Advances in immunosuppression, along with consensus-driven clinical care by multidisciplinary teams, have enhanced the early survival of patients undergoing heart transplantation (HT). Despite improvements in early morbidity and mortality, late outcomes at 5 and 10 years still remain poor for those HT recipients who have successfully navigated the initial challenges of rejection and infection (1). Although further optimization of therapeutic strategies to prevent early rejection remains an important goal, there is now a critical and growing need to develop a strong evidence-base that can identify strategies to tailor immunosuppressive therapy, limit renal damage, manage coronary allograft vasculopathy, characterize newer forms of rejection, and ultimately, improve late outcomes in these patients. Recognizing this, the National Heart, Lung, and Blood Institute (NHLBI) sponsored a workshop entitled, “Cardiac Transplantation Research in the Next Decade: A Goal to Evidence Based Outcomes” in August 2010. The goals of the workshop were to identify the highest-priority research gaps in the field of HT and to elicit recommendations for future research strategies.

There currently exists limited randomized clinical trial evidence for standard management practices in HT beyond the first year. Scientific evolution in the field of HT remains dominated by registry-driven multicenter studies, single center observational studies, and pharmaceutical industry-sponsored randomized controlled trials (RCTs) focusing on early outcomes (2–4). Although registry-based publications have yielded groundbreaking information that has guided therapeutic directions, each of the landmark databases in cardiac transplantation have significant limitations, including incomplete data, lack of adjudication, or a lack of comprehensive patient enrollment beyond early time points (1,5–7). The field has also been hampered by a lack of research infrastructure, such as research networks or consortia, to facilitate multicenter investigations.
Despite the low numbers of heart transplants that occur in the United States yearly, approximately 2,200, there are several compelling reasons for the NHLBI to provide a national platform for conducting clinical studies in this field (1). First, compared with other medical and device-based therapies, HT is associated with the most enduring gain in quality of life and survival, with a median survival of 10 years (1). There are twice as many patients listed for HT annually as there are donor hearts available, and despite parallel advances in ventricular assist device therapy, approximately 8% of these patients die awaiting a suitable allograft (7). In addition, the candidate pool is evolving and becoming even more complex with the advent of mechanical circulatory support, the growing number of adults with congenital heart disease who have failing hearts with few reparative options, and the rising population of end-stage heart failure (HF) patients who require multi-organ transplantation (8). Additionally, more than 20% of patients who undergo HT do not survive beyond 3 years. Of those that do survive beyond 3 years, a population of approximately 20,000 to 40,000 patients, the majority are afflicted with the long-term complications associated with immunosuppression, such as metabolic syndrome, chronic kidney disease, cardiac allograft vasculopathy, and malignancy (1). This underscores a need to address both morbidity as well as survival issues in this large prevalent population of patients. Because HT patients are meticulously followed, this population is uniquely poised for enrollment in clinical trials.

The charge to the workshop participants was to focus on those specific areas in HT that required unique NHLBI leadership and to develop recommendations that were visionary, practical, and that would have both short- and long-term impact on the field. The working group (WG) identified 4 broad challenges in HT and strongly encouraged incorporating basic science investigations into all clinical studies. Because the HT population is relatively small, the WG recommended concerted efforts to develop a research infrastructure that facilitates enrollment of de-novo and existing HT recipients into clinical trials to optimize research within the field. Although the National Institute of Allergy and Infectious Diseases has successfully supported HT research as part of 2 consortiums addressing transplantation research in all organs, entitled Clinical Trials in Organ Transplantation and Clinical Trials in Organ Transplantation in Children, there is a need for a complementary but more specialized HT network that could potentially facilitate multiple trials and studies focused on cardiac issues. The 4 broad key challenges and corresponding recommendations identified by the WG are listed in Table 1 and discussed in the following text.

