In Reply: As a long-time IRB advocate and member, I concur with Dr Feldman’s assertion that “IRBs should be strengthened, knowledgeable, and independent.” I reaffirm, however, that to strengthen IRBs, evidence of their effectiveness is needed, along with criteria to measure how strong and effective they are. Without evidence, it is not known how well IRBs fulfill their mission of protecting research participants and promoting ethical research. Nor is it known the extent to which “... inappropriate or ineffective IRB review [leads] to preventable, unnecessary, or inappropriate research risks...” It is not clear what part the adequacy or failure of IRB review played in the complex set of facts and events that preceded the tragic death of Jesse Gelsinger.

The goal of IRB review is to promote ethical research and prevent inappropriate or unnecessary use or exposure to risk of human research participants. Feldman suggests that IRB review is analogous to preventive medicine, which has the goal of preventing disease or harm from disease. He further states that evidence of preventable illness, just like evidence of preventable research transgressions, makes a case for the need for effective prevention. Important, however, is that clinicians and public health officials do rely on evidence of the risks, benefits, and effectiveness of an intervention in preventing HIV or injuries or other conditions to justify adopting one particular preventive intervention rather than another and to defend the necessary investment of resources. In a similar way, evidence of the burdens, benefits, and effectiveness of IRB review in preventing ethically inappropriate research or research harm is needed to justify expanded application of IRB review to research and related activities, to understand the focus of IRB review and justification for inconsistencies, to avoid unnecessary interference with socially valuable and ethical research, and to defend the considerable investment of time and resources devoted to IRBs.

Feldman comments that my focus appears to be that IRBs create barriers that unnecessarily impede valuable and ethically appropriate clinical research. Many critics believe that IRBs do create unnecessary barriers. I argue that evidence is needed regarding the frequency and type of research that is impeded by IRB requirements, as well as more evidence about research that is promoted by successful IRB review.

Christine Grady, RN, PhD
cgrady@nih.gov
Department of Bioethics
National Institutes of Health Clinical Center
Bethesda, Maryland

Financial Disclosures: None reported.
Disclaimer: The views expressed are those of the author and do not necessarily reflect those of the Clinical Center, the National Institutes of Health, the Public Health Service, or the US Department of Health and Human Services.

RESEARCH LETTER

Estimated Supply of Organ Donors After Circulatory Determination of Death: A Population-Based Cohort Study

To the Editor: Increased use of donors after circulatory determination of death (DCDD) has been advocated as the most viable method for increasing the supply of transplantable organs.1 However, the number of potential DCDD in the United States remains uncertain, with estimates accruing from retrospective single-center experiences in adult4,5 or pediatric3 hospitals. We conducted a prospective, population-based cohort study to estimate the potential increase in the supply of deceased donors that might accrue from optimal use of controlled DCDD, donors in whom life-sustaining therapies are withdrawn and organs are recovered following the loss of spontaneous circulation.

Methods. In-hospital deaths were evaluated throughout the highest-volume US donor service area (DSA) comprising eastern Pennsylvania, southern New Jersey, and Delaware. The DSA’s 134 acute care hospitals were stratified by their numbers of deceased donors in the preceding year (level 1, ≥20; level 2, 10-19; level 3, 5-9; level 4, ≤4), median intensive-care-unit bed number, racial distribution of the local county, and geographic region. A 100% sample (23 hospitals) was selected from strata including hospitals in which 10 or more deceased donors were available in the prior year, along with a 25% stratified random sample (27 additional hospitals) from the 111 remaining lower-volume hospitals.

All patients dying within 90 minutes following withdrawal of life-sustaining therapy from July 1, 2008, through June 30, 2009, who were 70 years or younger and had no exclusionary diagnoses (eg, metastatic cancer, ...
human immunodeficiency virus, West Nile virus) were identified. Clinical and demographic data were abstracted. Using prespecified criteria developed by surgeons experienced in using DCDD organs (Table 1), each organ was categorized as optimal, suboptimal, or ineligible for transplantation, and each donor was similarly categorized based on the highest ranking assigned to one of his or her organs.

