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### Is this a non-inferiority trial?

Crawford *et al*<sup>1</sup> have set out to investigate whether screening for suicidal ideation among people who attend primary care services and have signs of depression increases the short-term incidence of feeling that life is not worth living. It seems to me that this is a non-inferiority trial, i.e. the authors want to show that screening is no worse than not screening. This raises a number of design issues.

First, the trial is powered to detect an increase in the proportion who felt their life was not worth living from 30% to 45%. This seems a clinically large increase and suggests that anything short of a 50% increase in relative risk is acceptable. Second, having calculated the sample size based on relative risk, they analyse the main results using odds ratios rather than relative risk, so that it is difficult to see what sort of increase in relative risk was found and impossible to see the confidence interval around the relative risk. Third, if this is seen as a non-inferiority trial, arguably screening would be regarded as non-inferior provided that the possibility of the suicidal ideation rate being 50% worse than non-screening could be ruled out (in the sense that the 95% confidence interval for the difference in ideation rates would not include 50% inferiority relative to the non-screened group).<sup>2</sup> We only have the confidence interval around the odds ratio to go on, but given how wide that is, it is highly likely that the confidence interval would include the 50% increase in relative risk. For these reasons I think the results should be treated with caution.

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**Authors' reply:** Peter O'Halloran raises a good point about this study: it was underpowered. Even slightly higher levels of suicidal thinking among people who are screened for suicide risk would be clinically important and our study was only powered to detect a fairly large difference.

However, at the start of the study we faced a dilemma; a sizeable minority of local general practitioners told us that they were uncomfortable asking people with depression about suicidal thoughts because they were concerned that this could 'make them feel suicidal'.<sup>1</sup> Subsequent discussions with medical students and trainee psychiatrists (and indeed members of the ethics committee that reviewed the study protocol) revealed that these concerns were shared by others. A sample size calculation based on a

non-inferiority hypothesis and using a smaller but still clinically important difference in levels of suicidal thinking would have required a sample size several times larger than the one we recruited. As Norman and colleagues have recently pointed out,<sup>2</sup> sample size calculations are usually a compromise between statistical considerations, economics and logistical constraints. When we embarked on the study we knew that we did not have the resources to recruit a sample large enough to detect a small difference in levels of suicidal thinking among those who were and were not screened. However, we hoped that we could rule out the possibility of a large difference and this is therefore what we set out to do. The 95% confidence intervals around the odds ratio for the likelihood of suicidal thoughts among those that were screened were broad (0.66–1.18) and are compatible with either higher or lower levels of suicidal thinking in those who are screened compared with those who are not. Despite this limitation, these are the first data that test the veracity of a belief that was held by many and may have been an obstacle to screening for risk of self-harm in this high-risk group.

As we pointed out in the Discussion of our paper, it was not possible to collect data needed to calculate relative risks associated with screening because this would have meant collecting baseline levels of suicidal ideation from all those in the study. This would have exposed those in the control arm of the study to the very factor that the study was designed to examine.

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### Delay in starting clozapine and treatment guidelines

There is a reasonable level of information to suggest that clozapine is effective in patients who have treatment-resistant schizophrenia. Hence, clozapine should be started at the right time so that patients can draw maximum benefit from it. In this vein, the article by Howes *et al*<sup>1</sup> provides important insights into the clinical practice with regard to the use of clozapine. The authors showed that clozapine is delayed by about 4 years and many patients are treated with polypharmacy and receive higher than recommended doses, which is contrary to the recommendations made by several practice guidelines. However, it is important to note that the conclusions drawn about the delay in starting clozapine might not be a true reflection of actual delay, because often patients who are offered clozapine refuse to take it. Hence, some of the delay may be due to lack of agreement of the patient and this in general does not reflect the delay in the clinician offering the medication. It would have been better had the authors extracted the data pertaining to initial offering of clozapine and the number of patients who refused clozapine at the first instance as part of this study. This would have actually given the true clinical picture.

Another issue is the definition of duration of illness used. The authors have defined duration of illness as 'the time from the first recording of the diagnosis of a psychotic illness by a clinician to the present', which may not be a true reflection of duration of