**Challenge #1: Optimize and Individualize Immunosuppression**

**Therapies and Improve Late Allograft Outcomes Mediated by Immune and Non-Immune Factors**

Greater efforts should be focused on developing optimal practices that individualize immunosuppression therapies and manage the long-term effects of these drugs. In addition, research strategies need to address the non-immune complications of immunosuppression, such as diabetes mellitus, hypertension, obesity, the metabolic syndrome, chronic kidney disease, and malignancies.

**Recommendations.** A key research priority should be to develop clinical trials that evaluate how calcineurin inhibitor (CNI) sparing and elimination approaches, coupled with intensive strategies aimed at modifying non-immune risk markers, affect late outcomes. Pharmacogenomic, systems biology, and other basic science investigations into the responses of the individual to immunosuppression should be incorporated into these trials. Fundamental research aimed at elucidating potential biomarkers that might help diagnose and predict acute and chronic rejection could play a critical role in advancing the clinical care of HT patients.

**Discussion.** Late outcomes in the HT population remain poor with a median cardiac allograft survival of 11 years, a statistic that has not improved in over a decade (1). The major causes of late morbidity and mortality are chronic kidney disease, cardiac allograft vasculopathy (CAV), and malignancy (1).

Immediately after transplant, immunosuppression therapy typically consists of a CNI, cyclosporine or tacrolimus, a purine synthesis inhibitor such as mycophenolate mofetil, and corticosteroids (5). The dosing of these drugs, which have a narrow therapeutic index, is typically based on the weight and renal function of a patient (5). Although other factors might play a significant role in the dosing and selection of immunosuppressive drugs, individual characteristics such as age, sex, race, and antibody status are not currently taken into account routinely (5). In addition, during follow-up, there are no algorithms that incorporate individual characteristics into a standard assessment for tailoring immunosuppression. Because the primary focus in these patients is preventing rejection, many recipients receive higher doses of these drugs than might be needed. This higher exposure might contribute to complications of obesity, chronic kidney disease, hypertension, and hyperglycemia. Strategies aimed at individualizing immunosuppression should minimize adverse events, preserve immunologic outcomes, and have a beneficial impact on late outcomes.

To address this broad challenge, the WG recommended pursuing trials that addressed 2 specific issues—evaluating an early CNI sparing approach and investigating the impact of intensive risk marker modification on early and late
outcomes, including major adverse cardiac allograft events, solid cancers, renal failure, and graft and patient survival. Because of the synergy of immune and non-immune variables on morbidity and mortality, the WG urged the consideration of factorial trial designs that would be able to address both questions concurrently. The WG also stressed the importance of planning trials with adequate sample sizes to ensure the study power necessary to evaluate hard endpoints such as survival. The WG suggested pursuing adaptive clinical trial strategies and other study design approaches to maximize the yield of information. This would be best accomplished by the development of a cooperative trial network or consortia to optimize participation.

Potential ideas for trials that were discussed included testing a CNI-free regimen or early weaning of this class of drugs. The WG believed that trials evaluating lipid lowering and blood pressure and glucose control would be relatively straightforward to implement yet would have the potential for significant impact on long-term cardiovascular outcomes. Emerging data suggest that targeting the renin-angiotensin-aldosterone system after HT has a beneficial impact on non-immune risk factors and particularly on the development of CAV (9–11). Possible investigations might include identifying optimal therapeutic targets for lipid lowering and blood pressure control, which have not yet been defined in the HT population. Basic science studies should be included in these clinical trials to understand mechanisms of action and develop novel therapeutic targets. The WG urged pursuing basic studies to investigate how to prevent early injury and inflammation, induce tolerance, target the innate immune system, and refine anti-proliferative therapy.

The WG advised that histological and serological biospecimen collection and banking should be an integral part of all NHLBI sponsored studies, either with well-formulated prospective hypotheses or to facilitate retrospective ancillary studies. To address the critical question about how to personalize and provide a metric for optimal immunosuppression, the WG urged using high throughput pharmacogenomic technologies and a systems biology approach of assessing individual responses to these therapies. Again, the WG urged that focused basic science studies be included in these approaches to better elucidate mechanisms of cardiac allograft injury, repair, and fibrosis at a vascular and allograft level.

