Author Affiliations: Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland (Sharfstein); Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland (Stuart); American Enterprise Institute, Washington, DC (Antos).

Corresponding Author: Joshua M. Sharfstein, MD, Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, 615 N Wolfe St, Room W1033F, Baltimore, MD 21205 (joshua.sharfstein@jhu.edu).

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Sharfstein reported helping to establish Maryland's system of global hospital budgeting as secretary of the state's Department of Health and Mental Hygiene as well as organizing a policy academy for states on global budgets with support from the Robert Wood Johnson Foundation and the Milbank Memorial Fund. Since 2015, he has consulted with large health systems for Sachs Policy Group, including on the topic of global hospital budgeting. Dr Stuart reported receiving personal fees for consulting with RTI on its evaluation methodology. Dr Antos reported being the vice chair for Maryland's Health Services Cost Review Commission.

1. Sharfstein JM, Stuart EA, Antos J. Global budgets in Maryland: assessing results to date. *JAMA*. 2018;319(24):2475-2476. doi:10.1001/jama.2018.5871

2. Haber S, Beil H, Amico P, et al. Evaluation of the Maryland all-payer model: third annual report. https://downloads.cms.gov/files/cmmi/md-all-payer-thirdannrpt.pdf. Accessed April 12, 2018.

Odds Ratios vs Risk Ratios

To the Editor Dr Norton and colleagues[1] described significant limitations of odds ratios (ORs) but they did not report one important advantage of ORs compared with risk ratios (RRs): the magnitude of the association between an exposure and a dichotomous outcome is invariant to whether the outcome is defined as event occurrence (eg, death) or nonoccurrence (eg, no death; ie, survival).[2]

This advantage can be illustrated with a purely hypothetical example of a randomized trial of the effect of a new treatment for profound sudden sensorineural hearing loss of unknown etiology on hearing at 1 month. Suppose that the probability of hearing recovery at 1 month among patients who received the new treatment is 0.30 and the probability among those who received placebo is 0.15. The RR for hearing recovery comparing patients who received the new treatment with those who received placebo would be 2.00 (0.30/0.15) and the OR would be 2.43 (0.30/0.70 ÷ 0.15/0.85). Now suppose that the outcome had been defined as persistent hearing loss at 1 month instead of hearing recovery; in that event, RR′ (the RR for the complement of the outcome) would equal 0.82 and OR′ would be 0.41. The OR′ equals the reciprocal of the OR (that is, 1/OR): 0.41 = (1/2.43). However, the reciprocal of the RR (1/2.00) equals 0.50, not 0.82. Thus, RR′ does not equal (1/RR). If RRs were used to report the trial results, the magnitude of the effect of the new treatment would depend on whether the outcome had been defined as hearing recovery or persistent hearing loss; this would not be true if ORs were used to report the results.

Sahai and Khurshid[3] have shown that this can be demonstrated analytically and applies generally. This characteristic of ORs and RRs is important because it is arbitrary whether an outcome is defined as an event or its complement. For example, in a study of the effect of skin examination behaviors on melanoma, should the outcome be melanomas less than 2 mm in thickness or greater than 2 mm in thickness?[4]

Risk ratios offer multiple advantages over ORs for reporting results with dichotomous outcomes, but they have the disadvantage that their magnitude depends on whether an outcome is defined as an event or its complement. If RRs are used to report results, investigators should explain why the outcome was defined as it was and should consider reporting the RR for the alternative definition.

Jeffrey Sonis, MD, MPH

Author Affiliation: University of North Carolina at Chapel Hill.

Corresponding Author: Jeffrey Sonis, MD, MPH, Department of Social Medicine, CB 7240, School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7240 (jsonis@med.unc.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. Norton EC, Dowd BE, Maciejewski ML. Odds ratios-current best practice and use. *JAMA*. 2018;320(1):84-85. doi:10.1001/jama.2018.6971

2. Cook TD. Advanced statistics: up with odds ratios! a case for odds ratios when outcomes are common. *Acad Emerg Med*. 2002;9(12):1430-1434. doi:10.1197/aemj.9.12.1430

3. Sahai H, Khurshid A. *Statistics in Epidemiology: Methods, Techniques, and Applications*. Boca Raton, FL: CRC Press; 1996:25-26.

