Cooperation in Clinical Trials

William C Wood, MD, FACS, FRCS Eng (Hon), FRCP&S Glasg

Thank you, Dr Urist, for your kind introduction. Fellows of the Southern, guests, my wonderful wife, Judy, one of my daughters, Kris, who is able to be present, and her husband, Michael, my son, Bill, and future presidents of the Southern . . . I begin by stating my humble but profound thanks for the honor of serving as the president of this Society . . . It is a great honor to follow in the footsteps of people whom I admire and many of whom I consider dear friends. Last year, President LD Britt magnificently made the point that the Southern Surgical Association is regional in name only. I must confess that the president also presides in name only. The major responsibility for leading and directing our association falls on the council and our secretary, not on your president. The late President Brad Aust pointed out in his address that the presidential duties include such arduous matters as consulting on the dinner menu and the wine and participating in the selection of the scientific program abstracts. His major obligation is the preparation of the Presidential Address. President James O’Neill kindly sent me a selection of prior presidential addresses early in the year to assist me, and in the case of his own, perhaps intimidate me. You may have noticed that I included in my salutation, “and Future presidents of the Southern . . .” That is because virtually every presidential address begins with the note that the prior presidential addresses have just been read. I became sadly aware that future presidents read these addresses that they have previously heard delivered because, like commencement speeches, the carefully wrought, elegantly phrased statements leave no imprint on the memory. One’s presidential address, like one’s funeral, requires that you be present with assembled family and friends. The great difference is that only for the presidential address do you need a manuscript, but only what you say at your own funeral will be long remembered.

Choosing a topic proves difficult not because there are so few options, but so many. There is a great temptation to pass on some great life lesson such as:

- Cooking lesson #1: Don’t fry bacon in the nude.
- My wife says, “Some days I wake up grumpy, other days I let him sleep.”
- Or, looking to the future, I want to die in my sleep like my grandfather, not yelling and screaming like the passengers in his car.

My topic selection was aided by the report of the Institute of Medicine issued earlier this year. It is entitled “A National Cancer Clinical Trials System for the 21st Century,” the subtitle is “Reinvigorating the NCI Cooperative Group Program.”

The major goals from the Institute of Medicine report were to: (1) Improve speed and efficacy of trials from design to completion; (2) Incorporate innovative science and trial design; (3) Improve the selection, support, and completion of cancer clinical trials; and (4) Incentivize participation of patients and physicians. These were extremely similar to the recommendations of the Armitage report, which had been commissioned by the Board of Scientific Advisors of the National Cancer Institute (NCI) more than a decade earlier and very like those of the commission led by Dr Karen Antman some years before that. Over all of this time, the numbers of patients accrued to studies had increased, the number of trials had increased and the support provided by the NCI had proportionally decreased considerably, making the bulk of support arise from individual institutions and cancer centers, with time provided as a donation of all of the investigators. This is in contrast to the work we are doing in the basic sciences, which is funded by the NCI, with a significant indirect funding to the institutions as well. Indirects for the cooperative group trials are limited to 20% versus the usual 50% to 100%.

I would like to consider with you the contributions of cooperative clinical trials illustrated by those on breast cancer. I chose breast cancer because the success over the years of the clinical cooperative groups has been quite remarkable (Fig. 1). I will point out an inflection in about 1985 and suggest some of the reasons for that, and from that time, mortality from breast cancer has fallen from about 55/100,000 down to about 32/100,000 now, and it shows every evidence of continuing to decline.

We all recognize the importance of the prospective, hypothesis-driven, randomized clinical trial, the first published example of which was a trial in 1948, 2 years before the curves begin in Figure 1. The randomized clinical trial’s importance arises from the very nature of the scientific
method. This is taught to school children as: (1) Posit a hypothesis; (2) Design an experiment to test that hypothesis; (3) If the experiment confirms the hypothesis, build on it; (4) If the experiment is inconclusive, redesign the experiment; and (5) If the experiment refutes the hypothesis, posit a different hypothesis. It’s only after a few years of working in science that one recognizes that one may never see that fifth point carried out in practice. If the experiment refutes the hypothesis, we redesign the experiment, use a different breed of mouse, a different cell line, or a different agent until we are able to confirm our hypothesis.

