

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Posttraumatic growth and its relationship to quality of life up to nine years after liver transplantation: a cross-sectional study in Spain
AUTHORS	Pérez-San-Gregorio, María Ángeles; Martín-Rodríguez, Agustín; Borda-Mas, Mercedes; Avargues-Navarro, María Luisa; Pérez-Bernal, José; Conrad, Rupert; Gómez-Bravo, Miguel Ángel

VERSION 1 - REVIEW

REVIEWER	Wenceslao Peñate Universidad de La Laguna, Tenerife, Spain
REVIEW RETURNED	06-May-2017

GENERAL COMMENTS	<p>Review manuscript "Posttraumatic growth and quality of life up to more than nine years after liver transplantation: a cross-sectional study"</p> <p>This research deals with a relevant clinical topic in health studies, such as, psychological processes associated to patients with organ transplantations (specifically, liver transplantations). Together with the topic, sample is a special strength (a final sample of 216 person with liver transplantation) of the study. Also, processes assessed are pertinent, and the consideration of post-traumatic growth (PTG), especially. Results have a direct translational utility. As critical aspects, I suggest the following commentaries (basically formal aspects) to authors:</p> <ul style="list-style-type: none">- In abstract section, they point out how PTG's factors are associated with quality of life, but, only one factor attained statistical significance. In this sense, perhaps it could be more precise if they only mention this variable in the abstract.- The recruitment of patients (and caregivers) is described, but not their provenance (yes in in 'procedure' subsection). I think it could better mention in 'participants' subsection.- Patients and caregivers are described, but general population not (authors send readers to a previous study). Maybe some data about this sample (size, general characteristics), provides readers a better comprehension of its comparability.- For specific statistical analyses, authors divided sample in three groups, according statistical criteria. I think an explanation of this decision (against, for example, clinical criteria), is needed. Also, I cannot reach to understand why there are slight size differences in subsamples, depending on variable to contrast.- At the beginning of page 9, authors use the expression 'influence'. I think is more correct the expression 'associate'. Because this is a cross-sectional study, expressions around causality must be taken carefully. <p>That is all.</p>
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REVIEWER	Dr. Juliet Wakefield Nottingham Trent University, UK.
REVIEW RETURNED	07-Jun-2017

