Symposium: Legislative Review

Protecting the delivery of heart failure: Regenerative Medicine/Stem Cell Therapeutics: Potential protections afforded by the Department of Health and Human Services and Health Resources Service Administration’s Bureau of Special Programs

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Abstract Advances in stem cell science and potential clinical applications have brought clinical medicine closer to the actualization of Regenerative Medicine—an extension of transplantation of organs and cells and implantation of bioprosthetics and biodevices. The goal of such therapeutics will be intervention prior to onset of severe individual disability, enhance organ function and enhance patient performance status without incurring the economic impacts of standard organ transplantation. Regenerative Medicine is already demonstrating proof of principle or efficacy in restoration of myocardial contractility, joint mobility and function, immune competence, pulmonary function, immunologic self-tolerance, motor function and normal hemoglobin production with the next targets—diabetes mellitus (type I and type II), neurologic injury, hepatic dysfunction preparing to enter trials.

Expenditures on health care needs of an aging U.S. citizenry approximate 20-25% ($3 trillion) of U.S. GDP currently and may grow to 40% of U.S. GDP by 2025. As the potential of Regenerative Medicine is clinically realized, the societal impact and economic benefits will be disproportionately magnified in the economies of industrialized nations. The experience of the Department of Health and Human Services (HHS), United Network for Organ Sharing (UNOS), the National Bone Marrow Donor Registry (NBMDR), and the National Vaccine Injury Compensation Programs (NVICP) can help ensure that as Regenerative Medicine strives to achieve clinical benefits while avoiding decimation of therapeutic options by product liability and medical malpractice concerns—concerns that crippled the U.S. vaccine manufacturing industry until the creation of the NVICP.

The first 50 years of organ/cell/tissue transplantation demonstrates that clinical reality of allogeneic and autologous transplantation can antedate complete understanding of the basic science underlying successful transplantation. Product liability and medical malpractice liability have not impeded the development and growth of organ/cell/tissue transplantation despite increased risks of infection, malignancy and cardiovascular disease in transplant recipients. Currently, human transplantation is only performed using FDA/CBER-approved, non-embryonic stem cells from peripheral blood, bone marrow or umbilical cord blood. Federal legislation passed in 2005 (HR2520 and S1317: The Bone Marrow and Cord Blood Cell Transplantation Program) authorizes the Secretary of Health and Human Services acting through the Director of HRSA to ensure uniform stem cell units distribution and outcomes monitoring via the federally-designated C.W. Bill Young Cell Transplant Program.

Historically in the U.S., human biological therapies (vaccines, organ transplant and stem cell transplant) have required federal protections to ensure continued distribution, fair access and avoidance of inhibitory product liability via protections afforded under the “stewardship” of the Secretary of Health and Human Services. The National Childhood Vaccine Injury Act of 1986 established the NVICP to equitably and expeditiously compensate individuals, or families of individuals, who have been declared injured by vaccines, thereby stabilizing a once imperiled vaccine supply by substan-

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tially reducing the threat of liability for vaccine companies, physicians, and other health care professionals who administer vaccines. Vaccines were the first biologies administered to U.S. citizens en masse and presage stem cell therapeutics (which may similarly be administered to millions) will similarly necessitate that a Stem Cell Injury Compensation Program (SCICP) will also need to be in place to demonstrate an intention to do good, an understanding that industry may do well, but that the health care consumer has a right of protection—all recognized from the outset. The Federal Tort Claims Act (FTCA) addresses liability claims via the Executive, Judicial and Legislative branches of Government, providing an umbrella of liability protection to other participants in the stem cell unit "chain of custody" under the FTCA—similar to the protection from product liability seen in organ and stem cell transplantation for the past 40-50 years.

Efficacious development of regenerative medicine capabilities will mandate controlled access must first be provided for individuals with life-threatening diseases without therapeutic options or unable to benefit from or receive proven therapeutic options (ALS, cardiomyopathy and deemed not a candidate for heart transplantation, IDDM with hypoglycemic unawareness and no allogeneic source of traditional islet cell replacement available via HRSA) and mandates the prompt adoption of business and legal principles to ensure that the fate of the vaccine manufacturing industry does not become the fate of the stem cell therapeutics industry.

If legal and regulatory concerns consume an increasing percentage of health care dollars that could be focused upon innovation, the Regenerative Medicine model will have not realized its full potential.

