Premature Termination of Clinical Trials

To the Editor: Drs Psaty and Rennie[1] discussed ethical imperatives against premature discontinuation of clinical trials for financial reasons. They argued that this causes harm by breaking the implicit and explicit agreements with research participants, investigators, and the oversight bodies that approved the protocol. Although the authors focused on industry-sponsored trials, their arguments actually apply to all clinical research regardless of sponsorship.

Investigator-initiated studies, for instance, often have less structure and ongoing oversight than do large industry-sponsored clinical trials but the obligations to the participants are no less. Despite this, such projects are often prematurely terminated for a variety of reasons not prespecified in the protocol and contrary to the original study intent and design. In my experience, reasons cited for premature termination of investigator-initiated studies include loss of extramural funding, difficulty in completing the study as originally planned, and the investigator simply thinking that the study has accrued enough data, despite the explicit power calculation in the originally approved protocol. Although some of these may occur under a broad rubric of "feasibility,"[2] their impact is no less than the inappropriate termination of a study for commercial reasons. In fact, there is a parallel between a sponsor's commercial rationale and an investigator whose grant-finding period has expired. Both have failed to meet their obligations to the study's participants.

In many studies, the opportunity to contribute to scientific knowledge is the only benefit that justifies the risks to participants. The National Institutes of Health General Clinical Research Centers now require data and safety monitoring procedures for all protocols, and the ability to complete the study as designed is part of the monitoring process.[3] Additional investigator training may also be required, as the explicit statement of these concepts is relatively new and perhaps unfamiliar to many investigators. When initiating a clinical study, all investigators must develop a greater sense of commitment and responsibility to complete the study as designed and approved.

Eric P. Brass, MD, PhD
Harbor-UCLA Center for Clinical Pharmacology
Torrance, Calif

1. Psaty BM, Rennie D. Stopping medical research to save money: a broken pact with researchers and patients. *JAMA.* 2003;289:2128-2131.
2. Lievre M, Menard J, Bruckert E, et al. Premature discontinuation of clinical trial for reasons not related to efficacy, safety, or feasibility. *BMJ.* 2001;322:603-605.
3. Brass EP. Implementation of a data and safety monitoring program in a general clinical research center. *J Investig Med.* 2001;49:479-485.

This letter was shown to Drs Psaty and Rennie, who declined to reply.—ED.

RESEARCH LETTERS

The World Trade Center Disaster and Intrauterine Growth Restriction

To the Editor: Exposure to air pollution has been associated with intrauterine growth restriction (IUGR)[1,2] and preterm births.[3] Similarly, high levels of polycyclic aromatic hydrocarbon (PAH)-DNA adducts in umbilical cord leukocytes (which are related to prenatal exposure to air pollution) also have been associated with reduced size at birth.[4]

The destruction of the World Trade Center (WTC) in New York City on September 11, 2001, released a toxic atmospheric plume that contained soot, benzene, PAHs, heavy metals, pulverized glass and cement, and alkaline particulates. We evaluated whether exposure to these materials in lower Manhattan was related to impaired fetal growth or other adverse pregnancy outcomes.

Methods. We established a cohort study of 187 women who were pregnant and present in 1 of 5 exposure zones near the WTC at 9 AM on that day or within the succeeding 3 weeks. Most participants were self-referred in response to media publicity of our investigation. Additional recruitment was achieved by sending letters to nearly 3000 obstetricians in the greater New York City area, distributing fliers in lower Manhattan, and advertising in local newspapers. Because there exists no WTC registry of pregnant women, it is not possible to estimate the total number of potential participants.

As a comparison group, we evaluated a consecutive series of all pregnant patients under private care who delivered at Mount Sinai Medical Center on the Upper East Side of Manhattan during the same time period, and who were not known to have been in lower Manhattan on September 11, 2001 (n=2367). Patients under private care constituted an appropriate comparison group, as participants in the WTC cohort

GUIDELINES FOR LETTERS. Letters discussing a recent *JAMA* article will have the best chance of acceptance if they are received within 4 weeks of the article's publication. They should not exceed 400 words of text and 5 references. Letters reporting original research should not exceed 600 words and 6 references. All letters should include a word count. Letters must not duplicate other material published or submitted for publication. Letters will be published at the discretion of the editors and are subject to editing and abridgment. A signed statement for authorship criteria and responsibility, financial disclosure, copyright transfer, and acknowledgment is required for publication. Letters not meeting these specifications are generally not considered. Letters will not be returned unless specifically requested. Also see Instructions for Authors (July 2, 2003). We prefer that letters be submitted electronically to jama-letters@jama-archives.org. Letters may also be sent by surface mail to Letters Editor, *JAMA*, 515 N State St, Chicago, IL 60610, or by fax to (312) 464-5225 (please also send a hard copy via surface mail).

Letters Section Editor: Stephen J. Lurie, MD, PhD, Senior Editor.

were delivered either by private obstetricians (n=174) or midwives (n=8). Five were lost to follow-up as described below.

