Author's response to reviews

Title: Design and evaluation of software for the objective and easy-to-read presentation of new drug properties to physicians

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Author's response to reviews: see over
We thank all reviewers for their sound criticisms, questions and suggestions.

Reviewer's report

Title: Design and evaluation of software for the objective and easy-to-read presentation of new drug properties to physicians

Version: 3 Date: 10 June 2014

Reviewer: Emmanuel Chazard

Reviewer's report:

I thank the authors and the editor to enable me to review this interesting paper. In this work, the authors design, present and evaluate a computer software that enables to present the main properties of new drugs to physicians, in comparison with existing drugs that can be used for the same therapeutic indication. The outcome is a user-friendly software, which gets good evaluation results. The paper is clearly structured and well written.

***** Major Compulsory Revisions *****

The objective is properly defined at the end of the introduction. Its formulation is perhaps a little too wide compared with the software that is proposed: this software is able to display comprehensive information about new drugs, only when older drugs already exist for the same therapeutic indication. The design that is proposed is probably not suitable if a new drug is the first one for a given indication. Please clarify this in the introduction and, if possible, in the abstract.

Our response: If there are no other drugs in the indication concerned, then the drug may be considered truly innovative. In such cases, the information is less rich for safety and ease of use representation, because there is no comparator. Similarly, if the comparator is a placebo, there are no comparative data concerning safety and ease of use. This is now explained in detail in the discussion.

Five new drugs have been selected for the evaluation. Among the 40 drugs approved in 2008-2010, are those 5 drugs the only ones with a significant benefit? If not, the readers should be aware of the reasons why those 5 drugs have been chosen: randomly / because more comparative results where available / because the results of those studies where significant / because the SPCs were more complex, etc.

Our response: The five drugs were selected on the basis of the following criteria:

- Recently approved in Europe and the USA
- Providing real innovation (e.g. new molecule)
- Compared with another active ingredient or placebo.
We now explain the choice of drugs in more detail in the “Choice of drugs” section of the “Methods”.

The readers would appreciate to have an idea of the effort needed to document a new drug: what kind of professional is able to enter the information (pharmacist, physician, with or without programming skills, etc.)? How much time should it require for each new drug (1 hour, 1 day, 1 week, etc.)? You could feed the discussion by indicating the average number of new drugs per year, so that the reader could figure out the annual amount of work necessary to update the data. Is the information described in a structured way, or are HTML pages manually designed?

*Our response:* Information can be introduced into the system by a pharmacist without programming skills. For each drug, it takes between half a day and two days to add the information required, depending on the number of drugs in the therapeutic arsenal and the number of adverse reactions to the new drug and its comparator. The information is structured in the SPC, but less so in the evaluation reports of the HAS.

It is difficult to give a precise number of new drugs per year, because this is highly dependent on country. There are about 50 new drugs per year in France.

We have added more detailed information about the introduction of information into the system to the discussion.

The discussion should discuss what happens if a drug is the first one for a given therapeutic indication.

*Our response:* If the drug concerned is the first for a given therapeutic indication, then it is truly innovative.

In such cases, the information is less rich for safety and ease of use representation, because there is no comparator.

This is now explained in the discussion.

The discussion should also discuss how to manage situations where the therapeutic indication of two drugs slightly differs (e.g. different ages of the patients, first-line or second-line products, etc.): should the drugs be considered as independent, or should this difference in the indication appear as an attribute, on the same way as the contraindications?

*Our response:* As explained in our previous study [8], we compare new drug only with existing drugs for exactly the same indication. The therapeutic arsenal is identified for the indication concerned in the evaluation reports. If a new drug is approved for many indications, a separate representation is made for each indication.
If a contraindication is indicated in the sources used, it will be shown in the "Contraindications" section (for example, the drug contraindicated for use in children under the age of four years).

This point is now explained in the discussion.

***** Minor Essential Revisions *****

“analyze the available information he consider” => “analyze the available information he considers”

*Our response: The text has been corrected.*

“we listed all the possible values that the system can use” => “we listed all the possible values that the system could use”

*Our response: The text has been corrected.*

“We developed the prototype in PHP / MySQL.”: MySQL is not a language. The prototype is then developed in PHP & SQL, and is run on an Apache (?), PHP and MySQL server.

