alerts or the launch of pharmaceutical industry promotions). In cases such as these, the use of a control group in our study adds an additional strength (Stata J 2015; 15: 480-500) that is lacking in most of the studies with ITS, which seldom use a control group (J Clin Epidemiol. 2015; 68:950-6).

Thanks to your remarks, we have:
1. added more text to the Methods section (page 7).
2. listed an additional strength in the Discussion section (page 14)

One of the strengths of our study lies in its methodology: the ITS design enables control by design of potentially confounding variables that remain unchanged across the study period (socio-demographic variables, determinants of prescribing, and determinants of drug supply), since these remain constant or with minimal variations across the pre- and post-intervention periods.20,21

Another strength is the use of ITS with control group, especially in view of the fact that most ITS studies do not generally use one.22 The advantage of this methodology is that it allows one to control for the effect of external factors which occur at the same time as the intervention and might otherwise confound the action or the treatment. This aspect is highly relevant, since in the present case, without such adjustment (see Table S2) the conclusions obtained at an out-of-hospital level would be different (i.e., without a control group significant changes are indeed in evidence). This indicates that there seems to be time-dependent confounding which could not have been controlled for without the use of a
control group.

3. included two more references (nos. 20 and 21)


Reviewer 2, point 2. My second remark is related to the specification of the model presented, in particular on the interaction term between time and the pre- and post-intervention periods. These two variables actually measure the same concept of time. Does the addition of these two variables not expose the model to multicollinearity issues, which may even undermine the estimates' validity?

Reply:
Many thanks for your comment.
The presence of the inclusion of lower-order interaction terms (ZX, ZT, XT) is due to the need to maintain the hierarchical principle when it comes to constructing the model, even though the terms included might not be statistically significant. For fuller information, please consult:
• An Introduction to Statistical Learning: with Applications in R. Escrito por Gareth James, Daniela Witten, Trevor Hastie, Robert Tibshirani. Page 89.
In our case, on introducing a higher-order interaction term (Z•X•T), the lower-order interaction terms (Z•X, Z•T, X•T) must be introduced into the model along with the independent terms of the variables which take part in the interaction (X, Z, T).
2 Thanks to your comment, this aspect has now been clarified in the manuscript (see the Material and methods section, page 9- paragraph 2-Statistical analysis subsection):
It should be noted that the inclusion of the terms ZX, ZT and XT, as well as X, T and Z responds to the need to maintain the hierarchical principle, and to the need to maintain them even though they may not be statistically significant.

Reviewer 2, point 3. My final remark is rather a question and is as follows: What is the rational for examining the effect of the intervention on outpatient prescriptions? This should be clearly stated in the background but also taken into account in the discussion and conclusion sections, which is not currently the case.

Reply:
Many thanks for this comment.
One of the goals of this study was to evaluate whether a change in a hospital drug formulary would have an effect on out-of-hospital prescribing, the so-called induction effect of hospital prescribing on primary care (references 2,3,4 and 5).
This hypothesis has already been tested with another therapeutic group -low molecular weight heparins- in the same setting (Implement Sci 2019; 14: 75), and we sought to evaluate whether it might also be applicable to the bronchodilator medication therapeutic group.
The following amendments have now been made to the manuscript to make these aspects clearer:
In the Introduction (page 5, paragraph 3)
Recent studies conducted by our group found that a change in low molecular weight heparins (LMWH) in the HDF also had an important impact on the out-of-hospital setting. Even so, it is not known whether this effect is generalisable or, on the contrary, depends on other factors, such as therapeutic
group, type of formulary change (withdrawal, restriction on use, or inclusion) or other contextual factors, e.g., the marketing of new drugs.

Under Objectives (page 5, paragraph 3)
Accordingly, this study set out to evaluate the impact on these two health-care settings (hospital and/or primary care) of a change in a hospital drug formulary affecting......

In the Discussion section (page 13, paragraph 3)
The possible impact at an out-of-hospital level is a relevant aspect for ascertaining the induction effect of the hospital intervention on primary care.

In the Conclusions section (page 15)
Yet, the results of this study indicate that these changes in hospital prescribing patterns did not generate induction in prescribing in the out-of-hospital setting, which indicates in turn that the effect of induction cannot be generalised to all classes of medications and situations. Hence, there is a need for more studies that would make it possible to identify which factors are associated with out-of-hospital impact. At all events, changes in the HDF are very effective, though their effect may well be restricted to the hospital setting.

