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

David C. Landy, PhD, MPH
Eric M. Hecht, MD, MSPH

Author Affiliations: Department of Epidemiology and Public Health, University of Miami Miller School of Medicine, Miami, Florida (ehecht@med.miami.edu).
Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Hecht reported holding a portfolio of stocks and bonds that includes some investments in health care companies. Dr Landy reported no disclosures.

1. Ioannidis JP. Mega-trials for blockbusters. *JAMA*. 2013;309(3):239-240.
2. Eisenstein EL, Collins R, Cracknell BS, et al. Sensible approaches for reducing clinical trial costs. *Clin Trials*. 2008;5(1):75-84.
3. Schultz WB. Bolstering the FDA's drug-safety authority. *N Engl J Med*. 2007;357(22):2217-2219.
4. Platt R, Wilson M, Chan KA, Benner JS, Marchibroda J, McClellan M. The new Sentinel Network—improving the evidence of medical-product safety. *N Engl J Med*. 2009;361(7):645-647.
5. Golub RM, Fontanarosa PB. Comparative effectiveness research: relative successes. *JAMA*. 2012;307(15):1643-1645.

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.

John P. A. Ioannidis, MD, DSc

Author Affiliation: Stanford Prevention Research Center, Stanford University School of Medicine, Stanford, California (jioannid@stanford.edu).
Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Ioannidis JP, Karassa FB. The need to consider the wider agenda in systematic reviews and meta-analyses: breadth, timing, and depth of the evidence. *BMJ*. 2010;341:c4875.
2. Kennedy HL, Rosenson RS. Physicians' interpretation of "class effects": a need for thoughtful re-evaluation. *J Am Coll Cardiol*. 2002;40(1):19-26.
3. Ioannidis JP, Evans SJ, Gøtzsche PC, et al; CONSORT Group. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med*. 2004;141(10):781-788.

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-

Table 1. Demographic and Injury Characteristics of Children and Adolescents Presenting to 2 Urban Level 1 Trauma Centers, 2000-2008

	No. (%) of Patients[a]		
	Firearm Injuries (n = 129)	Other Injury Mechanisms (n = 6791)	*P* Value
Male sex	103 (79.8)	4359 (64)	<.001
Age, y			
4-6	4 (3.1)	1910 (28.1)	<.001
7-10	6 (4.6)	1919 (28.3)	
11-14	31 (24.0)	1760 (25.9)	
15-17	88 (68)	1202 (17.7)	
Race/ethnicity white non-Latino[b]	23 (23.5)	3534 (53.3)	<.001
Injury Severity Score, median (IQR)[c]	10 (4-19)	9 (4-10)	<.001
Self-inflicted	18 (14.0)	62 (0.9)	<.001
Intensive care unit requirement	65 (50.4)	1311 (19.3)	<.001
Death	17 (13.2)	116 (1.7)	<.001

Abbreviation: IQR, interquartile range.
[a] Unless otherwise indicated.
[b] Patients (or family members) reported their self-identified race/ethnicity to the hospital registration clerk in response to open-ended questions.
[c] Provided as a means to further characterize the populations affected by firearm injuries.

Table 2. Multiple Logistic Regression Analysis of the Independent Effect of Firearm Injuries on Death and Requirement for Intensive Care

	Odds Ratios (95% CI)	
	Bivariable	Multivariable
Death		
Firearm injury[a]	9.71 (5.35-17.61)	9.93 (4.30-22.92)
Age per 1-y increment	1.06 (1.01-1.10)	0.96 (0.91-1.01)
Sex[b]		
Male	0.88 (0.62-1.26)	0.86 (0.55-1.34)
Female	1 [Reference]	1 [Reference]
Race/ethnicity[b]		
Other than white non-Latino	1.23 (0.87-1.76)	1.48 (0.94-2.31)
White non-Latino	1 [Reference]	1 [Reference]
Injury Severity Score per point increment	1.14 (1.12-1.15)	1.14 (1.12-1.16)
Temporal trend per 1-y increment	0.92 (0.86-0.98)	0.89 (0.81-0.97)
Intensive care requirement		
Firearm injury[c]	4.22 (2.82-6.29)	2.35 (1.40-3.93)
Age per 1-y increment	1.12 (1.10-1.13)	1.11 (1.08-1.13)
Sex[d]		
Male	1.18 (1.04-1.34)	1.14 (0.97-1.33)
Female	1 [Reference]	1 [Reference]
Race/ethnicity[d]		
Other than white non-Latino	0.88 (0.78-0.99)	0.98 (0.85-1.14)
White non-Latino	1 [Reference]	1 [Reference]
Injury Severity Score per point increment	1.18 (1.16-1.19)	1.18 (1.16-1.19)
Temporal trend per 1-y increment	0.93 (0.91-0.95)	0.92 (0.89-0.94)

[a] Compared with other injury mechanisms, the multivariate model *C* statistic was 0.93.
[b] The total number of deaths was 133 (82 males, 66 other than white non-Latino, and 7 missing race/ethnicity variable).
[c] Compared with other injury mechanisms, the multivariate model *C* statistic was 0.85.
[d] The total number requiring intensive care was 1376 (929 males, 589 other than white non-Latino, and 56 missing race/ethnicity variable).

cents aged 4 to 17 years (hereafter referred to as youth). Trauma registries are mandated in Colorado and include all level 1 trauma center patients with 1 or more of the following criteria: in-hospital death (deaths at scene are not included), admission to hospital unit, highest level trauma team activation, longer than 12 hours of observation, or Injury Severity Score[6] (ISS; range, 0-75) greater than 9.