**Challenge #2: Expansion and Optimization of the Donor and Recipient Candidate Population**

The demand for donor hearts far outstrips the supply, and novel approaches are needed to expand and optimize both the donor and recipient population (7). This issue could be addressed by comparing long-term mechanical support with HT in specific populations and investigating methods to standardize how donors are reviewed and used. Currently, the definition for a “marginal donor” varies considerably among institutions, and there is conspicuous reluctance to use hearts from donors older than 60 years of age. Research that informs the questions underlying this reluctance might provide convincing data that ultimately leads to the expansion of the donor pool.

**Recommendations.** The WG recommended a randomized trial comparing the transplantation of hearts from older donors with the implantation of left ventricular assist devices (LVADs) as destination therapy in recipients >70 years of age, in whom there is clinical equipoise about the optimal therapy. Basic science investigations addressing fundamental questions about senescence in aged donor organs and recipient immune systems should be conducted in parallel with studies in these populations. Further research to enhance donor use by exploring novel strategies to limit development of ischemia-reperfusion injury should also be pursued.

**Discussion.** The WG acknowledged the heterogeneity in the evaluation of prospective donors and in the definition of the “marginal” donor organ across centers and organ procurement organizations. Because the criteria used by the United Network of Organ Sharing criteria and third-party payers to assess the quality of transplant programs are based largely on 1- and 3-year outcomes, most institutions exercise caution in using donor hearts that might be less than perfect, citing an inability to assume such risk without supporting evidence (12). However, single center studies from large-volume centers that use donors rejected by many centers as marginal have demonstrated satisfactory early and intermediate outcomes (13–15). Examples of such cases include marginal donors transplanted into older recipients or into recipients with ongoing comorbidities such as diabetes mellitus and peripheral vascular disease, which would have otherwise precluded the use of donors from the standard list.

The WG suggested that one strategy to expand the donor pool might be to investigate the use of marginal donors in elderly recipients, a population in whom there is clinical equipoise about the optimal therapy for end-stage HF. Currently, the major factors that are taken into account when matching donors to recipients are blood type, height, and weight (5), but there are no standard guidelines for the weighting of other relevant factors in decision-making, resulting in considerable inconsistencies in the types of donor hearts that are accepted at different institutions. For example, in some institutions, donor hearts with slightly depressed ejection fractions or mild left ventricular hypertrophy might be deemed adequate, whereas in other programs such donor hearts would be discarded. Without clear evidence about the outcomes associated with different donor characteristics informing the donor selection process, it is probable that many potentially useful organs are currently being discarded (16,17). Because an important rate limiting factor in HT is the number of available donor organs, studies that define how to optimize donor use and develop biomarkers to define organ utility might increase the donor...
pool by providing evidence that would support the use of those organs deemed to be less than perfect.

The WG also encouraged research to optimize donor organ use by limiting the ischemia-reperfusion injury that commonly occurs in donor hearts. Strategies that prevent prolonged ischemia time or render hearts resistant to injury, such as hypothermia or the use of agents that mimic preconditioning or target the mitochondrial permeability transition pore or other mediators of this innate protective mechanism, might achieve tissue preservation and maintain viability for transplantation (18,19).