GENERAL COMMENTS	<p>This article explores post traumatic growth (PTG) and quality of life in liver transplant patients. I think that the paper is interesting and has a general appeal. However, I would like to bring the following issues to the authors' attention.</p> <p>It would be good to make it clear in the Abstract that specific additional analyses were conducted on the sub-set of participants for whom caregiver data was available (otherwise it looks odd to report 240 participants in the Abstract when it sounds like analyses were only conducted on 216 of them). This should also be made clear in the Method section of the paper.</p> <p>Take care to avoid causal language in the paper (e.g., "Our findings highlight the protective role..."; "impact"; "influenced")</p> <p>The authors mention a number of studies that have looked at PTG in recipients of other organs. Is there any evidence or reasoning to make us think that a liver transplant will be different/special to these other organ transplants in how it relates to PTG and life quality?</p> <p>Page 4: The key idea of PTG could be explained in more detail. For example, the key idea of growth (that people gain a higher level of functioning than they had previously) is key. More background about this important idea is required.</p> <p>Page 4: The Scignaro et al. paper did not investigate the implications of PTG for affective regulation. It showed that PTG positively predicted identification with the family group and the transplantee group over time. Since the authors note that this paper and the Zieba paper are the only two papers that have explored PTG in liver transplant patients, these papers should be discussed in more detail, and the contribution of the present study to this pre-existing literature should be highlighted. It would also be good to explore the Fox paper in more detail-why might this finding have been discrepant?</p> <p>Page 4, line 50: how does the clinical importance of PTG in liver transplant patients logically lead to the authors deciding to compare PTG in recipients and caregivers?</p> <p>Page 5: present hypotheses in future tense-they are predictions. Regarding the latter hypothesis-would it not make more sense to control for length of time since the transplant, and (hopefully) show that PTG is an important predictor of life quality, even after controlling for time since the transplant?</p> <p>Page 5: Are the values after the plus/minus symbol standard deviations? If so, this should be indicated with 'SD ='</p> <p>Page 5: what are low, intermediate, and high levels of education?</p> <p>Page 5: More information is needed about the general population sample (number of males and females, mean age, SD age, age range, etc.)</p> <p>Page 5: Need to make it clear that the score on the medical parameters is obtained by scoring participants one point for each complication that they had, leading to a value that could range between 0 and 16 inclusive, and that higher values mean poorer health.</p> <p>Page 7: line 34: Do the reliability values of 0.67 to 0.93 relate to the present data, or to citation 23? Reliability should be presented for data from the present study.</p> <p>Page 8 (top): Repetition from earlier.</p>
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	<p>Page 8 onwards: I think that the results could be presented in a more logical way-perhaps by presenting all findings regarding the full 240 participants first, and then presenting the results from the 216 participants for whom there is also caregiver data available. The paragraph in the middle of page 12 feels separate-maybe it should have its own sub-heading? Is the final paragraph on page 12 still referring to the data after it has been split into PTG groups? Overall, I think that a more logical story could be told.</p> <p>Page 8, line 43: is there any rationale from the literature for why these groups were defined in this way? I have the same question regarding the PTG groups on page 12.</p> <p>Page 8, line 55: Since the groups are defined by time, do you mean "There was no significant effect of group, since transplantation...". If so, is the next sentence not a repetition?</p> <p>Page 12: Avoid using the word 'step' in relation to analyses unless you are conducting a regression where you enter difference variables at each step.</p> <p>Page 14 (top): This was not the case for all sub-scales: patients did not all show lower general health than the general population.</p> <p>Page 14, line 7: do you mean 'decreased'?</p> <p>Page 14, paragraph 2: Were any analyses conducted to explore whether the high PTG vs. Population difference and the low/medium PTG vs. Population difference differed significantly from each other?</p> <p>Discussion: An important limitation of the study is that it is not longitudinal. It would be interesting to explore individuals' change in PTG over time, and this would allow the authors to make stronger claims regarding causality, as well as exploring potential mediating variables.</p> <p>Tables: It would be good to state in the label exactly what analysis was carried out, so that the reader can easily understand what they are looking at.</p> <p>Figures: Figure 3: what is meant by 'less/medium/more'? Figures are generally quite confusing-it would be easier to follow them if the graph was underneath the Figure rather than incorporated into it. The paper needs to be edited for grammar, expression, and typos. Overall, I feel that addressing these issues will increase the chances of publication.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

This research deals with a relevant clinical topic in health studies, such as, psychological processes associated to patients with organ transplantations (specifically, liver transplantations). Together with the topic, sample is a special strengthen (a final sample of 216 person with liver transplantation) of the study. Also, processes assessed are pertinent, and the consideration of post-traumatic growth (PTG), especially. Results have a direct translational utility.

Answer: Thank you for the encouraging comment.

As critical aspects, I suggest the following commentaries (basically formal aspects) to authors:

1) In abstract section, they point out how PTG's factors are associated with quality of life, but, only one factor attained statistical significance. In this sense, perhaps it could be more precise if they only mention this variable in the abstract.

Answer: We have changed the abstract according to your suggestion and mention only the significant dimension vitality.

2) The recruitment of patients (and caregivers) is described, but not their provenance (yes in in 'procedure' subsection). I think it could better mention in 'participants' subsection.

Answer: We agree with your suggestion and have included the description of the participants' provenance in the "participants" subsection.

3) Patients and caregivers are described, but general population not (authors send readers to a previous study). Maybe some data about this sample (size, general characteristics), provides readers a better comprehension of its comparability.

Answer: As suggested, we have presented more details (size, sociodemographic variables) about the general population sample.

4) For specific statistical analyses, authors divided sample in three groups, according statistical criteria. I think an explanation of this decision (against, for example, clinical criteria), is needed. Also, I cannot reach to understand why there are slight size differences in subsamples, depending on variable to contrast.

Answer: We divided the sample in three subgroups based on the time and PTG factors, because these factors were the main independent variables in our study. This decision was based on the consideration that time since transplantation as well as PTG have important implications for quality of life. Obviously the analysis of other subgroups would have been possible, but for lack of space we had to confine our analysis to the main subject of our study.