In both groups we measured demographic characteristics, gestational age, birth weight, and the presence of IUGR (birth weight <10th percentile for gestational age[5]), preterm birth (<37 weeks), and low birth weight (<2500 g). Participants also were asked to complete the PostTraumatic Stress Disorder (PTSD) checklist[6]; we defined probable PTSD as a score greater than 50.

Our study was approved by the institutional review board of Mount Sinai School of Medicine, and all participants provided either written or oral (n=17) informed consent.

Results. In the WTC group, 3 had miscarriages and 2 were lost to follow-up, leaving 182 participants in the WTC cohort. The distribution of the women according to their exposure zone was as follows: south of Murray Street (39.6% of the sample, including 12 pregnant women who were in one of the towers); south of Chambers Street and north of Murray Street (32.4%); south of Canal Street and north of Chambers Street (16.5%); Brooklyn Heights (1.7%); and the easternmost part of New Jersey across the Hudson River from the WTC (0.6%). In addition, there were 17 (9.3% of the sample) pregnant women who were present in the area within the following 3 weeks.

Most women in the WTC cohort were white (72.5%), married or living with a partner (96.2%), aged 30 years or older (84.6%), and college graduates (82.4%). The demographics of the comparison cohort were similar, except for age (mean 34.6 in the WTC cohort vs 32.4 years, $P<.001$).

No significant differences were found between the groups for mean gestational age (39.1 weeks in the WTC cohort vs 39.0 weeks, $P=.55$) or mean birth weight (3203 g vs 3267 g, $P=.14$). There were no significant differences in the frequency of preterm births (9.9% vs 9.2%, $P=.76$) or low birth weight (8.2% vs 6.8%, $P=.47$).

The WTC cohort, however, had a 2-fold increased risk of IUGR compared with the Mount Sinai cohort (presence of IUGR in the WTC cohort, 15 [8.2%]; in the Mount Sinai cohort, 89 [3.8%]; unadjusted relative risk, 2.19; 95% confidence interval [CI], 1.30-3.71). This difference remained significant after controlling for race/ethnicity, sex of infant, maternal age, parity, and cigarette smoking (adjusted odds ratio, 1.90; 95% CI, 1.05-3.46). Other potential confounding factors such as marital status, education, prepregnancy weight, and pregnancy-induced hypertension were not statistically significant in this model.

The frequency of IUGR did not differ between women enrolled during pregnancy and those enrolled after delivery (9.2% vs 7.6%, $P=.69$). The adjusted odds ratios were 2.05 (95% CI, 0.90-4.71) for those recruited before delivery and 1.78 (95% CI, 0.79-3.88) for those recruited after delivery. No significant difference in the frequency of IUGR was observed according to trimester at the time of exposure to the WTC attacks. Finally, no association was found between probable PTSD and the relative risks of preterm birth ($P=.88$), low birth weight ($P=.22$), or IUGR ($P=.94$).

Comment. We found an apparent association between maternal exposure to the WTC disaster and IUGR, suggesting that this event had a detrimental impact on exposed pregnancies. This may have been mediated through exposure to PAH or particulate matter. A number of other birth outcomes, however, did not differ between the cohorts. Possible long-term effects on infant development are unclear and will require continuing follow-up.

Gertrud S. Berkowitz, PhD
Mary S. Wolff, PhD
Teresa M. Janevic, MPH
Department of Community and Preventive Medicine
Ian R. Holzman, MD
Department of Pediatrics
Mount Sinai School of Medicine
New York, NY

Rachel Yehuda, PhD
Department of Psychiatry
Bronx Veterans Affairs Medical Center
Bronx, NY

Philip J. Landrigan, MD
Department of Community and Preventive Medicine
Mount Sinai School of Medicine
New York

Funding/Support: This research was supported by grants from the National Institute of Environmental Health Sciences (NIEHS P42 ES07384-07S1) and The September 11th Fund created by The United Way of New York City and The New York Community Trust.

1. Dejmek J, Selevan SG, Benes I, Solansky I, Sram RJ. Fetal growth and maternal exposure to particulate matter during pregnancy. *Environ Health Perspect*. 1999; 107:475-480.
2. Bobak M, Richards M, Wadsworth M. Air pollution and birth weight in Britain in 1946. *Epidemiology*. 2001;12:358-359.
3. Ritz B, Yu F, Chapa G, Fruin S. Effect of air pollution on preterm birth among children born in Southern California between 1989 and 1993. *Epidemiology*. 2000; 11:502-511.
4. Perera FP, Whyatt RM, Jedrychowski W, et al. Recent developments in molecular epidemiology: a study of the effects of environmental polycyclic aromatic hydrocarbons on birth outcomes in Poland. *Am J Epidemiol*. 1998;147:309-314.
5. Brenner WE, Edelman DA, Hendricks CH. A standard of fetal growth for the United States of America. *Am J Obstet Gynecol*. 1976;126:555-564.
6. Schlenger WE, Caddell JM, Ebert L, et al. Psychological reactions to terrorist attacks: findings from the National Study of American' reactions to September 11. *JAMA*. 2002;288:581-588.