**Challenge #3: Characterize and Address the Comorbidities Encountered in the Pre-Transplant Population**

The lack of standard clinical approaches creates considerable variability in treatment assignments in different institutions and even among cardiologists within the same institution. The WG participants agreed that continuing advances in mechanical circulatory support have had a profound impact on the field of HT and have significantly changed the candidate population (20–22). The patients currently evaluated with advanced HF differ markedly from those seen 10 years ago, but medical therapy and triage decisions are based only on data derived from earlier populations that did not receive the benefits of early institution of current HF therapies to delay disease progression. The WG participants recognized that there is a critical need for evidence-based management strategies for many aspects of the clinical management of the pre-transplant population. However, they felt it was imperative to address three major clinical issues—the cardio-renal syndrome, the progression of secondary pulmonary hypertension, and right ventricular failure—and called for RCTs evaluating these specific problems. The WG recommended developing robust clinical tools to characterize the pre-transplant population and optimize the timing and selection of candidates for HT directly, for mechanical circulatory support as a bridge to transplantation, and for mechanical circulatory support as an alternative to transplantation for patients with substantial comorbidity burden or other risks for good post-transplant survival.

**Recommendations.** Clinical trials evaluating management strategies for renal insufficiency, secondary pulmonary hypertension, and right ventricular failure in the pre-transplant population should be emphasized. Researchers should develop a database that would capture the evolving phenotypes of the advanced HF population, define the most current pre-transplant risk factors, and allow investigators to identify the most optimal candidates from the limited donor pool.

**Discussion.** The WG recognized that there were myriad approaches to handling pulmonary hypertension and the cardio-renal syndrome in the pre-transplant population (23–28). To address the optimal management strategy for pulmonary hypertension, the WG urged pursuing a trial evaluating the impact of a strategy of early LVAD implantation versus chronic inotropic therapy as a primary bridge to transplantation in patients with end stage HF and elevated pulmonary artery pressures due to chronic left HF and pulmonary venous hypertension.

Similarly, the WG group urged pursuing a randomized trial to evaluate best practices for the cardio-renal syndrome. The cardio-renal syndrome, a poorly understood process, is associated with adverse post-transplantation outcomes and is often exacerbated by the inherent nephrotoxicity of immunosuppressive drugs (1,5). The WG recommended a randomized trial to assess outcomes of combined heart-kidney transplantation versus other renal-sparing strategies in candidates with diminished renal function.

The WG strongly advised that basic science investigations and bio-specimen repositories should be embedded within any randomized trial evaluating these 2 major clinical challenges. In particular, they felt that it was important to emphasize the role of renal histology in understanding the cardio-renal syndrome.

The WG also recognized that increasing the number of HT that occurs annually depends not only on an enhanced understanding of the donors but also on a greater knowledge of the current phenotypes of recipients. At present, there are no ongoing, complete, adjudicated databases that define the pre-transplant population adequately to provide a clear window into the most current clinical issues that afflict this population. The WG recommended developing a funded database with a bio-specimen bank that would better define pre-transplant risk factors—including clinical features, biomarkers, and genes—that would allow clinicians and investigators to track the changes in this population as it evolves and progresses with the advent of novel therapies. The WG suggested creating a national database, with all transplant centers enrolling patients listed each year for HT.

**Challenge #4: Characterize and Understand Antibody Mediated Rejection**

In the past, the major immunological challenge to survival in the early post-transplant period was cellular rejection. However, there is growing recognition that antibody mediated rejection (AMR) might account for significant early and late morbidity and mortality (29,30). Much progress needs to be made to better understand AMR at a histological, serological, and clinical level. In addition, there are few evidence-based strategies for the prevention and amelioration of AMR.

Even though the WG identified AMR as a major research gap, they also emphasized that AMR and cellular rejection are different aspects of the process of rejection. The group concurred that the overall course of rejection is mediated by both cellular and soluble antibody factors, acting in concert over time, with changing roles in the lifetime of a graft, and with varying contributions in different patients.
**Recommendation.** The WG urged the development of a large-scale robust analytical database with a bio-bank to characterize the pathophysiology and natural history of AMR. In addition, therapeutic interventions for prevention and treatment of manifest AMR require study in RCTs.

**Discussion.** Antibody mediated rejection is now increasingly recognized in the HT population, typically occurs early, in the setting of sensitization to the allograft, and is associated with hemodynamic compromise and late development of CAV. Recent evidence suggests that even asymptomatic AMR is associated with a higher risk of CAV and worse cardiovascular mortality (31,32). The augmented immunosuppression required during treatment of AMR is more aggressive and complex than that for cellular rejection and is associated with a higher incidence of infection and predisposition to malignancy.