To establish three groups of equal size based on the time since transplantation, we created the categories less time (≤ 3.5 years), medium (> 3.5 to ≤ 9 years) and more (> 9 years).

To establish three groups of equal size based on the PTG score we created the categories low (0 to 59 points), medium (60 to 77 points) and high (78 to 105 points). With regard to the small differences in group sizes in the PTG subgroups: completely equal group sizes were not possible based on the distribution of PTG scores, and therefore, this was the best possible solution.

5) At the beginning of page 9, authors use the expression 'influence'. I think is more correct the expression 'associate'. Because this is a cross-sectional study, expressions around causality must be taken carefully.

Answer: We agree to your comment and have changed the expression.

Reviewer: 2

This article explores post traumatic growth (PTG) and quality of life in liver transplant patients. I think that the paper is interesting and has a general appeal.

Answer: Thank you for the encouraging comment.

However, I would like to bring the following issues to the authors' attention.

1) It would be good to make it clear in the Abstract that specific additional analyses were conducted on the sub-set of participants for whom caregiver data was available (otherwise it looks odd to report 240 participants in the Abstract when it sounds like analyses were only conducted on 216 of them). This should also be made clear in the Method section of the paper.

Answer: We agree that this difference in sample sizes may be difficult to understand in the abstract. We have therefore revised the abstract to clarify this point.

2) Take care to avoid causal language in the paper (e.g., “Our findings highlight the protective role...”; “impact”; “influenced”).

Answer: We have carefully changed the wording throughout the manuscript.

3) The authors mention a number of studies that have looked at PTG in recipients of other organs. Is there any evidence or reasoning to make us think that a liver transplant will be different/special to these other organ transplants in how it relates to PTG and life quality?

Answer: Posttraumatic growth has been studied before in lung transplantation and HSTC. In general, both are associated with significantly lower survival rates (Kirk et al., 2014) from the surgery itself and after one year than liver transplantation. Bearing in mind the likelihood of death associated with the medical intervention, the impact of lung transplantation as well as HSCT may be even more traumatic for recipients than liver transplantation, which may result in the activation of even more resources, and thereby induce greater posttraumatic growth. This is obviously only one aspect which may underlie different psychological responses to different types of organ transplantation. We pointed this out in the Introduction.

4) Page 4: The key idea of PTG could be explained in more detail. For example, the key idea of growth (that people gain a higher level of functioning than they had previously) is key. More background about this important idea is required.

Answer: According to your suggestions, in the revised manuscript we have explained the key concept of PTG in more detail and elucidate the theoretical background, e.g., the positive psychology movement.

5) Page 4: The Scignaro et al. paper did not investigate the implications of PTG for affective regulation. It showed that PTG positively predicted identification with the family group and the transplantee group over time. Since the authors note that this paper and the Zieba paper are the only two papers that have explored PTG in liver transplant patients, these papers should be discussed in more detail, and the contribution of the present study to this pre-existing literature should be highlighted. It would also be good to explore the Fox paper in more detail-why might this finding have been discrepant?

Answer: In the revised manuscript we have described and discussed both papers more in detail and highlight the contribution of the present paper to the pre-existing literature. Furthermore, we have explored in detail the discrepant findings in the Fox paper.

6) Page 4, line 50: how does the clinical importance of PTG in liver transplant patients logically lead to the authors deciding to compare PTG in recipients and caregivers?

Answer: There has been growing evidence for relevant psychological stress in primary caregivers, who may even show symptoms of traumatization, before and after liver transplantation (Malik et al., 2014; Rodrigue et al., 2011; Weng et al, 2011; Young et al., 2003, 2017). Against this backdrop, we were interested in the comparison of posttraumatic growth in these two groups. Furthermore, as there is a close mutual relationship between the caregiver and liver transplant recipient, traumatization and posttraumatic growth in both patients and caregivers have important implications for their coping strategies and quality of life, as well as compliance and satisfaction with medical care (Pérez-San-Gregorio et al., 2017). We have clarified this in the revised section of the Introduction.

7) Page 5: present hypotheses in future tense-they are predictions. Regarding the latter hypothesis-would it not make more sense to control for length of time since the transplant, and (hopefully) show that PTG is an important predictor of life quality, even after controlling for time since the transplant?

