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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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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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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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

under-reporting of non-breast cancer deaths in the test group.

We declare that we have no competing interests.

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Jayant Vaidya and colleagues[1] claim that TARGIT treatment results in increased survival since the number of non-breast cancer deaths are higher in the external beam radiotherapy (EBRT) cohort. The investigators cite higher incidences of cardiac toxic effects and deaths from non-breast cancers in the EBRT group as the major cause for the difference in overall survival, even though the TARGIT group currently has a higher, although not significantly breast cancer death rate (2·6% *vs* 1·9%, p=0·56).

The data, with a 29-month median follow-up, show a total of 37 deaths in the TARGIT group, from all causes, and 51 deaths in the EBRT group, from all causes. The authors included deaths from stroke and ischaemic bowel disease as cardiac toxic effects. However, these diseases are caused by narrowing of the arteries (arteriosclerosis) or clot formation, which are unlikely to result from any purported radiation damage to cardiac vessels or valves caused by the EBRT breast treatment. Moreover, deaths from other cancers are not credible to attribute to the breast EBRT treatment. The latency period for induced cancers from breast treatment is well established to be at least 15–20 years. Even after developing a radiation-induced cancer, treatments should prolong survival for several further years, even if cure is not affected. Thus, it is impossible for the 12-year old TARGIT-A study[1] to affect other cancer deaths. If you include only cardiac deaths and breast cancer deaths, the difference between TARGIT and EBRT is only two patients, and is thus hardly significant.

The authors state that although cardiac deaths from radiotherapy typically do not manifest until 7–10 years after treatment (well outside the median follow-up of this study), a recent study[2] that included patients treated as late as 2001 shows that significant cardiac toxic effects are apparent within the first 4 years. Since 35% of the trial patients (1222 patients) had a median follow-up of 5 years, they claim that the study[2] supports the increased toxic effects with EBRT noted in the TARGIT trial.[1] This statement is supported neither by the science nor by any evidence the investigators present.

Darby's study[2] began in 1958 and ended in 2001, so most of their patients were treated with outdated radiotherapy techniques and equipment, and before the era when cardiac toxic effects from breast irradiation were fully appreciated. Furthermore, 76% of the patients in Darby's study[2] had radiation after mastectomy, which is known to result in higher doses to the heart, especially for left breast irradiation. The consensus is that modern radiation techniques should limit the cardiac dose to less than 2 Gy for left-breasted tumours, and to less than 1 Gy for right-breasted tumours. These small doses result in very low cardiac toxic effects. In Darby's study,[2] the median heart dose for a cardiac event was 4·9 Gy, with heart doses as high as 25 Gy. The risk of cardiac toxic effects rose with increasing dose. All modern radiation treatment planning systems have constraints that limit the cardiac dose, so it is unlikely that any centre participating in the study would deliver high cardiac doses, and any EBRT breast radiation study should surely include the requirement to limit the dose to the heart for EBRT radiation. Furthermore, even with data from Darby's study, for doses limited to 3 Gy, the increased risk of death from ischaemic heart disease over 30 years is less than 1%—data that hardly support the TARGIT investigators' assertions. Although the authors state that data for comorbidities were not collected at the time of randomisation, the exclusion criteria listed on ClinicalTrials.gov excludes "Patients with any severe concomitant disease that may limit their life expectancy." It should have been the responsibility of the participating centre to undertake such screening.

To prove their contention of reduced cardiac toxic effects with TARGIT, the authors should have taken four things into account. First, they should have calculated the heart dose for those patients who had a cardiac event. (There are only a total of eight EBRT patients so this would not be too burdensome). Second, they should have identified and presented in the paper whether the left or right breast was irradiated in those patients that died from cardiac toxic effects. Third, the authors should have identified the time after the completion of EBRT that the cardiac events occurred. Finally, they should have indicated whether deaths occurred in those who actually received the prescribed treatment since they used the intention-to-treat population to establish non-breast cancer deaths. 26 patients assigned to EBRT actually received TARGIT; were any of the eight deaths in the EBRT group in these 26 patients?

Clinicians, on the basis of the existing immature TARGIT-A data, would be well advised not to suggest that TARGIT treatment can result in improved non-breast cancer survival.

JKH has received honoraria from IntraOp Medical for proctoring sessions at new institutions using a Mobetron. MJS sometimes speaks at satellite symposia on behalf of Xoft IORT balloon devices. AIR and DEW declare that they have no competing interests.