To gain a better understanding of this unique form of rejection, the WG recommended creating an observational longitudinal database, which would include a bio-specimen bank and phenotype information. A bio-repository that would collect, catalog, and store tissue, serum, and DNA would be a critically important feature. Such a database would help investigators characterize the pathophysiology of AMR, create standardized definitions of this entity, identify individual risk factors, identify biomarkers, and ascertain the impact of this form of rejection on long-term outcomes (33). Importantly, researchers should develop a standardized approach to the histological definition of AMR and optimal surveillance strategies for early detection of this entity. In addition, randomized trials need to be conducted to evaluate the efficacy of various strategies that attempt to prevent this form of rejection (34).

**Clinical Trials in HT**

Conducting clinical trials in HT presents unique challenges, of which perhaps the most daunting is addressing the small population of HT patients, the majority of whom are taking multiple concurrent medications and have many comorbidities. Thus, patient recruitment is a critical rate limiting step. Some potential solutions might be to form national and international networks of committed investigators and proactively identify strategies for recruitment and retention as well as strategies for coordination of sites across North America and globally. In addition, a crucial step would be to conduct pilot studies to evaluate the best methods for screening and recruitment.

To ensure the quality of future clinical trials in HT, investigators should also proactively address essential issues of trial conduct such as blinding, crossovers, drop-outs, surrogate endpoints, and adaptive monitoring designs. Importantly, investigators must address how these elements must be uniquely modified or interpreted in the context of the HT population. In addition, investigators should design rigorous endpoint definitions, efficient data collection forms, and streamlined and comprehensible informed consent forms that reflect the challenges distinct to HT. To ensure the highest quality clinical trials, investigators should also plan to invest time and funding into organizing standardized oversight committees, such as Data Safety and Monitoring Boards, Protocol Review Committees, Executive Committees, Clinical Events Committees, and Publications Committees. Finally, a critical step to ensure that the highest quality fundamental and translational science investigations take place within future HT clinical trials will be to proactively plan basic and mechanistic studies at the beginning of the trials and ensure that efforts are made to secure funding.

**Table 1 High-Priority Knowledge Gaps in Heart Transplantation and Potential Research Approaches**

<table>
<thead>
<tr>
<th>Gap in Knowledge</th>
<th>Clinical Approach</th>
<th>Fundamental Science Approach</th>
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<tr>
<td>- Individualizing Immunosuppression</td>
<td>• RCT of Calcineurin Inhibitor Sparing or Elimination Approaches in Immunosuppression</td>
<td>• Pharmacogenomics, Systems Biology, and Other Basic Science Approaches to Elucidate:</td>
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<td></td>
<td>• RCT of Intensive Risk Marker Modification</td>
<td>o How to Individualize Immunosuppression</td>
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<td>o Mechanisms of Cardiac Allograft Injury, Repair and Fibrosis</td>
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<td>• Understand the Role of Biomarkers in Predicting and Diagnosing Rejection</td>
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<td>- Improving Late Outcomes</td>
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<tr>
<td>- Expand and Optimize Donor and Recipient Candidate Populations</td>
<td>• RCT of Destination LVAD vs. Older Donors in Elderly Recipients</td>
<td>• Fundamental Investigations of Senescence and the Immune System</td>
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<tr>
<td></td>
<td>• Novel Strategies to Limit Ischemia-Reperfusion Injury</td>
<td>• Develop Strategies to Prevent the Deleterious Effects of Ischemia and Reperfusion Injury</td>
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<tr>
<td>- Characterizing and Addressing Comorbidities Encountered in the Pre-Transplant Population</td>
<td>• RCT of LVAD vs. Inotropes for Treatment of Pulmonary Hypertension Associated with End-Stage HF</td>
<td>• Understanding the Role of Renal Pathology and the Cardio-Renal Syndrome</td>
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<td></td>
<td>• RCT of Combined Heart-Kidney Transplant vs. Other Renal Sparing Strategies</td>
<td>• Focusing on Renal Pathology as a Predictor of Outcomes</td>
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<tr>
<td></td>
<td>• Database to Capture Evolving Phenotypes of Advanced HF Population</td>
<td></td>
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<tr>
<td>- Characterize and Understand AMR</td>
<td>• Large-Scale Longitudinal Database with a Biobank Repository</td>
<td>• Identify Biomarkers to Diagnose and Predict Onset of AMR</td>
</tr>
<tr>
<td></td>
<td>• Therapeutic RCT Based on Emerging Fundamental Science</td>
<td>• Define Pathological Correlates of Therapeutic Targets and Outcomes</td>
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AMR = antibody mediated rejection; HF = heart failure; LVAD = left ventricular assist device; RCT = randomized controlled trial.
for dedicated core laboratories that focus on specific areas, such as biological markers, DNA banks, and imaging.