Answer: As suggested, we have now presented our hypotheses in the future tense. The suggested reformulation of the second hypothesis is an extension of our approach and a reasonable alternative, however, it would imply other statistical analyses as well as rewriting their presentation. Therefore, we decided to stick to our initial hypothesis. Nevertheless, as an additional analysis, we did calculate the correlation between PTG and duration of time since transplantation: $r=0.119$, $p=0.065$, $n=240$. The low correlation coefficient underlines the independence of these two factors and the validity of our approach.

8) Page 5: Are the values after the plus/minus symbol standard deviations? If so, this should be indicated with 'SD ='.

Answer: Yes, they are. We have indicated SD as suggested.

9) Page 5: what are low, intermediate, and high levels of education?

Answer: We have clarified this categorization in the revised manuscript.

- High level of education: completed university or A levels.
- Intermediate level of education: completed high school.
- Low level of education: did not complete high school.

10) Page 5: More information is needed about the general population sample (number of males and females, mean age, SD age, age range, etc.).

Answer: As suggested, we have presented more details (size, sociodemographic variables) about the general population sample. We could only present those data given in the original article by Schmidt S, Vilagut G, Garin O, et al. Reference guidelines for the 12-Item Short-Form Health Survey version 2 based on the Catalan general population. *Med Clin (Barc)* 2012;139:613–25.

11) Page 5: Need to make it clear that the score on the medical parameters is obtained by scoring participants one point for each complication that they had, leading to a value that could range between 0 and 16 inclusive, and that higher values mean poorer health.

Answer: We have clarified the scoring on medical parameters in the revised manuscript.

12) Page 7: line 34: Do the reliability values of 0.67 to 0.93 relate to the present data, or to citation 23? Reliability should be presented for data from the present study.

Answer: As suggested, in the revised manuscript, we have presented the data from the present study and deleted the data previously presented from citation 23. Cronbach's alpha in our study ranged from 0.72 to 0.89.

13) Page 8 (top): Repetition from earlier.

Answer: To avoid repetition, we have cut this section and moved all the relevant information to the instruments section.

14) Page 8 onwards: I think that the results could be presented in a more logical way-perhaps by presenting all findings regarding the full 240 participants first, and then presenting the results from the 216 participants for whom there is also caregiver data available. The paragraph in the middle of page 12 feels separate-maybe it should have its own sub-heading? Is the final paragraph on page 12 still referring to the data after it has been split into PTG groups? Overall, I think that a more logical story could be told.

Answer: According to your suggestion, we have completely restructured the presentation of results. We now present all our findings for all 240 participants first, and afterwards, the analysis of the subset of 216 recipients with their caregivers. Furthermore, we have completely revised the presentation with regard to the association of time and posttraumatic growth, to integrate the paragraphs mentioned in your comment in the text better. We think that the revised Results section tells a more coherent story.

15) Page 8, line 43: is there any rationale from the literature for why these groups were defined in this way? I have the same question regarding the PTG groups on page 12.

Answer: The rationale for defining three groups of equal size on the basis of percentiles for our independent variables PTG and time was based on theoretical and practical considerations. First, we wanted the division into different groups to differentiate adequately between individuals with regard to the relevant variable. Second, group size had to be large enough to ensure the possibility of finding statistically significant differences between groups, and finally group definition should be of practical relevance in terms of identification of relevant subgroups in clinical practice.

Regarding the literature, our research team had previously applied this subgroup definition in studies including clinically relevant independent variables (Pérez-San-Gregorio et al., 2013, 2017; Rodríguez et al., 2005).

16) Page 8, line 55: Since the groups are defined by time, do you mean “There was no significant effect of group, since transplantation...”. If so, is the next sentence not a repetition?

Answer: Thank you for your comment. We have now clarified the wording. In the sentence mentioned, the interaction between group (caregiver, recipient) and time since transplantation on PTG is addressed. In the following sentence the main effect of time since transplantation is mentioned. In the revised version we changed the sentence as follows:
“There was no significant effect of between-group interaction and time since transplantation on posttraumatic growth ($F=0.196$, $p=0.822$; Table 5, Figure 4).