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Authors' reply

Regarding the follow-up, it is tempting to speculate that in the future a difference in local recurrence will become apparent and that the trend in lower overall mortality will disappear, but neither our data[1] nor previous trial results support this speculation. Statistically, to use median follow-up on its own without taking into account the absolute number of patients is inappropriate. Biologically, the temporal distribution of local recurrence shows that the first 2–3 year period covers the peak hazard of local recurrence after surgery (see figure 2 in Cheng and colleagues' paper[2]). Importantly, results from various clinical trials have shown that the effect of local therapy such as surgery or radiation is mainly seen in the first 5 years, with the peak of the hazard by the first 2–3 years. The lines representing local recurrence between radiotherapy and no radiotherapy in Kaplan-Meier plots remain almost parallel after 5 years in the NSABP B06, NSABP B04, and the Oxford Overview. The conclusion of the 25-year follow-up of the Swedish trial[3] of radiotherapy versus no radiotherapy was explicit: "Radiotherapy protects against recurrences during the first 5 years of follow-up." Whatever difference was going to be noted at 25 years was already seen at 5 years, with most of the difference already seen by 2–3 years (as seen figure 2A in Wickberg and colleagues' paper[3]). The TARGIT-A trial[1] has a substantial number of patients (n=1222) with a median follow-up of 5 years, and 2232 patients had a median follow-up of nearly 4 years.

Regarding non-breast cancer deaths, we found that in the 52 deaths we have recorded so far, the ratio of TARGIT:EBRT was 17:35; such a notable baseline imbalance in cardiac morbidity favouring TARGIT seems unlikely in a randomised trial of this size. We noted a significant difference in non-breast cancer mortality with a high degree of confidence (p=0·0086), which seems to lead to a trend in reduced overall mortality with TARGIT.[1]

Our data are consistent with the recent analysis of Darby and colleagues.[4] They reported that the risk is highest in the first 10 years—during this period, the risk of cardiac mortality is increased by 16·3% (95% CI 3·0–64·3)—ie, a risk ratio of 1·163 (1·03–1·643) per Gy.[4] Presence of ischaemic heart disease (equally balanced between cases and controls) has a multiplicative effect and the risk ratio rises to 13·4% (95% CI 7·65–23·58) per Gy. As the risk increases linearly with dose, for a typical patient with an exposure of 3 Gy, the risk would be three-times higher with a relatively wide upper confidence limit. These estimates are consistent with the TARGIT-A trial results.[1]

One might expect irradiation for left-sided cancers to result in higher cardiac toxic effects. However, the ratio of cardiac risk of left:right sided cancers is small (1·34 as per Darby and colleagues).[4] Furthermore, Darby and colleagues[4] recorded no significant effect of laterality on cardiac toxic effects per Gy. With modern radiotherapy designed to reduce cardiac dose, the absolute difference between sides is likely to be even lower and undetectable with few events. So an absence of a difference between the left and right sides should not be interpreted as an absence of cardiac toxicity.


Jim West/Science Photo Library

In the TARGIT-A trial,[1] the 5-year risk of non-breast cancer mortality was 1·4% (TARGIT) versus 3·5% (EBRT). The absolute difference in non-breast-cancer mortality was 2·1%, about a third of which (0·6%) was from cardiac causes. This small increase in non-breast cancer mortality might have been uncovered early in the TARGIT-A trial because of the otherwise excellent outcome from breast cancer (5-year mortality 2·2%). In older trials, this small but lethal effect might have been masked until the early high breast cancer mortality (eg, 30% at 5 years in the CRC1 trial) diminished in later years.

Furthermore, intraoperative irradiation of a fresh tumour bed has been shown to abrogate the stimulatory and inflammatory effects of surgical wounding.[5] Could this possibly have systemic beneficial effects that contribute to the reduction in non-breast-cancer mortality? This bold conjecture is supported by the observation of a significant reduction in non-breast cancer mortality when patients receive TARGIT plus EBRT compared with EBRT alone.[6] The hypothesis can be fortuitously tested in the TARGIT-B superiority trial in higher risk women (TARGIT boost plus EBRT *vs* EBRT boost plus EBRT).

Although non-inferiority trials are becoming more common, especially when cure rates are high and a reduction in treatment toxicity without a loss of efficacy is desirable, the concept of non-inferiority can be difficult to grasp. The TARGIT-A trial was such a non-inferiority trial, which means that