Walter Cannon, in his 1945 book, *The Way of an Investigator*, pointed out that we always worry about the validity of our own experimental research. When we see an article on the same subject, we read it with interest to see if we had made some fundamental error in our experimental design or our interpretation, which our friend, in his or her study, has corrected, showing our experiment to be faulty. Yet we totally trust the data coming from the laboratory of a friend. On the other hand, we would die for our own hypotheses because we “know” they are correct. Yet we smile at the hypotheses of our friends that we realize are fundamentally flawed. Our understanding of surgery, of medicine, of science, and of life influences the way we see and interpret everything. We call this bias, except when speaking of our own perceptions.

Clinical trials are hugely expensive experiments, not merely because of the millions of dollars involved, but much more because people willingly agree to participate with their lives and health in these studies. Great progress is made, not when we compare one product with another (toothpaste A with toothpaste B), but when we are able to address a concept. In the United States, NIH funding allows us to address conceptual, hypothesis-driven issues. Industry funded trials must be different. They are to allow registration of a new agent with the FDA or to demonstrate the commercial viability of the product they are testing.

I will use as an example the concept or hypothesis that higher dose chemotherapy is better than lower dose. In the early 1980s, this was greatly debated, with some believing that tumors were either sensitive or not and one need not give doses of chemotherapy that produce toxicity to achieve a benefit. Others believed that the greater the dose, the greater the toxicity the patient could tolerate, and the greater the likelihood of benefit. In advanced disease, you could observe the effect on the tumor, but with adjuvant trials there was nothing to monitor, so many investigators found it difficult to tolerate any toxicity in treating these healthy patients who may already be cured. Analysis of trial data showed that many patients received half the dose that was called for and often for an abbreviated period of time. Dr Gianni Bonadonna analyzed two of his trials of CMF (cyclophosphamide, methotrexate and fluorouracil) as an adjuvant for breast cancer and demonstrated that the women who received the full dose for the full duration clearly did better than those who received reduced doses or reduced durations. Others answered that the ability to tolerate higher doses of chemotherapy or not differentiates between people likely to live longer or not. It was simply a biochemical fitness assay and not necessarily the cause of longer survival. This was addressed in an intergroup study led by Cancer and Leukemia Group B, Trial 8541, looking at dose and dose intensity of adjuvant chemotherapy. A standard dose of 6 cycles of cyclophosphamide, Adriamycin (Pharmacia), and fluorouracil (CAF) was packed into 4 cycles—a 50% increased dose at each treatment. On the other hand, the third arm reduced that to a lower dose, such as we saw frequently given, and for 4 cycles instead of 6 (Table 1).
Table 1. Cancer and Leukemia Group B, Trial 8541

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<th>CAF</th>
<th>Cyclophosphamide</th>
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CAF, cyclophosphamide, Adriamycin (Pharmacia), and fluorouracil; TD, test dose.

The first thing we learned was that before the study had nearly completed accrual, many if not most medical oncologists in the United States had switched to our highest dose intensity, once we showed that it could be safely given to women in the outpatient setting. So great was the bias that “more is better” in this country that this had become the new standard, replacing the published and usual dose intensity. We did show that the lowest dose intensity was inferior, both in pre- and postmenopausal women in terms of disease-free survival. When this was published in the New England Journal of Medicine, the study that accompanied it was our analysis of the same group of patients with HER2 testing to detect that group of women who overexpressed HER2, which others had previously shown to be associated with greater risk than the group that did not overexpress HER2. In this group there was a dramatic difference in disease-free survival, depending on which dose intensity of chemotherapy was given. This benefit was limited to the 30% who overexpressed HER2 (Fig. 2); the other 70% of patients did just as well with the lowest dose for a shorter period of time as they did with the higher dose (Fig. 3). This was not a test of inferiority and did not have sufficient numbers to say that they were all equal for that group of patients, but it strongly suggested that there are subgroups of disease that require certain treatments or certain dose intensities and that many people do not require this intensity. This is a call for predictive assays.