Pursuing significant scientific questions is essential to moving the field of HT forward. However, the WG noted, an equally important factor to advancing knowledge in this field will be how well those questions are answered through rigorous trial design and conduct.

The Role of the NHLBI in Facilitating HT Research

There is a critical need for studies in HT that evaluate prevention and treatment strategies rather than evaluating the efficacy of single drugs or interventions. In addition, research in HT needs to expand from focusing on early outcomes to also addressing late morbidity and mortality. National Heart, Lung, and Blood Institute and other federal agency support of such efforts might be particularly important, because industry sources are unlikely to independently fund research in these areas. The WG believed the best way to address many of the current scientific gaps was through RCTs, with complementary basic science and mechanistic investigations embedded in the studies. In addition, the WG encouraged the NHLBI scientific staff to educate the HT research community about the opportunities and mechanisms for research support that are already available through the Institute.

Investigators in HT have a critical responsibility to apply for grants and generate interest and enthusiasm in the academic medical community for research and enrolling patients. When developing new research proposals, the NHLBI encourages investigators to capitalize on novel scientific opportunities, public-private partnerships, and attainable short-term goals. There are a number of mechanisms at the NHLBI available to HT investigators interested in pursuing research support (Table 2). The standard R01 mechanism can provide up to $499,999 per year in direct costs for smaller projects in basic or clinical science. In addition, mechanisms exist for investigator-initiated projects exceeding $500,000/year. These mechanisms include grants for large, multi-center clinical trials (R01 or U01) and program project grants (P01). A complete description of how to apply for these large grants can be found at the NHLBI website (35).

Individuals interested in submitting an application covered by these guidelines are strongly encouraged to begin informal discussions with NHLBI scientific staff as early as possible in the process of planning their research proposal. Proposals with budgets exceeding $1.51 million/year require investigators to make a presentation to NHLBI staff and submit a letter requesting permission to submit a large application.

Funding opportunities for clinical trial pilot studies (R34) are also available at the NHLBI. The purpose of the R34 planning grants is to provide funding for preliminary studies to obtain data critical to the successful design of a full-scale clinical trial. An R34 can provide key early data that might help applicants develop a robust and competitive investigator-initiated clinical trial (36).

Summary

It is imperative that researchers address the critical scientific gaps in HT by developing high-quality RCTs and concurrent basic science studies that investigate the fundamental processes of immunology, pharmacogenomics, inflammation, and repair. Moving the field of HT forward will depend on an improved understanding of individualized immunosuppression, a greater knowledge of how to select and manage donors and recipients, and a strong focus on improving long-term outcomes by increasing the 10-year cardiac allograft disease-free survival. Through dedicated efforts by the research community and the support of the NHLBI, the goal to develop evidence-based outcomes in HT over the next decade can evolve from concept to reality.

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