The Diabetes Transplantation/Regenerative Medicine Model is the first organ to cell transplant model outside of oncology to demonstrate the regenerative medicine paradigm. Since all human tissues can be already recapitulated by human stem cells and key patent holders already exist, outlet or distribution of "more-than-minimally-manipulated stem cell units" as an IND approved under FDA/CBER guidelines can be accomplished via the current HHS/HRSA/Dept of Transplant methodology. As cardiovascular stem cell researchers develop human therapeutics utilizing more-than-minimally-manipulated stem cell products, they could be afforded protections from product liability historically enjoyed by the transplant community. Extending the Diabetes Transplant/Regenerative Medicine Model to the more than 5 million Americans with chronic heart failure, cell-based therapies to regenerate myocardial contractility could fill an existing void and be delivered in conjunction with and consistent with existing distribution of organs and tissues via HRSA/Department of Transplantation. (J Geriatr Cardiol 2006;3:171-83.)

Key Words regenerative medicine; stem cell; heart failure

**Abbreviations**

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<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>CBER</td>
<td>Center for Biologics Evaluation and Research</td>
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<td>DOJ</td>
<td>Department of Justice</td>
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<td>DoT</td>
<td>Division of Transplantation (in HRSA)</td>
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<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>FTCA</td>
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<td>HCT/P</td>
<td>Human Cells, Tissues and Cell/Tissue Products</td>
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<td>HHS</td>
<td>Department of Health and Human Services</td>
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<td>Health Information Portability and Accountability Act</td>
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<td>HRSA</td>
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<td>HRSA/SPB</td>
<td>Special Programs Bureau (in HRSA)</td>
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<td>Hu-ESC</td>
<td>Human Embryonic Stem Cells</td>
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<td>Hu-nonESC</td>
<td>Human Non-Embryonic Stem Cells</td>
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<td>IDDM</td>
<td>Insulin Dependent Diabetes Mellitus</td>
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<td>IND</td>
<td>Investigational New Device or Drug</td>
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<td>LVAD</td>
<td>Left Ventricular Assist Device</td>
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<td>NBMDR</td>
<td>National Bone Marrow Donor Registry</td>
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<td>NMDP</td>
<td>National Marrow Donor Program</td>
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<td>NOTA</td>
<td>National Organ Transplant Act</td>
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<td>NVICP</td>
<td>National Vaccine Injury Compensation Program</td>
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<td>OPTN</td>
<td>Organ Procurement and Transplant Network</td>
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<td>SAE</td>
<td>Serious Adverse Event</td>
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<td>SCICP</td>
<td>Stem Cell Injury Compensation Program</td>
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<td>SPB</td>
<td>Special Programs Bureau (in HRSA)</td>
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<td>SRTR</td>
<td>Scientific Registry of Transplant Recipients</td>
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<td>QA/QC</td>
<td>Quality Assurance/Quality Control</td>
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<td>UNOS</td>
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**Introduction to regenerative medicine: beyond organ and stem cell transplantation**

Since 1968, successful human stem cell transplantation for treatment of malignancy, immunologic deficiency, and metabolic diseases has steadily expanded. Currently there are over 70 disease states in FDA-approved trials (e.g. heart failure, autoimmune disease) or with full FDA-approval for human stem cell transplantation using stem cells from bone marrow, peripheral blood or umbilical cord blood. Neither excessive medical malpractice liability nor stem cell product liability has encumbered this growth. Nearly 40 years later, Regenerative Medicine, the application of the science of stem cell biology to stem cell-based therapeutic intervention, verges upon a broader realm of human clinical delivery—preventive medicine applications that seek to restore lost or declining parenchymal function. Advances in stem cell science and clinical applications are foreshadowing the actualization of Regenerative Medicine—an extension of transplantation or implantation of organs and cells.
The goal of such therapeutics is intervention prior to onset of severe individual disability. The intended methods of delivery are minimally-invasive techniques delivering functional stem cells or stem cell-derived parenchymal cells during brief or same-day hospitalizations.