The next example is tamoxifen as adjuvant therapy. It was shown to be clearly beneficial in recurrent breast cancer. It was no better than giving estrogen, but it had fewer side effects. Consequently, it was felt that it would be useful as an adjuvant for breast cancer patients. There were over 40 separate, prospective, randomized trials to test this hypothesis, with varying outcomes. This became a topic for debate at oncology meetings, with groups usually citing their own trial as the one in which they could place their faith. Richard Peto, now Sir Richard Peto (Fig. 4), head of the Clinical Trials Service Unit at Oxford University, was...
interested in gathering all of the investigators of these randomized trials and asking that we share our primary data with him so that he could perform a meta-analysis correcting all these data to common forms and analyzing them, not as a sum of numbers, but looking for the difference between expected and observed in each trial and that trial's statistical variance, and then doing a meta-analysis. This dealt with the reality of the play of chance in complex biological systems that can cause great difference in outcomes between different populations tested. It was based on the power of large numbers to an epidemiologist, the value of meta-analysis to a biostatistician, and was also based on the absolute necessity of collaboration and cooperation. Among those of us who agreed to participate, a major task became convincing every randomized trial investigator to join and share their data as well, so that there would not be a triumphalist bias toward those studies that had shown benefit and been easily accepted for publication and neglecting those that appeared to be negative trials that were much harder to publish. When we met, there were 42 different trials available that had addressed this question. Only 6 of them were positive trials with statistically significant evidence of benefit from giving adjuvant tamoxifen. Eight of the trials suggested that it was detrimental to give tamoxifen as an adjuvant rather than reserving it as something that could be used at the time of failure, although these were not significantly detrimental. The other trials suggested benefit, but they did not achieve statistical significance and had to be considered negative trials. When we were able to get all of these primary data and they were updated with a great deal of effort from the Oxford Clinical Trial Service Unit (CTSU), we had over 30,000 patients, with 8,000 deaths having already occurred. The mortality reduction was real by giving adjuvant tamoxifen at the time of surgery and the significance was $p < 0.00001$ (Table 2). The lesson from this was that major clinical questions require sufficient numbers to overcome the play of chance common in complex systems.

The benefit from targeting the group at significant risk of failure avoids the accrual of thousands of women who are not going to fail on either arm. Such numbers of low risk patients do not add anything but expense to a trial, so prognostic tests are important. It is not the number of people accrued to a clinical trial that provides accuracy, but the number of target events that occur. Also, great benefit comes from targeting the group capable of response, using predictive tests. It was nearly 10 years before we could convince the Oxford group to analyze and report separately the estrogen receptor positive and estrogen receptor (ER) negative patients. This was taken by our colleagues in the UK as a peculiar American fascination with subgroup analysis opening the dangerous possibility of undertreating ER negative patients, whom some believed would receive benefit. It turns out that roughly one-third of breast cancers are ER negative and these women receive no benefit from tamoxifen at all. Those who are ER positive have their annual risk of failure cut in half, not only for the 5 years that they take tamoxifen, but each year for 15 years. This despite a compliance in these various studies estimated between 60% and 85%. You can imagine how great the benefit would be with complete compliance with therapy.

In addition to minimizing the risk of beta errors suggesting no benefit where one actually exits, large meta-analyses also allow seeing trends and effects that would not be apparent, even in fairly large trials. At a gathering of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) in Oxford a few weeks ago, we saw that the tamoxifen’s prevention of recurrence, which is so dramatic in hormone receptor positive women, is limited to ER positive women. We had used the term hormone receptor positive to include ER negative but progesterone receptor (PR) positive women. In fact, there is no evidence of any benefit for that subgroup of women. Many investigators doubt that there is such a subgroup of women, that these women are either ER positive/PR negative or ER negative/PR negative and that finding a discordance suggests a laboratory error.

We are living through a tipping point in medical science. With the Human Genome Project we have begun to re-examine diseases beyond their phenotypes and syndromes to their genomic and proteomic expressions. An example is the 3 grades of breast carcinoma. Chris Sotiriou and colleagues' elegant genomic analysis reveals that grade I disease is discrete and can be identified by its genomic markers, having a different biology and markers than grade III disease. There is no grade II breast cancer; it is a mix of
about half genomic grade I and half genomic grade III. Hematoxylin and eosin stained slides cannot differentiate these as grades I or III. So genomic analysis is redefining the diseases that we treat. Many of you are familiar with the differing categories of breast cancer that are still in evolution.9,10 In a retrospective analysis of prospectively collected tumor from the National Surgical Adjuvant Breast Project (NSABP), genomic analysis revealed that three-quarters of the women with ER positive, node negative breast cancer received no benefit from chemotherapy beyond the benefit they got from tamoxifen alone. On the other hand, the quarter with a high risk genomic profile received far more benefit from this rather antique chemotherapy than had been imagined. We have just completed the accrual of 10,000 women to the TAILORx trial (Trial Assigning Individualized Options for Treatment [Rx]) to define the genomic break point of benefit from modern, more effective chemotherapy. This required the cooperation of all of the North American Breast Cancer Groups.