4. Dessinioti C, Geller AC, Stergiopoulou A, et al. Association of skin examination behaviors and thinner nodular vs superficial spreading melanoma at diagnosis. *JAMA Dermatol*. 2018;154(5):544-553. doi:10.1001/jamadermatol.2018.0288

In Reply We agree with Dr Sonis that ORs have one distinct advantage over RRs when reporting the association between a binary outcome and a risk factor. If the original OR was computed for the occurrence of an outcome, then the OR for the nonoccurrence of the outcome is the inverse of the original OR. There is no such convenient transformation for RRs. He illustrates this point with a simple example and explains that this is important because for many outcomes it is arbitrary whether to report the outcome as the event occurrence or nonoccurrence.

When deciding how to report the strength of association between a binary outcome and a risk factor, we want to emphasize that this property of ORs needs to be taken in context with other considerations. As discussed in our recent JAMA Guide to Statistics and Methods,[1] ORs have important limitations. These limitations include the lack of an intuitively appealing interpretation and the fact that the magnitude of the OR depends on an arbitrary scaling factor, making direct comparison of ORs across models and studies impossible.[2] Researchers should consider all of these issues when deciding how best to communicate results from a logistic regression model.

In addition, we extend Sonis' point regarding the advantage of ORs to include risk *differences*, measured as the arithmetic difference in 2 risks. Unlike risk *ratios*, the risk *difference* for the nonoccurrence of the outcome attributable to a specific risk factor equals the risk difference for the occurrence of the outcome multiplied by −1. Risk differences have the additional advantage of being less sensitive than ORs to changes in the arbitrary scaling factor.[2] Therefore, risk differences, also referred to as partial effects, are a useful way to report strength of association from a logistic regression.

Edward C. Norton, PhD
Bryan E. Dowd, PhD
Matthew L. Maciejewski, PhD

Author Affiliations: Department of Health Management and Policy, University of Michigan, Ann Arbor (Norton); Division of Health Policy and Management, University of Minnesota School of Public Health, Minneapolis (Dowd); Center for Health Services Research in Primary Care, Durham Veterans Affairs Medical Center, Durham, North Carolina (Maciejewski).

Corresponding Author: Edward C. Norton, PhD, Department of Health Management and Policy, University of Michigan, 1415 Washington Heights, Ann Arbor, MI 48109 (ecnorton@umich.edu).

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Maciejewski reported receiving personal fees from the University of Alabama, Birmingham, for a workshop presentation; being supported by a research career scientist award from the Veterans Affairs Health Services Research and Development and by the Durham Veterans Affairs Health Services Research and Development Center of Innovation; receiving grants from the National Institute on Drug Abuse and the Department of Veterans Affairs; receiving a contract from the National Committee for Quality Assurance to Duke University for research; and that his spouse owns stock in Amgen. No other disclosures were reported.

1. Norton EC, Dowd BE, Maciejewski ML. Odds ratios—current best practice and use. *JAMA*. 2018;320(1):84-85. doi:10.1001/jama.2018.6971

2. Norton EC, Dowd BE. Log odds and the interpretation of logit models. *Health Serv Res*. 2018;53(2):859-878. doi:10.1111/1475-6773.12712

Breakthrough Therapy Designation for New Drugs

To the Editor Mr Puthumana and colleagues[1] cataloged the trial characteristics of drugs granted Breakthrough Therapy designation by the US Food and Drug Administration (FDA), noting that pivotal trials supporting these approvals commonly lacked randomization, double blinding, and control groups; used surrogate markers; and enrolled small numbers of patients. The Breakthrough Therapy designation was developed with the explicit intent of enabling use of efficient trial designs incorporating the aforementioned elements if early evidence warranted it. When a drug shows a substantial improvement over available therapy early in development, optimizing further study to ensure timely patient access prevents patients from having to wait unnecessarily long for new treatment.