From 1900 to 2005, the average life expectancy of citizens of industrialized nations has risen nearly 20 years. Unfortunately, that same 20 year time period from 60 to 80 years of age is all too frequently encumbered by complications of atherosclerotic cardiovascular disease (myocardial infarction, heart failure, cerebrovascular accident, peripheral vascular disease), immunologic surveillance deficits (neoplasia, infection), and diabetes. Regenerative Medicine is already demonstrating early efficacy in a broad group of disease states. Restoration of myocardial contractility, joint mobility and function, immune competence, pulmonary function, immunologic self-tolerance, motor function and normal hemoglobin production have already been achieved in some human clinical trials. The next targets such as diabetes mellitus (type I and type II), neurologic injury, hepatic dysfunction, and others will also enter human clinical trials within the next 2 years either in the U.S. or outside the U.S.

Since the 1970s, Federal law has ensured financial health care support for our Nation’s citizens suffering from major organ failure requiring 1) extracorporeal therapeutics (e.g. dialysis) and 2) organ and stem cell transplantation (HHS/HRSA’s Division of Transplantation ensures that available organs, cells and tissues are distributed equitably and that pre- and post-transplant scientific data are collected, collated and applied toward future improvements in clinical transplant practice). Financial reimbursement for clinical delivery of pre- and post-transplant clinical activities is provided by transplant recipient’s federal and private health care insurance. This reimbursement scheme covers 1) pre-transplant evaluation and registration of potential transplant recipients, 2) organ/cell/tissue acquisition, 3) transplant surgery, 4) clinical follow-up and care post-transplantation, and 5) stem cell transplant—autologous or allogeneic, for patients with hematologic/oncologic diseases amenable to stem cell transplantation.

The intent of federal legislation enabling Medicare ESRD payments and organ and stem cell transplant coverage was to ensure the availability of life-sustaining extracorporeal treatments and transplants for American citizens in need of such treatments regardless of socioeconomic status. Generalizing to the current clinical reality, nearly 100,000 Americans are awaiting organ transplants with some estimates suggesting nearly 10-fold greater numbers of patients with organ failure who do not qualify due to disqualifying, concomitant medical conditions.

Expenditures on health care needs of an aging U.S. citizenry—afflicted by cerebrovascular disease, neuromuscular diseases, diabetes, organ failure (heart, kidney, pulmonary)—constitute an expanding proportion of U.S. health care dollars spent. Some of the largest growth in expenditures has been in the areas of organ transplant, oncology and stem cell transplant, extracorporeal therapies, implantable devices and protracted hospitalizations required by patients receiving such therapies. Annually, HHS/HRSA monitors U.S. expenditures of health care dollars which currently consume 20%-25% ($3 trillion) of U.S. GDP—and is anticipated to expand to 40% of U.S. GDP by 2025.

The actualization of improved clinical performance status and enhanced quality of life in patients in their 60s, 70s, 80s (and perhaps 90s) is within our grasp. To clinically implement the potential stem cell treatment revolution it is imperative that Regenerative Medicine clinical trials be designed with an eye toward protecting the development of Regenerative Medicine vis-a-vis the patient, treating physician, patent holders and investors in the development of the necessary technology. It is our position that the experience of HRSA’s Special Programs Bureau, United Network for Organ Sharing (UNOS), the National Bone Marrow Donor Registry (NBMDR), and the National Vaccine Injury Compensation Programs (NVICP), and the Federal Tort Claims Act (FTCA) could help to provide a safe harbor for the delivery of stem cell therapeutics and regenerative medicine.

C.W. Bill Young cell transplant program: HRSA prepares for the delivery of stem cell therapeutics and regenerative medicine

The first 50 years of organ/cell/tissue transplantation demonstrate that clinical reality of allogeneic and autologous transplantation can antedate comprehensive understanding of the basic science underlying successful transplantation. It may not be correct to assume that breakthroughs in stem basic science discoveries are required to harness the therapeutic potential of stem cells. Equally important, despite increased risks of infection, malignancy and cardiovascular disease in transplant recipients, product liability has not impeded the development and growth of organ/cell/tissue transplantation, and medical malpractice liability has also not impeded growth in the delivery of transplant medicine and surgery. Cadaver and living organ/cell/tissue donor-recipient pairing, achieved under the mandate of HRSA/DoT enforcement of equitable sharing of organs/cells/tissues, has ensured growth in U.S. transplantation. As transplantation has become more successful, the age of transplant recipients has expanded to include patients from birth to their 80s.

