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Authors' reply

We acknowledge the proposition raised by Dr Rose that a comparison of nicotine replacement therapy (NRT) and varenicline using equal pre-cessation treatment regimens may result in different efficacy outcomes from those found in our trial. However, we would like to reiterate that our open-label comparison of varenicline with NRT was a pragmatic trial based on current treatment regimen recommendations by the manufacturers of the products and in accordance with current recommendations for transdermal NRT use in established health guidelines.[1 2]

Dr Rose suggests that the imbalance in pre-cessation treatment between products in our trial reflects a flaw in the design of our study. The objective of this study was to compare a 12-week standard regimen of varenicline with a 10-week standard regimen of transdermal NRT. As the differentiation in treatment between products is openly acknowledged and justified, we would argue that differences in pre-cessation treatment do not reflect a design flaw but, rather, a potential limitation. Even though pre-cessation treatment was not directly referred to, our paper discusses the possibility of a treatment bias resulting from differences in treatment periods between products and recognises this as a limitation of the study.

While use of pre-cessation NRT may be being adopted in some cases, its use is not currently general practice. A standard regimen comparison, as with this open-label design, is therefore more likely to reflect results found in real-world settings. Indeed, recent real-world data from Stop Smoking Services in England provide further support for our findings of greater efficacy with varenicline compared with NRT.[3] The 4-week quit rates in participants set a quit date between April and September 2007 were: varenicline 64% (n = 32 879), bupropion SR 53% (n = 12 767) and NRT 48% (n = 243 123).

The evidence of improved efficacy of transdermal NRT when used during a pre-cessation period in comparison with NRT use without a pre-cessation period[4 5] may provide a rationale for conducting a comparison of varenicline versus NRT with equal pre-cessation treatment periods. The authors of the currently discussed open-label trial agree that this would certainly be an interesting study for future research.

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Clinically significant outcomes in smoking cessation

The study by Aubin *et al*[1] published in this issue comparing varenicline with nicotine replacement therapy (NRT). The authors have shown a significant difference in continuous abstinence rate at the end of treatment of 12 (or 11) weeks, favouring varenicline. However, the beneficial effect is not maintained in a significant fashion up to the end of the study period at 52 weeks. In this context, we would question the validity of measuring abstinence at 12 (or 11) weeks as a primary outcome. It is the long-term outcomes of a smoking cessation therapy that should be most clinically relevant, and therefore the most important finding in this trial. Indeed, the Russell standard recommends that, as a bench mark, quit rates should be assessed at 6 and 12 months and biochemically verified at each point.[2] Other comparative studies using NRT have also used 6- or 12-month periods to assess the efficacy.[3]

Given the fact that there was no significant difference in the abstinence rates at 12 months between the two treatments, it calls into question the cost-effectiveness of varenicline as a pharmacotherapy for smoking cessation. The courses of treatment used in the trial cost £163.80 and £76.31 for varenicline and NRT, respectively.[4] Clinicians are under pressure at all times to cut costs and be evidence-based, and this trial seems to show that there is currently no compelling reason to use the newer, more expensive agent in the smoking cessation clinic, apart from its apparent benefit in reducing craving and some other non-specific effects in the early phases of treatment.

We think the conclusions of the trial are presented in such a way as to give more emphasis to the efficacy of varenicline compared with NRT. But it seems that what this study really tells us is that there is no significant difference in long-term abstinence when comparing varenicline with NRT in an open-label comparison.

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Authors' reply

We recognise the relevance of showing long-term outcomes of smoking cessation therapies. However, many drug trials use end of treatment measures as primary outcomes.[1 2] Given the high attrition rates during the follow-up phase, choosing long-term primary outcomes has a high impact on the numbers of subjects needed. It is noteworthy that the study cited by Hillman *et al* failed to show any significant difference between the efficacy of a nicotine patch and placebo at 6 and 12 months of follow-up.[3]

We would like to acknowledge that the Russell standard includes six standard criteria.[4] One of these criteria is to use an "intent to treat" approach in which all randomised subjects are included in the analyses (unless they have died or moved to an untraceable address). Using an all-randomised population, our long-term quit