PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	MEDICATION SAFETY RISKS TO BE MANAGED IN NATIONAL IMPLEMENTATION OF AUTOMATIC SUBSTITUTION OF BIOLOGICAL MEDICINES – A QUALITATIVE STUDY
AUTHORS	Tolonen, Hanna M; Airaksinen, Marja SA; Ruokoniemi, Päivi; Hämeen-Anttila, Katri; Shermock, Kenneth M; Kurki, Pekka

VERSION 1 – REVIEW

REVIEWER	Professor Stephen Chapman Professor of Prescribing Studies Keele University UK
REVIEW RETURNED	25-Jul-2019

GENERAL COMMENTS	This is an interesting study, well conducted study with some significant limitations. In fairness to the authors, they do acknowledge these limitations. Nonetheless I would prefer some clarity on several issues. There is a disparity between table 1 showing the number of interviews /interviewees and the abstract -was it two or five patients that were interviewed? It would be useful for the authors to identify why i;1 , paired or group interviews were used. I have some concerns about extrapolation or lumping together view from individual interviews with views expressed in a group setting -the literature is clear that the dynamics of these two techniques are very different -one strong opinion from one individual in a group could influence the group and skew the results, particularly if there are hierarchical issues within the group. Much is made of patient perception - and the views expressed as "patient perception" outweigh the number of patients interviewed. There is often a difference between what patients actually think and what HCPs believe patients to think -the authors should make it clear which are views from patients and which are views expressed by HCPs as to what they believe patients to think eg "patient distrust n=11 -but only 2(or5) patients were interviewed. No patient quotes are included in the results. Similarly ,different professions may come at this issue fro different perspectives, yet their views are grouped together -it would be useful to know if HCPs views differed in any was, or at least clearly.demonstrate that they did not I would disagree that just because an administration device has a marketing authorisation it is acceptable and can be substituted ; our own published work has shown this not to be the case. The authors highlight that counselling should overcome this, but they need to take account of the weight (and trust) given by patients to HCPs -pharmacists, nurses and doctors are often perceived differently by patients.

	In figure 1 showing the interactions, the information flow appears to show a direct link from the prescribing physician direct to a community pharmacy. Given that most biologics are initiated in hospital , I'm not sure this is the case, and I'm not sure why the hospital pharmacy does not feature in this figure.

REVIEWER	Iga Pawłowska Medical University of Gdańsk, Poland
REVIEW RETURNED	07-Aug-2019

GENERAL COMMENTS	Thank you for the opportunity to review this valuable paper. It an original study concerning the automatic substitution of the biologic dugs by biosimilars. The study provides detailed knowledge concerning examines subject. Below are listed several questions concerning the paper: Method, page 5 Can you add more information about the Purposive sampling – method that has been applied. How did you find the participants (e.g. the patient, the nurse… why only one?) Had you known the participants personally before conducting the interview? The group is not so big, why were other people not invited to participative in the study? Was the study anonymous? Reading the Table 2 some participants can be identified via the citation from (e.g. nurse, because there was only one). Is it possible to use the brand name of the medicine (Neupogen) in Table 2? Page 13 Line 18.” Participants calculated a correlation between ….”. . In my opinion correlation is not the correct word since it reflects statistical analysis. Can you change the phrase?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

This is an interesting study, well conducted study with some significant limitations. In fairness to the authors, they do acknowledge these limitations. Nonetheless I would prefer some clarity on several issues.
There is a disparity between table 1 showing the number of interviews /interviewees and the abstract - was it two or five patients that were interviewed?

Authors' response: *Thank you for this comment concerning carrying out and reporting the interviews. Altogether, there were five participants from the patient organizations. They were interviewed in two interviews: in one interview there were two patient organization representatives and in the other interview three ones. We analyzed the data on the interview level (please see also the next response) and the number of the interviews were reported in the abstract. For the clarity of the abstract, we would like to keep the text as it is. However, if the Reviewers and/or the Editor considers it valuable, the number of participants can be added to the abstract as follows: "…community pharmacists (n=8 interviews/15 participants), authorities (n=7/18), prescribers (n=7/7), pharmaceutical industry and wholesalers (n=6/8), patients / customers (n=2/5), hospital pharmacists (n=1/6) and nurses (n=1/3)." In addition, the numbers of the interviews are now bolded in Table 1 (not marked as a change) to clarify the level of the analysis.*

It would be useful for the authors to identify why i;1 , paired or group interviews were used. I have some concerns about extrapolation or lumping together view from individual interviews with views expressed in a group setting -the literature is clear that the dynamics of these two techniques are very different -one strong opinion from one individual in a group could influence the group and skew the results, particularly if there are hierarchical issues within the group.