17) Page 12: Avoid using the word ‘step’ in relation to analyses unless you are conducting a regression where you enter difference variables at each step.

Answer: We have clarified the wording regarding statistical analyses and replaced the expression “step” with “part”.

18) Page 14 (top): This was not the case for all sub-scales: patients did not all show lower general health than the general population.

Answer: Thank you for your observation. We have corrected this error in the revised version.

19) Page 14, line 7: do you mean ‘decreased’?

Answer: The difference between quality of life in the population and the recipient group, in which more time had elapsed since transplantation, was greater than in the groups in which less/medium time had elapsed. Therefore, the difference increased. However, as the wording might have been confusing we have omitted it.

20) Page 14, paragraph 2: Were any analyses conducted to explore whether the high PTG vs. Population difference and the low/medium PTG vs. Population difference differed significantly from each other?

Answer: In table 4 all statistical analyses (unpaired t test and Cohen's d) between low/medium/high PTG and Spanish population sample can be seen. Unless you find it absolutely another statistical analysis necessary, we would stick to the analysis in Table 4.

21) Discussion: An important limitation of the study is that it is not longitudinal. It would be interesting to explore individuals' change in PTG over time, and this would allow the authors to make stronger claims regarding causality, as well as exploring potential mediating variables.

Answer: We completely agree with this assessment and have added this limitation to the limitations section.

22) Tables: It would be good to state in the label exactly what analysis was carried out, so that the reader can easily understand what they are looking at.

Answer: As suggested, in the revised version, we state in the label exactly what analysis was carried out.

23) Figures: Figure 3: what is meant by 'less/'medium/more'?

Answer: In Figure 3 less/medium/more refer to the three categories of time elapsed since transplantation: less (≤ 3.5 years), medium (> 3.5 to ≤ 9 years) and more (> 9 years). We have clarified the description of categories in the revised Figure 2.

24) Figures are generally quite confusing-it would be easier to follow them if the graph was underneath the Figure rather than incorporated into it.

Answer: We agree with your comment and have completely rearranged Figures 3 and 4. Now we present relevant data in two tables and a graphic illustration of the data separately.

25) The paper needs to be edited for grammar, expression, and typos.

Answer: We have carefully edited the paper as suggested.

Overall, I feel that addressing these issues will increase the chances of publication.

VERSION 2 – REVIEW

REVIEWER	Wenceslao Peñate Dto. Psicología Clínica. Psicobiología Y Metodología (Dt. Of Clinical Psychology, Psychobiology and Methodology) Facultad of Ciencias de la Salud (faculty of Health Sciences) Universidad de La Laguna
REVIEW RETURNED	10-Jul-2017

GENERAL COMMENTS	My comments to manuscript have been resolved satisfactorily by authors. I now think manuscript can be accepted for publication.
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REVIEWER	Dr. Juliet Wakefield Nottingham Trent University, England
REVIEW RETURNED	13-Jul-2017

GENERAL COMMENTS	<p>I feel that the manuscript has been much improved by revision-it is now more logical and coherent, and the structuring of the Results is now far clearer. I just have some final small queries/issues before (hopefully) final acceptance.</p> <p>Page 2 (and elsewhere): "duration since transplantation" is not the correct phrase -maybe "time since transplantation" or something similar</p> <p>Page 5: what is meant by "compliance"?</p> <p>Page 5: It is not clear how the findings from Fox et al. lead to the conclusion "that posttraumatic growth is not related per se to higher quality of life, but rather increases the likelihood of a flexible adaptation to a new situation, which in the long run is thought to be beneficial to personal wellbeing"</p> <p>Page 5: It is not clear why the authors predict that there will be a positive relationship between time since transplantation and pain- surely it could be argued that the opposite would be true?</p> <p>Page 9: The terms "less, medium, more" are used to define the 'time since transplantation' categories, but at this point the reader does not know what these labels signify. It would be good to explain these three categories earlier on. In fact, it would be good to explain how each variable was categorised when you introduce the relevant variable in the Method section.</p> <p>Page 9 (and elsewhere): Were the post-hoc tests corrected for familywise error (e.g., Bonferroni correction)?</p> <p>Page 9 (and elsewhere): It would be good to shift from a plus/minus sign to "SD = "</p> <p>Table 3: Rather than just "Intergroup Comparisons" as a label in the table, it would be good to make it clear that these are intergroup comparisons on time since transplant, and perhaps also remind the reader underneath the table about what "less, medium, and more" mean.</p> <p>Page 14: The final sentence on the page does not make sense.</p> <p>Page 20: Tedeschi and Calhoun's discussion of posttraumatic growth is not really a 'definition', since it explores the complexities and controversies around the term, rather than giving a simple meaning to the term-perhaps it's more of a description?</p> <p>A final through proof-read would also be a good idea.</p>
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