As The Southern Surgical Association, we have been particularly interested in the evolution of surgery for breast cancer. Two young investigators, Drs Edward M Copeland, III, and Kirby Bland, professors at the University of Florida in Gainesville, wrote a delightful review of papers in the first 100 years of the Southern entitled “Development of Current Concepts for the Treatment of Breast Diseases as Documented by the Transactions of the Southern Surgical Associations”11 (Fig. 5). It is a superbly written piece and covers the fine papers advocating more extensive surgery or less extensive surgery, more extensive or less extensive axillary treatment or no axillary treatment, and a variety of other observations about the extent of surgery for breast cancer. These institutional trials led to wonderful debates at the Southern and other surgical meetings. Dr. Bernard Fisher, with the NSABP in his Trial BO-6,12 a cooperative group trial demonstrating no difference in outcomes between modified radical mastectomy and breast-conserving surgery, convinced many, but not most, physicians and surgeons in the United States. Dr Umberto Veronesi, with the Milan Cancer Institute,13 convinced many in Europe, but not all. The power of meta-analysis was again demonstrated by the Early Breast Cancer Trialists’ Collaborative Group, showing that each of the 6 randomized perspective trials that had been done and presented showed no difference at all individually, and meta-analysis of them all
showed no advantage at all either. This led to the Consensus Development Conference of the National Institutes of Health in 1990 and was associated with a significant movement to breast conservation over the next few years in the United States.

Just this year the NCI cooperative group trials have answered a variety of surgical questions that have been debated for more than a decade. The American College of Surgeons Oncology Group’s trial Z0010 addressed the issue of immunohistochemical detection of sentinel lymph node and bone marrow sentinel lymph node micrometastases. A large trial from the Netherlands demonstrated a significant prognostic value to the detection of immunohistochemistry (IHC) positive cells in sentinel lymph nodes. They did this by selecting from their huge data bank only patients who had received no adjuvant therapy of any kind. Z10 addressed the question not of prognostic value in untreated patients, but of clinical utility. This required using multivariate analysis in adequate numbers and adequate follow-up, all of which were present in this study. It demonstrated clearly that in patients treated in standard fashion, with more than 85% receiving adjuvant systemic therapy, with sentinel lymph nodes negative by routine hematoxylin and eosin staining, there was no added clinical benefit of detecting IHC positive cells. This study also addressed the question of IHC positive cells in bone marrow. It demonstrated that bone marrow positive patients had a 90% survival at 5 years versus a 95% survival for those who were negative, with a p value of 0.015, confirming both analytical and clinical validity. But the important issue is, can this assay select sentinel lymph node negative patients who might not otherwise receive chemotherapy? Addressing this question in more than 5,000 patients, analyzed in multivariate fashion, bone marrow IHC did not have statistical significance, p = 0.16, and it consequently lacks clinical utility.

Sentinel lymph node biopsy, introduced by my mentor from my NCI fellowship, Dr Donald Morton, in melanoma and applied to breast by his colleague, Dr Armando Giuliano (Fig. 6), was hoped to sort the minority of patients with lymph node metastases who would benefit from axillary lymph node dissection for complete staging and axillary control from the majority, who were node negative and would not benefit. The NSABP many years ago did Trial B-04, which we would now consider underpowered, and drew the conclusion that there was no benefit to axillary dissection. Ironically, they now chose to address the question, if the sentinel lymph nodes are negative, is there a benefit to doing an axillary dissection anyway? In a very large, carefully done, well controlled trial, they demonstrated that there is no benefit to dissecting sentinel lymph node negative patients. Dr Giuliano led a trial by the American College of Surgeons Oncology Group asking whether, if the sentinel lymph node is positive, you need to dissect the axilla in patients.
who will be receiving breast conservation and radiation of the majority of the axilla as part of whole breast radiation. The trial was stopped short of its accrual goal because it was taking so long to accrue. With a median follow-up of more than 6 years, the incidence of local recurrence was 3.6% in those patients who had a completion axillary dissection and only half that, 1.8%, in patients who did not. The total regional failure or recurrence was 4.1% with axillary dissection and 2.8% without it. While the numbers do not allow a definitive statement of noninferiority, the failure to detect any evidence of benefit to offset the greater morbidity of axillary dissection, answers the question of clinical utility for most of us.