Authors' response: *Thank you for your significant comment. We fully agree that the dynamics of these two approaches are different. In order to obtain a wide range of opinions on the topic, we decided to merge the approaches. Invited organizations were given a free decision to name the interviewees. They were able to appoint one or more participants to the interview. In each interview, participants represented only one stakeholder group, and thus, the groups were homogeneous in relation to their views on automatic substitution. The challenge to combine two methods led to the decision to analyze the data on the level of the interviews, not by each interviewee. This has been added as a limitation to the Discussion section. Accordingly, the sections 'Sampling and recruitment of the interviewees' and 'Study participants' are revised.*

Much is made of patient perception - and the views expressed as "patient perception" outweigh the number of patients interviewed. There is often a difference between what patients actually think and what HCPs believe patients to think -the authors should make it clear which are views from patients and which are views expressed by HCPs as to what they believe patients to think eg "patient distrust n=11 -but only 2(or5) patients were interviewed. No patient quotes are included in the results. Similarly ,different professions may come at this issue fro different perspectives, yet their views are grouped together -it would be useful to know if HCPs views differed in any was, or at least clearly.demonstrate that they did not

Authors' response: *Thank you for this important comment. The aim of this study was to explore varying views from different stakeholders rather than to compare the differences. Differences in the stakeholder views should be the focus in future studies. The patient distrust was mentioned in 11 interviews which included both patient interviews (n=2) as well as interviews of non-patients. To clarify this in the manuscript, the level of the analysis was added to the Methods section. We also added one citation from the patient representative to Table 2. Table 3 has a footnote to emphasize the possible prone of the results. This issue has been added as a limitation to the Discussion section.*

I would disagree that just because an administration device has a marketing authorisation it is acceptable and can be substituted; our own published work has shown this not to be the case. The authors highlight that counselling should overcome this, but they need to take account of the weight (and trust) given by patients to HCPs -pharmacists, nurses and doctors are often perceived differently by patients.

***Authors' response*:** *Thank you for your comment. We agree that the marketing authorization cannot automatically command to substitution. Although the usability of the administration device is assessed during the marketing authorization assessment there may remain issues of safety and usability, especially regarding the interchangeability between different administration devices and substituting the device with another. Thus, as stated in the Administration devices section, the national authority will need to assess the suitability of administration devices for substitution in all relevant patient groups. This notion was also highlighted in the interviews (please see Table 3) as a method to minimize risk. Based on the Reviewer´s comment, we have revised the section Administration devices accordingly, to emphasize this issue.*

In figure 1 showing the interactions, the information flow appears to show a direct link from the prescribing physician direct to a community pharmacy. Given that most biologics are initiated in

hospital , I'm not sure this is the case, and I'm not sure why the hospital pharmacy does not feature in this figure.

Authors' response**:** *The substitution may not take place only when initiating the biological medication, although treatment naïve patients were identified the most suitable for the substitution. In the interviews, participants were suggesting stronger information exchange between physicians and community pharmacists (and also between nurses and community pharmacists). The absence of hospital pharmacists reflects the current situation of the clinical pharmacists in Finnish hospitals: There are several good initiatives of clinical pharmacy services in Finnish hospitals, but the services are not established widely particularly in patient counselling. In addition, the automatic substitution of biologics may not only take place in the initiation of the treatment and in this point the community pharmacists have the major role in patient counselling. The interactions and participants in the biological medicine treatments presented in Figure 1 are solely based on the interview data. However, we specified that it is particularly community pharmacists' responsibility to ensure that patients know how to use the medicinal products in section 'Education of healthcare providers and patient counselling' and clarified the legend of the Figure 1.*

Reviewer: 2

Thank you for the opportunity to review this valuable paper. It an original study concerning the automatic substitution of the biologic dugs by biosimilars. The study provides detailed knowledge concerning examines subject.
Below are listed several questions concerning the paper:
Method, page 5
Can you add more information about the Purposive sampling – method that has been applied. How did you find the participants (e.g. the patient, the nurse… why only one?) Had you known the participants personally before conducting the interview? The group is not so big, why were other people not invited to participative in the study?

Authors' response**:** *Thank you for your important comment concerning possible bias related to the selection of informants. The research group, which was constituted jointly by Finnish Medicines Agency Fimea and University of Helsinki, identified the stakeholders that were invited to participate in the study (please see Supplement Material 2). Stakeholders were interest groups, professional associations, and patient organizations. The organizations independently decided and nominated their representatives in the interview and their number. The representatives of the authorities were selected by the research group on the basis of their duties in regulatory affairs. The interviewer and the research group did not interfere with the selection of the interviewees and did not know most of the participants personally in advance. The section Sampling and recruitment of the interviews has been revised accordingly.*

Was the study anonymous? Reading the Table 2 some participants can be identified via the citation from (e.g. nurse, because there was only one).

Authors' response**:** *There were three nurses in the same interview (see Table 1). The participants were anonymized before conducting the analysis and reporting the results. It is not possible to identify the nurse or any other participants from the report.*

Is it possible to use the brand name of the medicine (Neupogen) in Table 2?

***Authors' response*:** *We are aware that the medicines should primarily be reported in INN names. However, this is a citation from the interview and the interviewee mentioned the brand name. We have added registration mark with the brand name, but we are not sure if it is appropriate to use this format in a scientific report. Therefore, we would highly appreciate further advises from the Editor how to revise this specific point.*

Page 13
Line 18." Participants calculated a correlation between ….". . In my opinion correlation is not the correct word since it reflects statistical analysis. Can you change the phrase?

***Authors' response*:** *Thank you for your notice. The sentence is now changed as follows: "Participants suggested an association between.."*

VERSION 2 – REVIEW

REVIEWER	Iga Pawłowska Medical University of Gdańsk
REVIEW RETURNED	24-Sep-2019

GENERAL COMMENTS	Thank you for the correction and all your answers. Now, It is ok.