suggested by Ian Cope, that there is no official definition of new psychoactive substances. Goodair and colleagues claim that there is no universal definition of novel psychoactive substances, but such a definition, created by the Home Office Advisory Council on the Misuse of Drugs,[2] was included in the previously mentioned report from the National Programme on Substance Abuse Deaths (NPSAD).[3] The weakness of the definition from the Advisory Council on the Misuse of Drugs is that it says little more than the generally accepted definition of legal highs—namely psychoactive substances that are not controlled by the Misuse of Drugs Act 1971.

We accept that deaths associated with non-psychoactive substances such as anabolic steroids should be reported along with deaths associated with substances that have been controlled for many years, but they should not be included in a table headed "novel psychoactive substances", as shown in the NPSAD report.[3]

In our letter,[4] we did not claim that the Office for National Statistics classified drugs as legal highs. Our reference to the term legal highs was aimed at media reports, as exemplified by the BBC.[5] Furthermore, our comments concerning the classification of anabolic steroids and DNP were aimed at the National Programme on Substance Abuse Deaths, not the Office for National Statistics .

We declare that we have no competing interests.

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Radiotherapy for breast cancer, the TARGIT-A trial

The TARGIT-A trial (Feb 15, p 603)[1] is a good example of trying to make data fit a pre-existing hypothesis; there are several major deficiencies in the analysis. Paramount among these deficiencies is the misuse of the non-inferiority criterion,[2] which requires the upper (90%) CI to be below a predefined value (here 2·5%). This criterion clearly fails when the appropriate 5-year Kaplan-Meier estimates are used, which in fact establish a 2% superiority of external beam radiotherapy (p=0·04) and a CI extending beyond 2·5%. Table 3 of the Article[1] uses crude rates that are substantially diluted by patients with short follow-up (only 611 [18%] patients had a 5-year follow-up). The effect is even clearer if locoregional recurrence or all recurrence is used, as in previous radiotherapy trials.[3]

Another common but well known danger is to focus attention on the most favourable subgroup.[4,5] The protocol clearly states that the primary analysis population includes all randomised patients. However, the report concentrates on the prepathology group. No correction for multiple comparisons or test for heterogeneity between groups is provided, and the data available suggest that it would not be significant. More should be said about all randomised patients.

Although a small increase in recurrence with a simpler therapy might well be acceptable in many circumstances, the present attempt to argue for virtually no difference by misuse of the non-inferiority criteria, focusing on the most favourable subgroup and not including all events affected by external beam radiotherapy does not give an objective assessment of this treatment modality.

I was chairman of the Data Monitoring Committee for the TARGIT trial previously but have resigned.

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The investigators from the TARGIT-A trial[1] claim to have established non-inferiority of intraoperative radiotherapy relative to external beam radiotherapy (EBRT) for breast cancer in terms of 5-year local recurrence. Assessment of local recurrence at 5 years by comparison of binomial proportions is appropriate only if 5-year follow-up is available for all patients, whereas only 611 of 3451 patients have reached this point.

This analysis, including the non-inferiority test statistic, is therefore unreliable. The most appropriate measure of non-inferiority given available data uses the survival analysis of local recurrence rates. Based on the

5-year estimates for local recurrence of 3·3% (95% CI 2·1–5·1) after intraoperative radiotherapy and 1·3% (0·7–2·5) after EBRT, the estimated hazard ratio (HR) is 2·56. The standard error of the HR can also be estimated,[2] suggesting an upper limit of 5·47 for its one-sided 95% CI. In view of the 1·3% local recurrence rate after EBRT, the local recurrence rate after intraoperative radiotherapy could therefore be as high as 7·1%, far exceeding the predefined non-inferiority limit.

The investigators present results for three cohorts of patients with varying lengths of median follow-up, claiming to portray the apparent stability of treatment effect estimates over time. The cohorts are nested within each other, thus patients with longest follow-up (who contribute most events) are analysed three times, generating a result of questionable validity.

Median follow-up is only 2·4 years, and a substantial increase in observed duration of follow-up is needed before any analysis of non-inferiority of local recurrence risk can reliably inform clinical practice. The TARGIT-A trial[1] remains inconclusive, and intraoperative radiotherapy using TARGIT remains an experimental treatment.

We declare that we have no competing interests.

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1 Vaidya JS, Wenz F, Bulsara M, et al, on behalf of the TARGIT trialists' group. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet* 2014; **383:** 603–13.

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Javant Vaidya and colleagues[1] report an increased risk of non-breast cancer deaths with external beam radiotherapy (EBRT) compared with intraoperative radiotherapy, highlighting the difference in cardiac events in the two treatment groups. Although the log-rank statistics show a significant difference in non-breast cancer deaths in the EBRT group, these deaths included stroke, bowel ischaemia, and other events unrelated to breast irradiation. Therefore, the number of cardiac events are small, and to suggest that the risk of cardiac death differs between EBRT and intraoperative radiotherapy would be premature.

Additionally, since the median follow-up of most patients was less than 5 years, it would be unexpected that these cardiac deaths were attributable to radiotherapy. If cardiac morbidity from radiotherapy occurs, existing studies suggest it would occur 10–20 years after radiotherapy treatment.[2] During this early follow-up, differences in baseline cardiac risk factors between study groups could account for this difference in cardiac deaths. Furthermore, in a study by Darby and colleagues,[3] the 95% CI for cardiac events for patients who received less than 2 Gy of radiotherapy ranged from –9 to 33 and included zero. This finding emphasises the uncertainty, or at least very low risk, of an absolute increased risk of cardiac disease from radiotherapy treatment.

Therefore, the increased risk of non-breast cancer events, including cardiac toxic effects, reported in this Article[1] should be interpreted with caution in view of the short follow-up period, small number of cardiac events, and scarce information regarding cardiac risk factors at baseline in the study groups.

We declare that we have no competing interests.

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1 Vaidya JS, Wenz F, Bulsara M, et al, on behalf of the TARGIT trialists' group. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet* 2014; **383:** 603–13.

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In reporting the testing of intraoperative radiotherapy against standard whole breast radiotherapy (WBRT), the investigators of the TARGIT trial[1] claim an excess of non-breast cancer deaths are "almost certainly" due to the adverse effects of WBRT.[2]

We argue that causation is very unlikely. The risk of a major cardiac event increases by 7% per Gy of mean heart dose.[3] Based on expected mean heart doses in the WBRT group of 1–5 Gy, radiotherapy cannot explain more than one of the 11 cardiovascular deaths. This is the case even if all eight cardiac deaths occurred in patients with left-sided cancers. Neither is it credible to attribute an excess of eight other, non-breast, cancer deaths in the WBRT group to radiotherapy. The NSABP B-04 trial[4] followed 1665 patients for a median of 21·4 years after randomisation with or without locoregional radiotherapy after mastectomy, confirming a small excess (n=6) of primary lung cancer that took more than 10 years to emerge. The excess was attributed to large anterior axillary radiotherapy beams. No excess of lung cancers was noted in 1261 patients in the B-06 trial[4] at a median of 19 years after randomisation with or without WBRT after lumpectomy. Lung cancer is the most common cause of death from other cancers in this context, but the TARGIT[1] investigators provide no information about tumour site in relation to randomisation.

The difference in non-breast cancer deaths between randomised groups in the TARGIT trial is explained either by imbalances in risk factors or by