Author's response to reviews

Title: Pattern recognition in menstrual bleeding diaries by statistical cluster analysis

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Author's response to reviews: see over
Dear Editor,

we are pleased to submit our revised paper “Pattern recognition in menstrual bleeding diaries by statistical cluster analysis” by Christoph Gerlinger, Jens Wessel, Gerd Kallischnigg and Jan Endrikat.

The recommendations of the editor and the referees have been incorporated into the revision as follows:

Editor:

Include more context information in the background section of your abstract, in addition to the aims of your study.

We modified the Background section of the Abstract as follows:
The aim of this paper is to empirically identify a treatment-independent statistical method to describe clinically relevant bleeding patterns by using bleeding diaries of clinical studies on various sex hormone containing drugs.

Referee 1:

Question # 1
The phrasing of the aim of the paper, however was not clear. (major compulsory revision)

See above, included in Editor’s suggestion.

Question # 2
Are the methods appropriate and well-described? The population studied was not clearly defined. What were the demographic characteristics of the women studied (e.g., age, body weight, BMI, purpose of sex hormone drug use, duration of treatment) (major compulsory revision)

We added a description of the population studied, i.e. the proportion of women taking the sex hormones for 1.) hormone replacement therapy, 2.) contraception, or 3.) endometriosis to the results section. These three indications imply the adherence to the commonly known contraindications for the use of these products, which include age, body mass-index, smoking, concomitant medication and other diseases. As we have stated in the methods section, we analyzed the first 90 days of the bleeding diaries because of the different durations of the trials.
Question # 3
“Bleeding intensity” categories were standardized according to WHO terminology as “none”, “spotting”, and “bleeding”. Although the authors defined “spotting” and “bleeding”, “none” was not defined. Does “none” mean total amenorrhea, or merely the absence of intermenstrual bleeding? (major compulsory revision)

The bleeding intensities were recorded daily by the women. Hence, “none” means no vaginal bleeding on a given day. We added the definition of “none” to the methods section.

Question # 4
I also could not understand the statement “The bleeding patterns in the diaries should be found by unsupervised pattern recognition”. (minor essential revision)

We agree with the Reviewer that this whole paragraph is not easy to understand without special statistical knowledge on pattern recognition. However, we believe that an explanation of the unsupervised pattern recognition method is beyond the scope of our paper and that it is sufficient to quote a relevant standard text book for those readers that are interested in the details of our statistical analysis.

Question # 5
The clinical trials involving use of sex hormone-containing drugs were not cited. (major compulsory revision)

We analyzed Bayer Schering Pharma AG’s clinical project databases that contain aggregated data of individual trials. Referencing all trials in our databases would be quite lengthy because we included all available data including phase I trials with only a few women each in our analyses. However, in order to come closer to your recommendation we modified the first paragraph of the method section as follows:

We analyzed bleeding diaries that were kept in clinical trials involving various products used for hormonal fertility control, hormone replacement therapy and endometriosis. Mono-preparations as well as combined preparations were included. Estrogens, e.g., estradiol, estradiolvalerate or ethinylestradiol and a large variety of modern progestins, e.g., levonorgestrel, desogestrel, dienogest or drospirenone, were the hormonal components of the drugs.

Question # 6
The Ward Method tends to join clusters with a small number of observations and is strongly biased toward producing clusters with roughly the same number of observations (Milligan, 1980) (major compulsory revision)

The Reviewer is correct in stating that the Ward method has a potential tendency to produce clusters of roughly the same number of observations. However, this potential tendency was not confirmed in our data as we observed clusters of 71, 386, 450, 590, 1235, and 1880 observations. We added the cluster sizes to the results section in order to allow the reader to judge this potential effect.
Question # 7
There is a need for a more detailed description of the bleeding patterns identified. In this aspect, the paper fell short of achieving its objective. (major compulsory revision)

We added the following phrases:
The cyclic bleeding patterns are clearly separated into a desirable bleeding pattern (number 1 in Figure 4), which is characterized by the regular monthly bleeding and a very low frequency of intracyclic bleeding during hormone intake, and an undesirable bleeding pattern (number 2 in Figure 4), which is characterized by a less regular monthly bleeding and a higher frequency of intracyclic bleeding, starting always in the middle of the cycle. …