The final intergroup trial was limited to women of 70 years or more with ER positive tumors, excised with clear margins, with no clinically positive lymph nodes (or no positive if sampled), who were willing to take tamoxifen for 5 years and to be followed clinically for possible recurrence. With these caveats, there is a difference in breast recurrence of only 6%. Thus, 319 women would need to receive breast irradiation to avoid 20 in-breast recurrences. There was no significant difference in death from any cause, in death from breast cancer, in distant metastases, or, surprisingly many, in ultimate breast preservation.

We live in an era of team science. We need to rapidly accrue large numbers to answer major questions. It is important to remind our younger members that you never lose by being inclusive but can often lose by being exclusive. It is very important if we are going to make rapid progress in curing cancer or in treating other serious diseases that we avoid duplication of trials. A few years ago we experienced such duplication with the Herceptin (Genentech) adjuvant trials, one by the NSABP, one by the Breast Cancer Intergroup, and one by the Breast International Group in Europe. These were published simultaneously and managed to coordinate, and integrate after the fact, the data from the NSABP and the Breast Intergroup. Dr. Martine Piccart, head of the Breast International Group, and I met to see if we could better integrate the leadership of our groups and consequently coordinate international clinical trials in breast cancer. This was enthusiastically supported by Dr. Jo Anne Zujewski of the NCI. It would necessitate not only a great deal of Internet traffic, but at least annual meetings to make this happen. Our goal was to achieve common endpoints rather than the varying definitions that the different groups were following, to have common data elements collected so that we could relate different arms of trials with common arms to one another, and to use common techniques for biospecimen collection so that we would be able to relate our correlative science studies, which are becoming increasingly important in defining breast cancer. It was hoped that we could develop working groups on difficult issues that require the entire world community to have sufficient numbers to answer them, such as male breast cancer, definitions for neoadjuvant therapy endpoints, survivor issues, and “triple negative” breast cancer. This lies outside the purview of the pharmaceutical firms that fund the Breast International Group or the NCI funding for the North American Breast Cancer Groups. Dr Larry Norton, of Memorial Sloan-Kettering, who is the chief scientific officer of the Breast Cancer Research Foundation, appreciated at once the potential of such a leveraged investment. He encouraged submission of a grant to the Breast Cancer Research Foundation, where he and Ms Evelyn Lauder lead a very large fund raising effort. It has enabled us to accomplish all the goals addressed in the last 5 years and is continuing under the leadership of Dr Nancy Davidson, Director of the University of Pittsburgh Cancer Center, and Baroness Martine Piccart of the Breast International Group.

The Institute of Medicine report also called for innovative trial designs. A wonderful example of such a design is I-SPY2, familiar to many of you, with co-principal investigators Dr Laura Esserman of the University of California, San Francisco, and Dr Donald Berry, Bayesin biostatistician and epidemiologist from MD Anderson. It incorporates an adaptive design where randomization is not 1 for 1, but is driven by real-time evidence of effect in this neoadjuvant trial and shifting away from treatments that appear to be less beneficial for certain subgroups and toward the opposite. It is just opening now across the nation and is eagerly anticipated as a way of introducing new agents and rapidly evaluating them. It also is evaluating an analysis of residual disease, measured both by breast MRI and by final pathology evaluation.

The Institute of Medicine report’s fourth thrust is to incentivize clinicians and patients to participate in clinical trials. The total NCI budget for 2009 was just under $5 billion. Almost $406 million of this goes to support the cancer centers and their research programs nationally. Over $780 million of it supports the intramural NCI, leaving less than $235 million to support all of the clinical cooperative group research done in the nation. For an example, in 2009, the Eastern Cooperative Oncology Group, probably the largest of the cooperative groups, had less than $16 million to perform all of its trials in all cancer types. Funding of the cooperative groups does
not enjoy the advocacy from clinical investigators that the basic scientists provide for basic research. Congress responds to the concerns expressed to them. If we value clinical research, we need to strongly support it, as do our colleagues who are devoted to supporting dollars for basic research. If this is a contest, they have won it handily. The next years are going to be very exciting ones in all of surgery. We increasingly are redefining disease on a genomic basis. The accrual of 10,000 patients to a trial of genomic evaluation, using the Oncoimmune Assay, completed in October exemplifies the need for and feasibility of cooperation to accrue the large numbers required to identify the subgroups of disease benefitting from a therapy.

