Reviewer’s report

Title: The cost of relapse, the predictors of relapse, and the role of prior relapse in the treatment of schizophrenia

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Reviewer: Terry J Lewin

Reviewer’s report:

Overall Comments:

This paper is well written and its overall purpose is clear (i.e., to examine relationships between relapse profiles, patient characteristics, and direct mental health costs). However, there appears to be a reasonable level of (unnecessary) redundancy in the way the findings are reported and the paper would benefit from a re-think of the basic analysis strategy. Notwithstanding, I do not feel that I am in a position to recommend exactly how the analysis strategy should be changed – so, my basic approach here is to outline some of the issues, and possible strategies, and to leave it to the authors to either more rigorously defend their current approach or to streamline the presentation with a more coherent analysis strategy.

Major Compulsory Revisions:

As noted above, the authors need to take this opportunity to review their analysis strategy – with the primary aim of reducing the level of redundancy and strengthening linkages between specific hypotheses and the reported analyses.

1. Major area of redundancy: Table 1 (baseline characteristics) and Table 2 (cost components) provide a breakdown by prior relapse status - Without Prior Relapse (an aggregation of groups NN and NR) vs. With Prior Relapse (an aggregation of groups RN and RR), while Table 3 (baseline characteristics) and Table 4 (cost components) provide similar material but separately for each of the four subgroups. Consequently, the analyses reported in these four tables address overlapping questions.

I appreciate the fact that it is not easy to resolve the issue of redundancy with respect to the current paper, but here are a few possibilities:

Possibility A – treat the analysis as fundamentally a two-way design (Relapse status prior to the index year – With vs. Without Relapse – by Relapse status during the index year - With vs. Without Relapse) – and use appropriate two-way ANOVA or ANCOVA related analyses.

Possibility B – treat the analysis as fundamentally a one-way design, with the existing four subgroups, and focus on three orthogonal contrasts, namely NN and NR vs. RN and RR (which is essentially the data currently reported in Tables 1
and 2), followed by NN vs. NR (addressing issues among those without a prior relapse), and then RN vs. RR (addressing issues among those with a prior relapse). This approach would involve a single coherent analysis strategy (i.e., planned orthogonal contrasts within the context of an ANOVA or ANCOVA model), but the reporting would represent an unfolding of the story – what was known at baseline and with what was it associated, and what additional information could be learned based on knowledge of subsequent relapse status.

Possibility C – treat the analysis as fundamentally a one-way design, with the existing four subgroups, and focus solely on simple comparisons among these subgroups (which is essentially the data currently reported in Tables 3 and 4) – here, however, you would essentially drop the current breakdowns in Tables 1 and 2 and rely on the pattern of subgroup differences to make inferences about the contributions of past relapse and subsequent relapse. My personal preference, in this case, would be to title the last column in the Table "Pattern of subgroup differences" and to make use of the actual subgroup codes. So, for example, for Age (in Table 3) instead of a P-value and subscripts (b,c,d,e), the last column would read "NN,NR>RN,RR ***" and so on for the other entries – so the pattern is clearly revealed in the information provided (without the need to look at footnotes). The current analyses in Table 4 would then be brought into alignment with those in the current Table 3 (instead of being reported as overall ANOVAs, etc, as is currently the case).

If the authors are still keen to report the data for the overall sample (N=1,557) (and this is not available in other publications or reports), then they might consider a new Table 1, in a multi-column format, which lists the baseline characteristics in the left-hand columns and the costs profiles in the right-hand columns (probably dropping the medication details – currently in Table 2 – in favour of the aggregated layout currently in Table 4). This would be followed by new Table 2 (based on the current Table 3) and new Table 3 (based on current Table 4).

The data currently reported in Table 5 is consistent with the orthogonal contrast strategy mentioned in Possibility B above – but it may need to be revisited, depending on the final approach taken. (See additional comments about the logistic regressions below).

Possibility D – a completely different strategy to the above would be to take more of an "illness trajectory" view, perhaps by collapsing the data into three groups – stable trajectory (subgroup NN), relapsing trajectory (combining subgroups NR and RN), and chronic or deteriorating trajectory (subgroup RR) – which would simplify reporting, possibly with the loss of little useful information from the current findings.

As already noted, (whichever approach the authors choose to take) strengthening linkages between specific hypotheses and the reported analyses will no doubt improve the paper and reduce some of the apparent redundancy.

2. Variables associated with subgroup allocations: Some of the data reported in
the current Tables is a little misleading or confusing, given its relationship to subgroup definitions, etc. For example, "hospitalized in the 1 year before enrolment" probably should be detailed in the text, not the tables, as it is one of the defining characteristics for baseline relapse status, is it not? – Consequently, how is it that 72% of the NR subgroup was hospitalised in the year prior to enrolment (as shown in Table 3). Likewise, what is the explanation for day treatment hospitalisation and emergency services usage for subgroup NN (as shown in Table 4) – given the variables contributing to relapse status – "psychiatric hospitalization, use of emergency services, use of a crisis bed, or a suicide attempt".

Minor Essential Revisions:

3. Logistic regressions: While the logistic regressions reported in Table 5 seem to be generally appropriate, the Odds Ratios (ORs) may be a little confusing for the average reader. For example, in the text, the authors state: "Overall (Table 5A), the predictors of subsequent relapse included presence of prior relapse, having health insurance, being medication nonadherent, younger at illness onset, and poorer functioning level". This list appears to be in approximate sequential order of the ORs – implying something about their relative contributions, etc. However, greater attention needs to be paid to the nature of the predictor variables – the first three are binary – hence, the OR refers to the shift from absence to presence of that attribute – whereas the last few are continuous and, therefore, respectively refer to the changing odds for each one unit on the age at illness onset, SF-12 physical composite, and SF-12 mental composite scores. It may be worth considering reporting each of the continuous variables in standardized (or z-score) form, so that the OR refers to a one standard deviation change – or, alternatively, another metric that would have some inherent real world or clinical value – such as a 10 unit change in age, or a 10 unit change in functioning, etc, etc.

Discretionary Revisions:

4. Typographical error in Table 1 – delete "Douglas E Faries/AM/LLy@LILLY," that appears to be embedded in the "Single marital status" variable name.

5. Abstract – restructure the Results section – to avoid the confusion generated by two sets of statements about the key predictors.

6. Although the definition of "Relapse" in the Measures section is clear, is it possible that some patients assigned to one of the "relapse" subgroups were in fact experiencing their first major episode of psychosis (and, hence, strictly speaking it is not a relapse)?

7. Why is "a diagnosis of a schizoaffective disorder" listed among the "prior covariates" (in the Statistical analysis section) when the focal diagnostic group includes participants "diagnosed with schizophrenia, schizoaffective, or schizophreniform disorder"?

8. The first line of the Results should probably only refer to the 1,247 (80%) who
did not relapse in the 6 months prior to the study period and the 310 (20%) who did – depending on how the subsequent analysis unfolds, etc.

9. "Seminal marker" (2nd paragraph of the Discussion) may be too strong a term, since the notion that prior instances of any given event are likely to predict the occurrence of subsequent instances is hardly a revolutionary or surprising finding.

10. Related to the above, since the initial focal point in the treatment process is a comprehensive clinical assessment (at which current and past history are typically examined), does knowledge about previous relapse episodes improve the prediction of current treatment costs over and above associations with current functioning and symptomatology (say, based on the PANSS, MADRS, SF-12, medication adherence)?

While this review tends to sound a little negative, I greatly appreciate the value of studies like US-SCAP and the need to better understand the real-world predictors of relapse (and associated costs).

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.