*Our response: The text has been corrected.*

About the Banque Claude Bernard: remember that all references, including URLs, must be numbered consecutively, in square brackets, in the order in which they are cited in the text. Please move the hypertext link to the bibliography.

*Our response: The text has been modified appropriately.*

The “young hospital physician specializing in public health” becomes a “public health intern” at the end of the paper. To my mind, the term “public health resident” would be more appropriate, as he/she is already involved in a specialty.

*Our response: The text has been modified accordingly.*

The resolution of Figure 1 is not sufficient. In addition, precise that the elements of Figure 1B are displayed in part 3 of Figure 1A. In the authors’ contributions, please precise who described the information about the drugs.

*Our response: We have added more detailed explanations to the legends of Figure 1 and other figures.*
We have added the following to the authors’ contributions: MI carried out the description of drugs and CD and AV verified the content.

We have not changed the resolution, because the figure was designed simply to show that the information presented is textual.

Verify that the use of grammatical tense is homogeneous (e.g. past simple and present simple). For instance, “we took into account (...) we consider (...)” => “we took into account (...) we considered (...)”

Our response: The text has been corrected as appropriate.

***** Discretionary Revisions *****

Could you give us some information about the screen size that is necessary to use the software? Could it be used on tablets or smartphones? Is the design responsive?

Our response: This software can be used on all computers, but in its current form it is most suitable for PCs and laptops (since 13”). It will be adapted for use with smartphones and tablets in the next version.

Eight percent of men are color blind, and are not able to distinguish red from green. Yet, in Figures 6 & 7, both ends of the color scales have the same texture, and appear to be the same for color blind people, or for normal people once printed in white & black. I suggest the authors would add a texture, or a printable character (+/-, etc.) or would discuss it in the discussion section.

Our response: We did not take this kind of color blindness into account, but, in any case, when the user places the mouse over the colored area, a text explaining the type of display appears. This is now explained in the discussion.

In Figure 7, I notice that, when there is an automatic linebreak in a cell, then the colored area is increased (see the line “hypersensibility...”), which could falsely lead the user to think the difference is more important. To avoid this kind of problem, it is usual to use colored pictograms with a fixed size instead of colored background for table cells. The table would also look more modern.

Our response: We agree and will take this excellent suggestion into account in the next version of the software.
In figure 7, the active substance may not be the same between the 2 drugs, so it is strange and confusing to use only one line: it would be probably better to have a line “hypersensitivity to XXX” and a line “hypersensitivity to YYY”, which would enable to have 2 different colors on each line if the active substances are different.

*Our response: We chose this type of presentation, with only one line for hypersensitivity to the active substance because there may be many active substances for the new drug and for the comparator. As a result, a number of lines can be reserved for active ingredients, which are, in any case, indicated at the top of the columns.*

*We will take this comment into consideration during the development of the next version of this software.*

At first sight it is hard to make one’s opinion on which drug is the best when a problem is a contraindication and is also a potential adverse reaction, such as hepatic impairment in Figure 7. Let’s imagine that Drug A is not contraindicated in case of hepatic impairment, but could induce such a reaction, and Drug B has a higher hepatotoxicity, so that it was contraindicated in this case even before the clinical trial: then the proportion of hepatic SAR cannot be compared. How does it appear in the SAR comparison? Could you discuss that point?

*Our response: The SPC contains not only the adverse events reported in clinical trials, but also any adverse reactions reported in pharmacovigilance studies. If the drug is contraindicated in a case, the potential adverse event is generally mentioned in the SPC, but with no information about its frequency.*

*Our software makes it possible to transmit information about the new drug. The physician must then interpret this information and come to his or her own conclusions.*

In Figure 10, I think that the users would appreciate to have bibliographic references for each paragraph, or at least the date of the report, as updates may exist for each document.