CHANGES MADE DUE TO ADHESION TO REPORTING GUIDELINES

On 2 April 2020, the editorial office made the following request: “Adherence to Reporting Guidelines. All submissions must include a populated checklist from the relevant reporting guideline(s) appropriate for the study design or type of report. The completed checklist(s) should be provided as an 'Additional file' and referenced in the text.”

Accordingly, we conducted a search for an interrupted time series checklist in the Equator initiative: https://www.equator-network.org/library/reporting-guidelines-under-development/reporting-guidelines-under-development-for-observational-studies/#92

As can be seen, the FERITS (Framework for Enhanced Reporting of Interrupted Time Series) initiative has not yet been developed. We therefore carried out a search of the literature in PubMed and located a recommendation for ITS published in a systematic review by R. Jandoc et al., shown as TABLE 2 (J Clin Epidemiol 2015; 68: 950e956). This in turn made it necessary to amend the manuscript in order to adapt it to the checklist.

Shown below are the changes made to adapt the manuscript to the above checklist:
1. item 3a: Page 5, penultimate paragraph, “State any prespecified hypotheses”. The following has been added to comply fully with item 3ª of the recommendations:

   Taking the theoretical model into account, we postulated the following hypothesis, namely, that a change in the HDF would influence intra- and out-of-hospital prescribing patterns, not only in terms of the target medication, but also in terms of the other medications belonging to the same therapeutic group.

2. item 6 a) y b): Page 8, first paragraph, Data-source subsection. The following sentence has been added to this paragraph to comply with items 6 a) and b) of the recommendations:

   There was no change in the data-registration system across the study period.

3. item 8a: Page 9, first paragraph-Statistical analysis subsection. The following sentence has been added to comply with item 8ª) of these recommendations:

   The model selected uses aggregate data collected over equally spaced intervals (monthly). The number
of measurements obtained was 13 points pre-intervention and 35 points post-intervention (Table S2), in the period from January 2014 to January 2018.

4. item 8: Page 9, first paragraph-Statistical analysis subsection. The following sentence has been added to comply fully with item 8 of these recommendations:

This model allows one to evaluate the longitudinal effect of interventions where randomisation is not feasible and one has the monthly data sequence of a large historical series.22

5. item 8e: Page 11, second paragraph. The following sentence has been added to comply with item m 8e) of these recommendations:

Two sensitivity analyses were performed: the first to assess the influence of the control group on the outcomes, applying a classic ITS model (without control group; Table S1);…

6. item 8g: Page 11, third paragraph. The following sentence has been added to comply with item 8g) of these recommendations:

The statistical software programme used for analysis purposes was IBM SPPS Statistics

7. item 12: Page 12, last paragraph. To comply fully with item 12, a new subsection has been added, entitled “Sensitivity analysis”, which reads as follows:

Sensitivity analysis
To evaluate the role of possible time-dependent confounding factors in the results, a traditional ITS analysis without control group was performed (Table S1). It was observed that if no adjustment was made for the control group, the effects of the intervention would indeed prove statistically significant in the out-of-hospital setting, with the use of the combination retained in the formulary as the sole ICS/LABA increasing both immediately (p&lt; 0.005) and in the long term (p&lt;0.005).

8. item 15d: Page 14, last paragraph. The following text has been added to comply with item 15d):

In our case, however, we consider these sufficient to capture the preceding trend, which is practically non-existent in all the dependent variables (see Table 2). Hence, in our study the principal effect of the short time window prior to the intervention would be to reduce statistical power. Even so, our sensitivity analysis without control group shows that there is sufficient power to detect statistically significant effects (see Table S2).

9. items 8e and 12: Provided in response to items 8e) and 12:

Table S1. Interrupted time-series segmented regression analysis without control group of inhaled corticosteroid and long-acting β2-agonist combinations (ICS-LABA).

10. items 9c), 10 a),b),c) and 11c) Provided in response to items 9c), 10 a),b),c) and 11c):

Table S2. Number of measurements, minimum, maximum, mean and standard deviation pre- and post-intervention in the intervention and control group.