Data were extrapolated to the entire DSA by multiplying the total number of donors identified at each hospital level by the inverse of the proportions of hospitals within each level included in the study. Confidence intervals were generated from Poisson distributions using Stata 10.1 (StataCorp, College Station, Texas). The study was exempt from institutional review board review.

Results. Among 39,993 in-hospital deaths in the DSA during the study period, 21,802 (54.5%) occurred at the 50 study hospitals. Of these, 130 (0.60%) were potentially eligible DCDD, including 52 (0.24%) optimal DCDD (eligible to donate ≥1 optimal organ) and 78 (0.38%) suboptimal DCDD (eligible to donate no optimal organs but ≥1 suboptimal organ). Of the potential DCDD, clinicians identified and referred 108 (49 optimal and 59 suboptimal; 83.1%) to the organ procurement organization (OPO) before withdrawal of life-sustaining therapy. The remaining 22 (3 optimal and 19 suboptimal) were identified through medical record review.

During the same period, 683 deaths (1.71% of all deaths) were prospectively or retrospectively identified as medically eligible donors after neurological determination of death. Table 2 provides the expected proportionate

### Table 1. Criteria for Defining Potential DCDD

<table>
<thead>
<tr>
<th></th>
<th>Kidney</th>
<th>Liver</th>
<th>Pancreas</th>
<th>Lung</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Optimal (all are required)</strong></td>
<td>Time to death ≤60 min Age ≤50 y</td>
<td>Time to death ≤30 min Age ≤45 y (age ≤40 y if stroke is COD) Tbil &lt;2 mg/dL ALT and AST ≤100 U/L</td>
<td>Time to death ≤30 min Age ≤35 y</td>
<td>Time to death ≤60 min Age ≤55 y P-F ratio ≥300 Clear chest radiograph</td>
</tr>
<tr>
<td><strong>Suboptimal (any one is sufficient)</strong></td>
<td>Time to death 60-90 min Age 51-70 y BMI &gt;35 History of diabetes ≥2 of following: stroke as COD, Cr &gt;1.5 mg/dL, history of hypertension</td>
<td>Time to death 31-60 min Age 46-60 y BMI &gt;30 Na &gt;155 mmol/L, or stroke as COD but not both Tbil &gt;2.1 mg/dL ALT or AST &gt;101 U/L</td>
<td>Time to death 31-45 min Age 36-45 y</td>
<td>Time to death 60-90 min Age 56-60 y Smoking history &gt;20 pack-years P-F ratio 200-299 Chest radiograph showing infiltrate, atelectasis, or edema History of cardiac disease</td>
</tr>
<tr>
<td><strong>Ineligible (any one is sufficient)</strong></td>
<td>History of chronic kidney disease Use of renal replacement therapy while in ICU Cr &gt;2.5 mg/dL plus UOP &lt;0.75 mL/kg/h Age &gt;60 y BMI &gt;40 Time to death &gt;60 min Both Na &gt;155 mmol/L and stroke as COD History of acute or chronic liver disease Tbil &gt;3 mg/dL ALT or AST &gt;300 U/L</td>
<td>History of acute or chronic liver disease</td>
<td>Time to death &gt;45 min Age &gt;45 y BMI &gt;30 History of diabetes, pancreatic disease, or alcohol abuse</td>
<td>Age &gt;60 y History of chronic lung disease P-F ratio &lt;200 &gt;1 Abnormality on chest radiograph</td>
</tr>
</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); COD, cause of death; Cr, serum creatinine; DCDD, donor after circulatory determination of death; ICU, intensive care unit; Na, sodium; P-F ratio, ratio of PaO2 to fraction of inspired oxygen (FIO2); Tbili, total bilirubin; UOP, urine output during final 6 hours of life.