My personal counsel for efficacy in clinical trials research:

- Choose clinically important questions.
- Conceptually simple experimental design.
- Large numbers to avoid play-of-chance and beta error.
- Limit accrual to people at significant risk (prognostic tests).
- Limit accrual to people in subgroups of benefit (predictive tests).
- Provide incentives for all.
- Get out of the way.

The next frontier will involve a rapid progress through redefinitions of cancer and other diseases and new experimental designs. We are seeing rapid movement in oncology from histologic typing to genomic typing to proteomic typing, and then we will move from genomics and proteomics to systems biology approaches that will probably yield far more effective therapies than those currently under study.

The goal in oncology is the interdiction of clinically occult cancer to minimize the effects of both the neoplasm and the treatment. This will require new resources, but especially a new level of cooperation and collaboration nationally and internationally. Who better to lead it than the friends and fellows of the Southern Surgical Association?

I close with my profound thanks to my precious family, my Lord for his abundant kindness to me, my magnificent colleagues in the Department of Surgery at Emory, their superb mentors, colleagues, and good friends who fill this room.

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Lessons Learned from a Single Center’s Experience with 134 Donation after Cardiac Death Donor Kidney Transplants

Alan C Farney, MD, PhD, Michael H Hines, MD, FACS, Samer al-Geizawi, MD, Jeffrey Rogers, MD, FACS, Robert J Stratta, MD, FACS

BACKGROUND: Reports of kidney transplantation from donation after cardiac death (DCD) donors describe high rates of delayed graft function (DGF).

STUDY DESIGN: From April 1, 2003 to October 17, 2010, we performed 134 kidney transplants from DCD donors including 120 (90%) from standard-criteria donors (SCDs) and 14 (10%) from expanded-criteria donors (ECDs). Nineteen kidneys were recovered from donors managed with extracorporeal interval support for organ retrieval (EISOR) after cardiac arrest to minimize ischemic injury.

RESULTS: Comparison of donor and recipient characteristics found no differences for cases managed with or without EISOR. Overall actuarial patient survival rates were 93%, 91%, and 89% at 1, 3, and 5 years, respectively, with a mean follow-up of 31 months. Overall actuarial kidney graft survival rates were 89%, 76%, and 76% at 1, 3, and 5 years, respectively. Actuarial graft survival rates of DCD ECD kidneys were 58% and 48% at 1 and 3 years, compared with 90% and 79% at 1 and 3 years for non-ECD grafts (p = 0.013). DGF occurred in 73 patients (54%) overall and was reduced from 55% to 21% (p = 0.016) with the use of EISOR in locally recovered kidneys. The mean resistance value on machine perfusion and the mean estimated glomerular filtration rate 1 month after transplantation were both improved (p < 0.05) in kidneys from donors managed with EISOR. Mean initial hospital stay was reduced from 8.0 to 5.0 days in patients receiving kidneys recovered with EISOR (p = 0.04).

CONCLUSIONS: EISOR is associated with a lower rate of DGF, lower graft resistance on machine perfusion, and shorter initial hospitalization. Kidneys from DCD SCDs have excellent medium-term outcomes and represent an important means of expanding the donor pool. Kidneys from DCD ECDs have inferior outcomes. (J Am Coll Surg 2011;212:440-453. © 2011 by the American College of Surgeons)

For patients with end-stage renal disease, kidney transplantation offers both additional years and improved quality of life.1-3 At the end of 2010, the United Network for Organ Sharing (UNOS) national waiting list for solid organ transplantation is approaching 120,000 registrations, including nearly 95,000 patients awaiting kidney or simultaneous kidney-pancreas transplantation.4 Median waiting times for kidney transplantation range from 600 to 2,000 days depending on geographic region and blood type.4 To address the growing disparity between organ supply and demand, recent efforts to increase the donor organ pool have incorporated the use of donors considered to be less than optimal, including older donors, donation after cardiac death (DCD) donors, and donors with comorbidities that are potentially detrimental to long-term graft survival.1-3,5,8 Fueled by National Organ Donation Breakthrough Collaborative initiatives and an Institute of Medicine report, expansion in DCD organ donation has occurred primarily in the controlled DCD donor (Maastricht category III and IV) setting.7,8

Compared with organs from donors who meet brain death criteria (donation after brain death), DCD or nonheart-beating donor organs are inevitably subjected to variable periods of warm ischemia after withdrawal of life support.