*Our response: The bibliographic reference is mentioned before the excerpt (text from the evaluation report, or from the SPC).*

*We have now added the date for each reference.*

An appropriate evaluation design would be to measure the time needed by physicians to answer correctly some simple questions about a new drug, with the full-text documents or with the software. Perhaps you could do that in this paper or propose this kind of evaluation protocol in the discussion.

*Our response: We now state in the discussion that we plan to carry out an evaluation with GPs only, focusing on the time required for GPs to answer questions about a new drug correctly on the basis of information provided by full-text documents or the software.*
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no financial competing interests. I know personally some of the authors.
Reviewer's report

Title: Design and evaluation of software for the objective and easy-to-read presentation of new drug properties to physicians

Version: 3 Date: 11 February 2014

Reviewer: Harry Hochheiser

Reviewer's report:

This paper identifies an interesting and relevant problem: presenting clear information to physicians regarding medications is certainly a worthwhile challenge. However, this manuscript has several significant limitations that call its value into question:

1. The theoretical background is very slim. Other than their own prior report, the authors cite very little background literature on medication information provision. Surely there are more papers on the presentation of medication information, clinician workflows, and related topics? There is scarcely any mention of such issues in this paper, leaving a lack of theoretical grounding.

Our response: This paper is focuses on the presentation of the properties of new drugs, and not on the more general problem of presenting clear information about drugs. Very little has been published on this specific topic. Indeed, we identify hardly any papers dealing with the properties of new drugs. We have tried to explain this more clearly in our paper. We now also cite four references (two from our laboratory), dealing with various aspects of the presentation of drug information.

2. The prior work from the authors' 2013 paper is not discussed in any detail, leaving the reader at a bit of a loss to understand the design decisions.

Our response: We have added more detail about our previous work, in which we described the context of use of new drug, the novelty of new drug, and various elements influencing the impact of new manufactured product with respect to a comparator. We now explain that we follow the same separation of information in the development of the new drug presentation.

3. The paper is poorly organized and important details are omitted. Discussions of some of the motivations behind the design are presented in methods, while specifics are presented in results. Screenshots are presented in figures 2-10, with no discussion of how the users would navigate between those components. How does the layout in figure 1 correspond to these figures.

Our response: We have deleted part of the methods section and we now explain navigation within the software in greater detail in the “Graphical presentation” section of the results. We have also modified the figure legends.
4. Discussion of some of the design choices is not clear. I counted five different uses of color coding to convey different types of information, with little indication of how these would be coordinated. There was very little justification for many of the design choices. As in point #1 above, additional grounding in prior studies regarding work practices and information needs may have been very useful here.

*Our response:* We keep the same meaning of color. Red always has a negative connotation, which is adapted to the particular context. We have tried to clarify this by adding a more detailed explanation to the “Choice of the type of graphical representation of information” part of the methods section.

5. The resulting design is not compelling. Screen shots from Figures 2-10 provide relatively sparse displays of information, without any indication of design elements, use of screen space, or other features that are either innovative or particularly useful. Figures and 3 are particularly hard to interpret - is a separate screen shot really needed to indicate the name of the new molecule? How can users interpret the plus, minus, and equal sign for a drug without any indication of the drug to which it is being compared.

*Our response:* We have added more detail to the “Graphical presentation”, “Description of the interface showing highly synthetic information” and “Description of the interface showing synthetic information” sections of the results and the figure legends.

The comparator is present on each page, at the bottom, after the approval date. We have tried to keep the text readable, by including in figures 4, 5, 7 and 8 only the relevant parts corresponding to the "Display area" (Area 3) of Figure 1. The static area remains present on each page. This information is now included in the “Graphical presentation” section of the results.

6. The evaluation is not informative. As the questionnaire is not provided, it is hard to interpret the results in detail, but the presumption is that the evaluation was not focused on completing specific relevant tasks. If it was, then the presentation of the evaluation methods should be clarified. If it was not, the evaluation was not at all convincing: I would expect an evaluation that at the very least asked participants to complete specific medication information tasks.

*Our response:* We now include the questionnaire in an appendix. The goal of this evaluation was to obtain a preliminary qualitative evaluation (except for the SUS score, which is semi-quantitative). We wanted to obtain the opinions of evaluators with different types of expertise and to determine whether any important information had been left out.

