Almost all the HRs summarized in our review had been adjusted in the original studies for smoking behavior, clinical conditions, and age, and many studies deleted the first few years of follow-up to minimize possible effects of illness-related weight loss. Thus we believe that almost all the studies in our review were adequately adjusted for these possible confounding factors.

In general, there is little evidence that illness-related weight loss is an important source of bias in these types of studies.[2] Seriously ill people who have lost large amounts of weight and are at high risk of dying may not be likely to participate in population studies.

Willett and colleagues cite a pooled study[3] that showed increased mortality in the overweight group. The investigators in that study deleted almost 900 000 individuals, the majority of the original 1.46 million participants, before arriving at their final results, arguing that it was necessary to exclude persons who had ever smoked and those with a history of heart disease or cancer.

As noted in our article, adding the final results of that study to our analyses did not change our summary HR for overweight. Also noted in our article, many studies in our review found that deletions for smoking and preexisting illness had almost no effect on their results.

We previously showed[4] that deletions for smoking and preexisting illness applied to national survey data resulted in findings that became more strongly negative for the overweight category and less positive for the obesity category, the opposite of the effects hypothesized by Willett and colleagues. The validity of results obtained after large-scale deletions to adjust for confounding by smoking or preexisting illness has not been demonstrated.

Our findings suggest that self-reported weight and height contribute more to bias than do smoking and preexisting illness.

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Disclaimer: The findings and conclusions in this report are those of the authors and not necessarily the official views of the Centers for Disease Control and Prevention or the National Cancer Institute.

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Mega-Randomized Clinical Trials for Blockbuster Drugs

To the Editor: Many commonly used medications lack information regarding their adverse effects, effectiveness relative to other treatment options, and mortality benefits. In his Viewpoint, Dr Ioannidis[1] suggested requiring pharmaceutical companies to fund mega-randomized clinical trials (RCTs) for medications with more than $1 billion in annual sales, using as an example a trial with 20 000 patients, 4 years of follow-up, and mortality as an outcome.

This plan draws on several popular themes such as limiting or redistributing excessive pharmaceutical company profits, relying on experimental design for causal inference, and using objective end points. We believe this plan lacks feasibility, and its anticipated value is unlikely to justify its expense.

This proposal's feasibility rests on conducting RCTs at a 90% discount to current costs. This estimate is derived from a data simulation study of expert recommendations for government-conducted RCTs that did not specify drug costs.[2] Following up 20 000 patients for 4 years using $42 million, as proposed, provides just $525 per patient-year.

Unless pharmaceutical companies are required to donate medications, this budget would not cover the medication costs, which would be $84 million assuming a minimal drug cost of $3 per day. Regardless of ultimate RCT costs, pharmaceutical companies would likely pass these costs onto payers, further increasing health care expenditures.

The proposed method may also fail to generate sufficient value for many blockbuster medications. Given their established efficacy, it is unlikely that RCTs of these medications could ethically include placebo controls. This would diminish their ability to detect adverse effects because active comparators will have their own complications.

Furthermore, active comparator RCTs could either report equivalence given intraclass medication similarities or statistically significant but clinically insignificant effects due to excessive statistical power. Mortality would be irrelevant for nearly two-thirds of the suggested medications that address non–mortality-related problems, such as arthritis, erectile dysfunction, and pain.

Recent initiatives are already addressing many of the issues underlying this proposal. In 2007, the ability of the US Food and Drug Administration to require pharmaceutical companies to conduct postapproval monitoring and remove approved drugs from the market was strengthened.[3] In 2008, the Food and Drug Administration launched the Sentinel Initiative to improve drug safety surveillance.[4] In 2009, the US government allocated $1.1 billion for comparative effectiveness research.[5] In 2010, the US government created the Patient-Centered Outcomes Research Institute to study clinically important outcomes.[5]

Additionally, other study designs such as pharmacogenomics may provide better value for many medication-specific issues.

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In Reply: Mega-trials for blockbusters are readily feasible. There would be no cost for the government or health care system. Drug production cost to industry (as opposed to sales cost) is negligible. The proposed mandate could easily stipulate that blockbuster manufacturers donate drugs and placebos for such trials. Total cost to the industry would be approximately 1% of their cumulative sales for the product.

Assume a reward mechanism in which a positive result in a trial that takes T years generates a 1-year patent extension. Expected sales with and without the trial are $M' = TS_0 + (t+1)S_pC + tS_n(1-C)$ and $M = (T+t)S_0$, respectively, in which t is the number of remaining years in the original patent after the trial finishes, C is the probability to get a positive result, and S_p, S_n, S_0 are average annual sales, if the result is positive, negative, or no trial is performed, respectively. The excess expected sales with the trial ($M' - M$) easily exceed the 1% cost, unless both C is low (it is unlikely to get positive results) and S_n is much less than S_0 (negative results are devastating for the drug market).

If the company believes that its drug is modestly likely to be effective, then it would expect to gain from the trial, even if a negative result causes a substantial decline in market share. Thus, companies that minimally trust their products should be favorable to enforcement of a mega-trial mandate. Companies that knowingly sell ineffective and harmful products would of course abhor these mega-trials. The proposed mandate would favor genuine corporate innovators and stall opportunists.

Use or not of placebo-controls should be decided on a case-by-case basis by nonconflicted investigators. I do not agree with the assumption of established efficacy. These mega-trials are important because usually benefit has not really been established, especially for major, hard outcomes.

Sometimes the best design would entail head-to-head comparisons of 2 or more agents, often blockbusters. These drugs may indeed differ in both effectiveness and adverse effects. This is important to document.[1]

Intraclass medication similarities are often quoted, but evidence to support the concept is thin and not tested with large-scale evidence.[2] Same-class drugs are not necessarily interchangeable; the proposed mega-trials can inform which are and which are not.

End points by definition will include mortality and major, important clinical outcomes for which there is no risk of clinical insignificance. Mortality is always an important outcome, even for drugs that treat arthritis, erectile dysfunction, or pain.[3]

Major clinical end points should exist for each drug and its uses. If not, why should we spend billions on a drug that cannot affect any major clinical end points?

The initiatives mentioned by Drs Landy and Hecht are all worthwhile efforts. However, they are of relatively narrow scope compared with a stable multibillion dollar agenda devoted to high-quality mega-trials. Instead of isolated efforts trying to impede industry cheating or sprinkling some money on dubious 1-time initiatives and comparative effectiveness chaos, the proposed agenda can improve patient outcomes, reward innovative companies that produce the best products, and sustain a high-quality RCT agenda.

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RESEARCH LETTER

Firearm Injuries of Children and Adolescents in 2 Colorado Trauma Centers: 2000-2008

To the Editor: Given recent firearm-related fatalities combined with declining gun research funding,[1] it is important to monitor firearm injuries in youths. Injury death rates are available but provide an incomplete picture of these potentially preventable injuries.[2]

Investigations on temporal trends of both fatal and nonfatal firearm injuries remain scarce.[3-5] Our objective was to investigate temporal trends of both fatal and nonfatal firearm injuries in children and adolescents presenting to 2 Colorado urban trauma centers.

Methods. We queried the trauma registries of 2 level 1 trauma centers in Denver and Aurora, Colorado, from 2000 to 2008 for all injuries occurring in children and adoles-