Bleeding pattern number 3 in Figure 5 shows amenorrhea, a pattern typical of post menopausal women taking continuously combined steroid hormone preparations. Bleeding pattern number 4 in Figure 5 can be interpreted as the pattern of fertile women which start continuous steroid hormonal treatment, e.g. for the treatment of endometriosis. The natural cyclic bleeding ceases during the first month of treatment and thereafter reaches amenorrhea as in pattern number 3. The bleeding patterns 5 and 6 in Figure 5 both show a high frequency of undesirable spotting or bleeding. Pattern 6 is worse than pattern 5.

Question # 8
Legends used are likewise rather confusing. (minor essential revision)

We thank the reviewer for this valuable remark. We made the legends of figures 2 and 3 as well as the titles of figures 4 and 5 more self-explanatory.

Question # 9
Limitations of the study are not clearly stated (major compulsory revision)

We agree and added the following paragraph at the end of the conclusion.
Using this cluster analysis with the method of Ward, treatments (medications and devices) having an impact on bleeding can be easily compared and categorized. This analysis is independent of the treatment’s route of administration (oral, transdermal, vaginal, intrauterine) and the duration of treatment. Hormonal and non-hormonal treatments can be easily compared. However, this method is only useful in large clinical trials to characterize a new product’s bleeding pattern but it is not meaningful for the physician treating an individual patient.
Since currently various innovative long-cycle contraceptive regimen are in development, this method might be useful to compare bleeding pattern from different studies using one uniform method.

Question # 10
Grammar and sentence construction have to be improved. (minor essential revision) NOTE: I emailed a copy of the whole journal with my suggested corrections (especially on grammar/sentence construction using email address editorial@biomedcentral.com)

Quality of written English: Not suitable for publication unless extensively edited

We thank the Reviewer for this careful review. We accepted all suggestions of the Reviewer, except those were we felt that it would be more appropriate to keep the exact statistical
technical term, e.g. “imputed”, rather than to use the more common but less precise term suggested by the Reviewer, e.g. “extrapolated”.

Referee 2:

This manuscript aims at finding clinically meaningful bleeding patterns as reported in bleeding diaries from clinical studies with steroidal hormones, either contraceptives or hormone therapy. The topic is of much interest since there has been considerable heterogeneity in studies reporting bleeding/spotting episodes in studies on women using hormones. Given this relevance, the own World Health Organization has issued recommendations for analyzing bleeding patterns in clinical trials, as adequately cited by the authors. Additional strengths of the manuscript include a good definition of the objectives, a well-selected list of references, and an adequate total length.

Question #1

The main problem, however, is that the concrete content and conclusions will perhaps be of little interest for clinicians. The analysis is focused on cluster algorithms that many clinical investigators/practitioners may find difficult to understand due to the lack of familiarity with these research tools.

We totally agree with this position. This tool is not useful for the physician treating an individual patient. It allows medication-approving authorities a comparison of different treatments from different studies. The treating physician, however, can use these results, to find the treatment with the best bleeding pattern. We added these limitations to the conclusion section.

Question #2

Another point refers to the limitation imposed by the fact that actually 27.9% of the women never bled during the period analyzed, and an additional 68.8% experienced a bleeding pattern that occurred only once. Authors should include in the manuscript an indication on whether this may, or may not, affect the consistency of their conclusions.

Apart from the women who never bled (amenorrhea is the desired bleeding pattern for post menopausal women taking continuously combined hormone replacement therapy) almost all women in our study had a unique individual bleeding pattern, i.e. for any two women there was at least one day on which the one woman bled and the other woman did not bleed. This is not surprising, as there are $3^{90} = 8.728*10^{42}$ different ways possible to fill out a 90-day bleeding diary with three bleeding intensities ‘none’, ‘spotting’, and ‘bleeding’.

The aim of our paper is to group the many different individual bleeding patterns into a few typical clustered patterns that can be interpreted clinically. We believe that this aim has been achieved in our paper.

Best regards,

Christoph Gerlinger on behalf of the authors