**Level of interest:** An article of limited interest

**Quality of written English:** Needs some language corrections before being published

*A professional scientific editor and translator has checked the English of this new version.*
**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.
Reviewer's report

Title: Design and evaluation of software for the objective and easy-to-read presentation of new drug properties to physicians

Version: 3 Date: 18 June 2014

Reviewer: Birgit Eiermann

Reviewers report:

Mayor essential revision

1. Please describe if there is any evaluation process of data from the SPC by the people entering data into the system. Or do you only use the exact wording of e.g. side effects, interactions. It is overall unclear how data are entered into the system.

Our response: The SPC for most of the elements (e.g. side effects, interactions) comes from a drug bank that uses a controlled vocabulary.

For identification of the type of novelty, the information is deduced from evaluation reports and SPCs for new drugs and for all the other drugs of the therapeutic arsenal, from sections such as mechanism of action and classification.

This is now made clear in the “Identification of the corpus of information concerning the drug in the used sources” section of the methods.

Minor essential revision:

2. Please specify throughout the whole manuscript what documentation did you use for data input into your system maybe with a link to the EMA site to the specific document. SPC, scientific discussion EMA, EPAR?

Our response: We now better describe the documentation used for data input into our system in “Identification of the corpus of information concerning the drug in the used sources”.

We have introduced a link to the evaluation reports on the HAS site.

The information provided in tables to visualize the impact of the drug in terms of safety and ease of use came from SPCs. Information about efficacy came from the evaluation report. The conclusions of the experts shown at the bottom of the table (Figure 5) were extracted from the evaluation report.

3. Please specify which parts of the SPC you are using by using the numeric values for the certain paragraphs (add in parenthesis e.g. if you mention interaction comparisons add (4.5) because sometimes it is unclear what you are using e.g. page 8 …., technical and regulatory data
Our response: For the representation of safety, we used sections of the SPC with the same denominations as were used in our software: adverse reactions, contraindications, drug-drug interactions, overdose.

The numerical values are the results of clinical trials described in the evaluation report.

For efficacy, the thick line is used to separate two areas: 1 – the numerical values from clinical trials, and 2 - the experts' conclusions from the valuation report.

For safety, the serious adverse reactions, with frequency intervals, reported in clinical trials are shown at the top of the table. The experts' conclusions were extracted from the evaluation report and are shown at the bottom of the table, below the thick line.

We have tried to improve the “Description of the interface showing synthetic information”.

We now include an explanation of the regulatory data, in parenthesis in the text.

4. Page 20: all legends to the figures should state what level of detail they represent: Highly synthetic, synthetic, detailed; terminology should be the same for a better understanding (e.g. figure 2 says “mostly synthetic”)

Our response: This has been done.

Abstract:
Language issues: please correct

Under: Methods:
ii) should be “a rapid understanding of the value…”

Our response: The text has been modified appropriately.

Minor Essential Revisions

5. Please specify: last sentence in methods:”was evaluated mostly qualitatively” – what does mostly mean. It was evaluated qualitatively only.

Our response: The prototype was evaluated qualitatively, except for the SUS score evaluation, which was semi-quantitative. This is now specified in the text.

Methods:
Language issues: please correct

Page 5: last sentence: …… he considers a particular….

Our response: The text has been modified.

Page 6: first sentence under Choice of type of graphical…..” we chose to use two-dimensional arrays in several places, as means of visualization (remove “a”)
Our response: The text has been modified.

Minor Essential Revision:

6. Here you describe already the layout and interface issues of you developed program. To follow the description it would be easier to refer to the figures in your paper for illustration. Please enter the figures where possible in parenthesis.

Our response: This has been done.

7. Please clarify the concept of thickness of lines in the table. It is still unclear, what a thick line means compared to a thin line. Maybe specify with an example in the existing figures

Our response: A thick line separates the numerical data from the experts' conclusions. We have tried to provide a clearer explanation in the “Choice of the type of graphical representation of information” section of the methods and results. This information has also been added to the legend of figure 5.