Variables reported had complete data, except for race/ethnicity (2.8% missing) and ISS (1% missing). Missing values were not associated with other variables, suggesting random missingness. Injury was classified as self-inflicted if there was unequivocal information that the patient injured himself or herself purposefully or by accident. Intention is not consistently reported and was not assessed.

The Colorado Multiple Institutional Review Board considered the study exempt and did not require informed consent.

We compared firearm injuries with other injuries regarding patient characteristics (age, sex, race/ethnicity [white non-Latino vs others], injury self-infliction, ISS, mortality, and intensive care requirement). We analyzed temporal trends regarding patient and injury characteristics as well as outcomes among fatal and nonfatal firearm injuries.

Wilcoxon or Spearman rank correlation tests were used for continuous variables and χ^2 or Fisher exact tests were used for proportions. The categorical outcomes were adjusted for age, sex, white non-Latino race/ethnicity, ISS, and temporal trends through logistic regression; and goodness of fit was assessed with *C* statistics. Variables are reported by triennials for simplicity but annual data were used for analysis.

Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc). Tests were 2-sided, with significance established at a *P* value of .05.

Results. Overall, 6920 youths were injured. Firearms caused the injury in 129 of these youths (1.9%) (2.1% in 2000-2002; 1.9% in 2003-2005; 1.6% in 2006-2008). Firearm-wounded patients were more likely to be adolescent males, and their injuries were more often self-inflicted compared with youths with other injuries (**Table 1**). Sixty-five patients (50.4%) with firearm injuries required intensive care vs 1311 patients (19.3%) with other trauma; 17 patients (13.2%) with firearm injuries died vs 116 (1.7%) with other trauma.

Firearm injury severity significantly increased over time (ISS of 9 in 2000-2002; 10 in 2003-2005; 15 in 2006-2008; Spearman test, $P = .048$), whereas no significant changes were detected over time by age, sex, race/ethnicity, case fatality, or intensive care requirement. Multivariable analysis for firearm injuries yielded an odds ratio for intensive care of 2.35 (95% CI, 1.40-3.93) and 9.93 (95% CI, 4.30-22.92) for death compared with those with other injuries (**Table 2**).

Discussion. Firearms were an important mechanism of injury in the youth in this study. Compared with other serious injuries, firearm injuries were more severe, more often required intensive care, and claimed more lives, justifying focusing on pediatric firearm injuries as a prevention priority.

Study limitations include trauma registry deficiencies (such as inconsistent capturing of intentionality and exclusion of deaths at scene, which is a significant fraction of firearm-related deaths); and data restricted to 2 trauma centers, which may not generalize to other regions. In addition, data were available only until 2008; however, there has been no substantial decline in published firearm death rates in Colorado since 2008 (2.2 per 100 000 persons aged 4-17 years in 2000, 1.9 in 2009, and 2.8 in 2011).

More recent data from other areas with detail on the circumstances of the firearm injury are needed.

Angela Sauaia, MD, PhD
Joshua I. Miller, MPH
Ernest E. Moore, MD
David Partrick, MD

Author Affiliations: University of Colorado School of Public Health, Denver (Dr Sauaia and Mr Miller) (angela.sauaia@ucdenver.edu); Denver Health Medical Center, Denver, Colorado (Dr Moore); and Children's Hospital Colorado, Denver (Dr Partrick).

Author Contributions: Dr Sauaia had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Sauaia.
Acquisition of data: Sauaia, Miller.
Analysis and interpretation of data: Sauaia, Miller, Moore, Partrick.
Drafting of the manuscript: Sauaia, Moore.
Critical revision of the manuscript for important intellectual content: Sauaia, Miller, Moore, Partrick.
Statistical analysis: Sauaia, Miller.
Administrative, technical, or material support: Sauaia, Partrick.
Study supervision: Sauaia, Moore.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

1. Kellermann AL, Rivara FP. Silencing the science on gun research. *JAMA*. 2013;309(6):549-550.
2. Annest JL, Mercy JA, Gibson DR, Ryan GW. National estimates of nonfatal firearm-related injuries: beyond the tip of the iceberg. *JAMA*. 1995;273(22):1749-1754.
3. Senger C, Keijzer R, Smith G, Muensterer OJ. Pediatric firearm injuries: a 10-year single-center experience of 194 patients. *J Pediatr Surg*. 2011;46(5):927-932.
4. Eber GB, Annest JL, Mercy JA, Ryan GW. Nonfatal and fatal firearm-related injuries among children aged 14 years and younger: United States, 1993-2000. *Pediatrics*. 2004;113(6):1686-1692.
5. Dowd MD, Sege RD; Council on Injury, Violence, and Poison Prevention Executive Committee; American Academy of Pediatrics. Firearm-related injuries affecting the pediatric population. *Pediatrics*. 2012;130(5):e1416-e1423.
6. Baker SP, O'Neill B, Haddon W Jr, Long WB. The Injury Severity Score: a method for describing patients with multiple injuries and evaluating emergency care. *J Trauma*. 1974;14(3):187-196.

CORRECTION

Incorrect Name in Citation: In the Medical News & Perspectives article entitled "Guideline Promotes Early, Aggressive Sepsis Treatment to Boost Survival," published in the March 13, 2013, issue of *JAMA* (2013;309[10]:969-970), a name was presented incorrectly in a citation. The citation should have appeared as (Levy MM et al. *Intensive Care Med*. 2010;36[2]:222-231). The article has been corrected online.