The authors noted that more than half of drugs receiving Breakthrough Therapy designation are anticancer agents. The use of surrogate end points in nonrandomized trials is common in oncology for 2 reasons. First, cancer has several established surrogate end points, leading to confidence in newly developed surrogate markers as strong candidates for approval decisions, always conditional on postmarket studies. Moreover, the majority of approval decisions involving surrogate end points resulted in the subsequent confirmation of benefit.[2] Second, recent oncology trials have been characterized by large magnitudes of response, leading to even greater confidence in the ability of surrogate markers to predict clinical benefit.[3] The FDA recently released a list of surrogate end points to increase transparency and outline when surrogate end points may be appropriate as a primary efficacy end point.[4]

The FDA's expedited programs, including Breakthrough Therapy designation, are designed for therapeutics that treat serious and life-threatening conditions and address unmet medical need. Expedited pathways are important to allow earlier access to promising therapies when the regular approval pathway could add years for traditional types of studies to be completed. Medical oncologists must of course use their best judgment to assess promising new therapies, matching the best available information to the individual needs of their patients, many of whom may have exhausted all other options, and the long-term outcomes of drugs granted Breakthrough Therapy designation must be monitored rigorously.

Edward J. Benz Jr, MD

Author Affiliation: Dana-Farber Cancer Institute, Boston, Massachusetts.

Corresponding Author: Edward J. Benz Jr, MD, Dana-Farber Cancer Institute, 450 Brookline Ave, D1644, Boston, MA 02215 (edward_benz@dfci.harvard.edu).

Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and reports serving on the boards of directors of Deciphera Pharmaceuticals, Advantagene LLC, and Konwledge2Practice. Dr Benz's wife is the designee of a trust fund that holds stocks in several biotech/pharmaceutical entities including Johnson & Johnson, Genentech, Pfizer, Merck, and Bristol-Myers Squibb, with total combined value of $150-$200 000.

1. Puthumana J, Wallach JD, Ross JS. Clinical trial evidence supporting FDA approval of drugs granted Breakthrough Therapy designation. *JAMA*. 2018;320(3):301-303. doi:10.1001/jama.2018.7619

2. Blumenthal GM, Kluetz PG, Schneider J, Goldberg KB, McKee AE, Pazdur R. Oncology drug approvals: evaluating endpoints and evidence in an era of breakthrough therapies. *Oncologist*. 2017;22(7):762-767. doi:10.1634/theoncologist.2017-0152

3. Blumenthal GM, Pazdur R. Response rate as an approval end point in oncology: back to the future. *JAMA Oncol*. 2016;2(6):780-781. doi:10.1001/jamaoncol.2015.6352

4. US Food and Drug Administration. Table of surrogate endpoints that were the basis of drug approval or licensure. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm613636.htm. Accessed August 6, 2018.

In Reply We agree with Dr Benz that clinicians must use their best judgment to determine whether to prescribe newly approved drugs granted Breakthrough Therapy designation. Furthermore, we applaud the FDA's efforts, directed by US Congress, to make more efficient determinations of drug safety and efficacy to allow promising new drugs to enter the market as quickly as the agency can responsibly do so. The purpose of our investigation[1] was to provide a systematic evaluation of the program to ensure that clinicians and their patients understand the clinical trial evidence being generated to secure FDA approval for drugs granted Breakthrough Therapy designation, thereby allowing them to make better informed decisions about whether to use these medications.

Although this program has had some demonstrated successes, there are also cautions that deserve consideration. First, there have been many more drugs granted Breakthrough Therapy designation than had been initially expected,[2] which may have implications for establishing qualifying preliminary clinical evidence standards.[3] Second, the reliance on surrogate markers as end points in trials to secure approval adds clinical uncertainty. For instance, trial-level validation studies of surrogate markers in oncology find low- or medium-strength correlations with overall survival.[4] Third, by relying on shorter, smaller trials focused on surrogate markers, postmarketing studies become critical to confirm safety and benefit. However, a recent FDA study of oncology drugs that qualified for Accelerated Approval, a related expedited regulatory pathway, showed that 40% have yet to complete confirmatory trials and 5% have since been withdrawn, the majority