8. Page 8: To describe the impact of the drug in terms of efficacy we used the results of clinical trials, based on the on primary endpoints mentioned in the evaluation report. Question: if endpoints differ between the drugs compared, which approach is used? Is it possible to describe?

Our response: This comment is interesting, but we take into account only the efficacy reported in clinical trials, in which the endpoints are identified. The endpoints are identical for the two drugs in the same clinical trial.

9. Under method of evaluation: specify what you mean in the first sentence “…..essentially qualitative evaluation”; as I understand you used a questionnaire for the evaluation of the tool regarding the content and the usability.

Our response: We have modified this sentence to make it clearer “Qualitative evaluation, except for the SUS score”.

10. You should also clarify the comparison of side effects if the terminology differs. Is there a process of grouping side effects to be able to compare because terminology differs widely in between SPCs.

Our response: Side effects are presented according to MedDRA, as in the drug database. This information has been added to the “Identification of the corpus of information concerning the drug in the used sources” section of the methods.

11. Comparisons of DDIs should be specified. If specific substances are not mentioned but e.g. “substrates of CYP3A4” will there be an extrapolation to be able to compare or do you always use the wording from the SPC.
Our response: We use the wording of the SPC and the evaluation report. This is now specified in the “Identification of the corpus of information concerning the drug in the used sources” section of the methods.

12. Question: Drug information in SPCs are not consistent and the same information can be found in various parts of the SPC. How do you compare these SPCs? Even the usage of SOC varies between SPCs and some do not follow the standards. How do you proceed?

Our response: Some parts of the SPC may change over time.

The interval between the approval date of the new drug and revision date for the comparator is not important, because the SPCs are updated regularly.

However, information about the frequency of adverse effects may be missing from the oldest SPCs. For this situation, we indicate "frequency unknown" by a "?", as shown in Figure 6.

Major Compulsory Revisions

13. Page 8: It is unclear how the process of consideration comparable drugs is performed. Is it just chosen from the SPC; is there a datamining process regarding indications of all drugs available; is it up to the medical knowledge of the person entering data into the system?

Our response: The comparator is selected from the studies presented in the evaluation report of the French National Authority for Health (HAS). For a new drug for a given indication, we have, in the best case, a comparator with the active ingredient; however, the new drug is frequently compared to placebo. We prioritize studies with a comparison against active ingredient because they are more informative.

This is now explained in the “Identification of the corpus of information concerning the drug in the used sources” part of the methods.

Results:

Minor Essential Revision:

14. On page 11: you describe figure one. What do you mean with “dynamic part”. Figure 1 shows an “Interactive area”. Do you mean that part?

Our response: We have used the words “part” and “area” interchangeability. We have now replaced “part” with “area” to prevent ambiguity.

15. Figure 4: you list all comparable drugs here. But reading you discussion you state, that you only compare with 1 drug. Do you always only provide comparison with one drug, or can the physician click on ticlopidine and see then the result of the comparison between prasugrel and ticlopidine? That is unclear. Please describe in the methods as well.
Our response: Figure 4 shows all the drugs that are prescribed for the same indication. The comparator is the drug compared with the new drug in clinical trials, as presented in the evaluation report.

This information is now presented in the “Identification of the corpus of information concerning the drug in the used sources” part of the methods section.

Discussion:

Major Compulsory Revisions

16. Limitations of the study should be mentioned. You state that the objective was to provide physicians (mostly GPs…). However in your evaluation you include only 3 GPs instead highly specialized physicians and professors who might not be in the drug prescribing process at all confronted with the problem of receiving information from drug industry only. Other limitations are the diversity of description of side effects and interactions in the SPCs which can make it difficult to provide conclusive information to the physicians especially if no editorial process is added.

Our response: We wanted to have diverse opinions on the different elements and the classification of items, and it was therefore interesting to obtain the opinions of professionals with different skills.

We now plan to carry out an evaluation with GPs only, to compare the times required by GPs to find the correct answers to questions about a new drug from full-text information and with the software.

We did not take red-green color-blindness into account, but, when the user places the mouse over the colored area, a text with a description is displayed.

These limitations are now considered in the discussion.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

'I declare that I have no competing interests.