### Table 2. Annual Potential for Total and Optimal Controlled Donors After Circulatory Determination of Death in a Donor Service Area

<table>
<thead>
<tr>
<th></th>
<th>Optimal DCDD</th>
<th>All Potential DCDD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DNDD Identified in 50-Hospital Sample</td>
<td>Predicted DCDD in DSA</td>
</tr>
<tr>
<td><strong>Eligible donors</strong></td>
<td>683 (632-736)</td>
<td>52 (59-68)</td>
</tr>
<tr>
<td><strong>Donors likely to have consented</strong></td>
<td>371 (334-411)</td>
<td>35 (24-49)</td>
</tr>
<tr>
<td><strong>Donors likely to have had ≥1 organ transplanted</strong></td>
<td>324 (290-361)</td>
<td>33 (23-46)</td>
</tr>
</tbody>
</table>

Abbreviations: DCDD, donors after circulatory determination of death; DNDD, donors after neurological determination of death; DSA, donor service area.

Data are presented as number or percentage and 95% confidence interval.

*Data presented as number or percentage and 95% confidence interval.

*Abbreviations: DCDD, donors after circulatory determination of death; DNDD, donors after neurological determination of death; DSA, donor service area.

See “Methods” section.

Based on the observations that consent was obtained from 33 of 49 potential optimal donors who were referred to the organ procurement organization (67.3%) and from 24 of 59 potential suboptimal donors who were referred (40.6%).

Based on the observations that among donors for whom consent was obtained, 31 of 33 potential optimal donors (93.9%) and 19 of 24 potential suboptimal donors (79.2%) had viable organs transplanted.
increases in this supply of deceased donors that could be obtained if all potential controlled DCDD were identified and referred to OPOs before withdrawal of life-sustaining therapy.

Comment. These findings suggest that optimal identification and management of potential controlled DCDD could increase the supply of deceased donor organs, but by no more than 25%. If only optimal DCDD were used, as has been advocated, DCDD would be unlikely to expand the deceased donor supply by more than 10%.

These findings likely represent best-case estimates given intentionally optimistic study assumptions. We based donor classifications on the standards of highly experienced DCDD transplant surgeons, allowed up to 90 minutes following withdrawal of life-sustaining therapy (rather than a more traditional 60 minutes) to accommodate the thresholds of some surgeons for procuring kidneys or lungs, and assumed that barriers to simultaneously procuring both abdominal and thoracic organs from DCDD can be overcome.

Scott D. Halpern, MD, PhD, MBE
shalpern@exchange.upenn.edu
Division of Pulmonary and Critical Care Medicine
University of Pennsylvania School of Medicine
Philadelphia
Barbara Barnes
Richard D. Hasz, MFS
Gift of Life Donor Program
Philadelphia
Peter L. Abt, MD
Division of Transplant Surgery
University of Pennsylvania School of Medicine

Author Contributions: Dr Halpern 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: Halpern, Abt.
Acquisition of data: Barnes, Hasz.
Analysis and interpretation of data: Halpern.
Drafting of the manuscript: Halpern, Barnes, Abt.

Critical revision of the manuscript for important intellectual content: Halpern, Hasz, Abt.

Statistical analysis: Halpern.

Obtained funding: Halpern.

Administrative, technical, or material support: Halpern, Barnes, Hasz.
Study supervision: Halpern, Hasz, Abt.

Financial Disclosures: None reported.

Funding/Support: Dr Halpern was supported by a Greenwall Foundation Faculty Scholar Award in Bioethics and by K08HS018406 from the Agency for Healthcare Research and Quality.

Role of the Sponsors: The funding sources had no role in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

Additional Contributions: David A. Axelrod, MD, MBA (Dartmouth-Hitchcock Medical Center); Anthony M. D’Alessandro, MD (University of Wisconsin); Robert B. Love, MD (Loyola University); Joshua D. Mezrich, MD (University of Wisconsin); Kim M. Olthoff, MD (Hospital of the University of Pennsylvania); and Abraham Shaked, MD (Hospital of the University of Pennsylvania), provided expertise regarding the designation of potential donors as optimal, suboptimal, or ineligible. None received compensation for their roles in this study.