My comments to manuscript have been resolved satisfactorily by authors. I now think manuscript can be accepted for publication.

Answer: Thank you for the encouraging comment.

Reviewer: 2

I feel that the manuscript has been much improved by revision-it is now more logical and coherent, and the structuring of the Results is now far clearer. I just have some final small queries/issues before (hopefully) final acceptance.

Answer: Thank you for the encouraging comment.

Page 2 (and elsewhere): "duration since transplantation" is not the correct phrase -maybe "time since transplantation" or something similar.

Answer: As suggested we have changed the term "duration since transplantation" to "time since transplantation".

Page 5: what is meant by "compliance"?

Answer: We meant the adherence to therapy, so we substituted the probably outdated term compliance to therapy adherence.

Page 5: It is not clear how the findings from Fox et al. lead to the conclusion "that posttraumatic growth is not related per se to higher quality of life, but rather increases the likelihood of a flexible adaptation to a new situation, which in the long run is thought to be beneficial to personal wellbeing"

Answer: We agree that our conclusion cannot be derived from the study by Fox et al. This study only shows a weak association between posttraumatic growth and quality of life. In the revised section we have clarified that the conclusion is our interpretation of a possible relationship between both constructs.

Page 5: It is not clear why the authors predict that there will be a positive relationship between time since transplantation and pain-surely it could be argued that the opposite would be true?

Answer: The positive relationship between pain and time since transplantation is assumed because the treatment by immunosuppressants is associated with pain, furthermore the likelihood of relevant comorbidities increases as time goes by. We have clarified our hypothesis in the introduction section as follows: "The negative association between time since transplantation and quality of life is based on the assumption that recipients may increasingly suffer from adverse side effects of immunosuppressants such as pain. Furthermore, in the course of time they may develop serious comorbidities."

Page 9: The terms "less, medium, more" are used to define the 'time since transplantation' categories, but at this point the reader does not know what these labels signify. It would be good to explain these three categories earlier on. In fact, it would be good to explain how each variable was categorised

when you introduce the relevant variable in the Method section.

Answer: As suggested we have introduced the relevant variable in the method section.

Page 9 (and elsewhere): Were the post-hoc tests corrected for familywise error (e.g., Bonferroni correction)?

Answer: The post-hoc tests were corrected for familywise error. We described the correction in the tables and the method section.

Page 9 (and elsewhere): It would be good to shift from a plus/minus sign to "SD = "

Answer: We changed this throughout the text.

Table 3: Rather than just "Intergroup Comparisons" as a label in the table, it would be good to make it clear that these are intergroup comparisons on time since transplant, and perhaps also remind the reader underneath the table about what "less, medium, and more" mean.

Answer: We clarified the label in table 3 and reminded the reader underneath the table about the categories of time since transplantation.

Page 14: The final sentence on the page does not make sense.

Answer: We completely agree. Therefore we revised this section and clarified the meaning.

Page 20: Tedeschi and Calhoun's discussion of posttraumatic growth is not really a 'definition', since it explores the complexities and controversies around the term, rather than giving a simple meaning to the term-perhaps it's more of a description?

Answer: We agree that it is rather a description of the construct than a definition. Therefore we changed the term define to describe.

A final through proof-read would also be a good idea.

Answer: We once again carefully checked the whole manuscript.

VERSION 3 - REVIEW

REVIEWER	Dr. Juliet Wakefield Nottingham Trent University, England, UK
REVIEW RETURNED	20-Jul-2017

GENERAL COMMENTS	I am happy with this final version.
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