Accuracy of a Local Surveillance System for Early Detection of Emerging Infectious Disease

To the Editor: Syndromic surveillance, based on analysis of clinical or administrative data to detect patterns consistent with emerging diseases, could allow for early recognition of attacks with biological or chemical weapons. Since the 2001 terror attacks, many institutions, encouraged by public health authorities and accreditation agencies, have sought to develop their own surveillance systems. However, the sensitivity and specificity of such single-institution systems have not been validated.

Methods. The emergence of West Nile Virus (WNV) as a widespread cause of neurological disease during the summer

assessed from computerized pharmacy registries. Use of benzodiazepines was observed in more than a quarter of the participants. During follow-up, use of benzodiazepines was not related to all-cause mortality. Similar to prior studies, however, we found an increase of mortality related to fracture in individuals who used benzodiazepines. The small number of deaths from fractures may explain the absence of statistical significance.

The use of benzodiazepines is common in individuals aged 85 years or older, although benzodiazepines are indicated only for a limited number of psychiatric disorders. In practice, clinicians should weigh the risks and benefits of benzodiazepine use. However, we did not find an increased risk of mortality related to benzodiazepine use.

David J. Vinkers, MD, MA
Jacobijn Gussekloo, MD, PhD
Department of General Internal Medicine
Roos C. van der Mast, MD, PhD
Frans G. Zitman, MD, PhD
Department of Psychiatry
Rudi G. J. Westendorp, MD, PhD
Department of General Internal Medicine
Leiden University Medical Center
Leiden, the Netherlands

Acknowledgment: This study was funded by unrestricted grants from the Netherlands Organisation of Scientific Research (ZonMw) and the Ministry of Health, Welfare, and Sports.

1. Taylor S, McCracken CF, Wilson KCM, Copeland JRM. Extent and appropriateness of benzodiazepine use: results from an elderly urban community. *Br J Psychiatry*. 1998;173:433-438.
2. Weintraub M, Handy BM. Benzodiazepines of long and short elimination half-life and the risk of hip fracture. *JAMA*. 1989;262:3303-3307.
3. Hemmelgarn B, Suissa S, Huang A, Boivin JF, Pinard G. Benzodiazepine use and the risk of motor vehicle crash in the elderly. *JAMA*. 1997;278:27-31.
4. Neutel CI, Pattel SB. Risk of suicide attempts after benzodiazepine and/or antidepressant use. *Ann Epidemiol*. 1997;7:568-574.
5. Buysse DJ, Ganguli MG. Can sleep be bad for you? can insomnia be good? *Arch Gen Psychiatry*. 2002;59:137-138.
6. Bootsma-van der Wiel A, van Exel E, de Craen AJM, et al. A high response is not essential to prevent selection bias: results from the Leiden 85-plus Study. *J Clin Epidemiol*. 2002;55:1119-1125.
7. de Craen AJM, Heeren TJ, Gussekloo J. Accuracy of the 15-item Geriatric Depression Scale (GDS-15) in a community sample of the oldest old. *Int J Geriatr Psychiatry*. 2003;18:63-66.
8. Folstein MF, Folstein SE, McHugh PR. "Mini-Mental State": a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975; 12:189-198.
9. Salzman C, ed. *Clinical Geriatric Psychopharmacology*. 3rd ed. Baltimore, Md: Williams & Wilkins; 1998.

CORRECTIONS

Omitted Financial Disclosure: In the Contempo Updates article entitled "Recent Advances and Future Frontiers in Treating Age-Related Cataracts" published in the July 9, 2003, issue of THE JOURNAL (2003;290:248-251), a financial disclosure was not reported. The following should have been included: "Financial Disclosure: Dr Donnenfeld receives research support from Alcon, which manufactures moxifloxacin and ciprofloxacin for ophthalmic use. He also receives research support and is a consultant for Allergan, which manufactures gatifloxacin and ofloxacin for ophthalmic use."

Addendum: In the Research Letter entitled "The World Trade Center Disaster and Intrauterine Growth Restriction" published in the August 6, 2003, issue of THE JOURNAL (2003;290:595-596), the following should have been added to the next to last paragraph in the "Methods" section: "One potential participant was not included in this study because the child was diagnosed with a disorder of presumed genetic origin."

Incorrect Author Initials: In the Original Contribution entitled "Childhood Cardiovascular Risk Factors and Carotid Vascular Changes in Adulthood: The Bogalusa Heart Study" published in the November 5, 2003, issue of THE JOURNAL (2003;290:2271-2276), there were incorrect author initials. On page 2272, the sentence that read "Images were recorded on S-VHS tapes and read by certified readers from the Division of Vascular Ultrasound Research (G.S.B., R.T.) . . . " should have read "Images were recorded on S-VHS tapes and read by certified readers from the Division of Vascular Ultrasound Research (M.G.B., R.T.) . . . ."