In this age of expanding organ failure in a progressively aging population, Regenerative Medicine (Stem Cell therapeutic development) is intended to increase organ function and enhance individual patient level of independence without incurring the economic impacts of standard organ transplantation. Due to the progressively growing gap between organ/cell/tissue recipients and potential donors, the need for alternative sources of functional, transplantable tissues has skyrocketed to previously unforeseen levels. Via the novel arena of stem cell/parenchymal cell production and manufacturing, the expanding organ/cell/tissue donor-recipient discrepancy may be “bridge-able.”
To date, human cell transplantation in the United States is performed using non-embryonic stem cells from peripheral blood, bone marrow or umbilical cord blood. Federal legislation passed in 2005 (HR2520 and S1317: The Bone Marrow and Cord Blood Cell Transplantation Program) authorizes the Secretary of Health and Human Services acting through the Director of HRSA to ensure the presence of 150,000 qualified stem cell units from umbilical cord blood for human transplantation. Transplanted stem cell units MUST be distributed and outcomes monitored via the federally-designated C.W. Bill Young Cell Transplant Program in compliance with relevant Public Health Service Acts. As specified in this bill, these units can already be used to treat currently FDA-approved oncolgic, hematologic and metabolic disorders and are designated to extend over to Regenerative Medicine for research and ultimately the treatment of parenchymal, organ failure. Since the development of Regenerative Medicine will impact 1) organ transplant physician, OPTN/UNOS practices and 2) stem cell transplant physician, NBMDR/C.W. Bill Young Cell Transplant Program practices, HHS/HRSA has officially begun to set the national tenor in its support and oversight of autologous and allogeneic parenchymal cell/stem cell transplantation in the development of Regenerative Medicine.

Health Resources Service Administration, the special programs bureau and potential cardiovascular disease regenerative medicine interventions

At the same time that safe, effective, and expanding peer-reviewed organ and stem cell transplantation has been delivered by HRSA for more than 3 decades, HHS has helped to ensure the availability of high-risk health care capabilities—organ and stem cell transplant (via HRSA) and vaccinations (via The National Vaccine Injury Compensation Program). Issues which development of Regenerative Medicine must take into account include 1) federal regulation of the distribution of human tissues (National Organ Transplant Act or NOTA), 2) potential stem cell product liability and 3) potential medical malpractice liability. HHS experience providing “stewardship” of organs and stem cells for transplantation and overseeing the compensation for vaccine injury could provide a basis for moving Regenerative Medicine forward without eliminating entrepreneurial interests in the development of Regenerative Medicine—note the growth of Cord Blood transplantation despite the PharmaStem patents litigation in the 1980s–1990s. HRSA Special Programs Bureau (HRSA/SPB) responsibilities include administration of the National Vaccine Injury Compensation Program (NVICP) and administration of the transplantation of organs, tissues, and bone marrow via the Division of Transplantation (DoT). DoT oversees three contracts to operate the 11-region, uniformly-governed, nationwide system facilitating the matching of solid organ donors and stem cell donors to patients in need of transplants. The 3 major contracts are the following:

1) Organ Procurement and Transplantation Network (OPTN), which facilitates matching deceased donor organs with patients in need of organ transplants;
2) Scientific Registry of Transplant Recipients (SRTR), which provides research and analytic support to the OPTN policy-development and evaluation process and information on solid organ transplant issues to the U.S. Department of Health and Human Services (HHS);
3) National Bone Marrow Donor Registry (NBMDR), which facilitates stem cell transplantation for patients in need via unrelated donors.

In addition, DoT is responsible for efforts to increase organ and tissue donation throughout the United States through development and implementation of national campaigns which include educational projects and grant programs.

To actualize the potential health care and economic benefits of Stem Cell Therapeutics (Regenerative Medicine) for individual patients and national interests, a comprehensive strategy will need to be in place to accommodate 1) processing, registration, collection and quality control (QC) of cells and tissues from cadaver and living donors, 2) processing, registration, delivery and QC of cells and tissues to recipients, 3) registration, production, real-time inventory control, QC and delivery of cells and tissues by stem cell patent holders/manufacturers, 4) longitudinal assessment of clinical outcomes to provide necessary feedback to continuously improve and redirect stem cell therapeutic delivery, and 5) provide timely compensation for patients who may suffer unintended consequences of myocardial regenerative therapies. Such a strategy must include 1) HIPAA-compliant patient medical data maintenance, 2) registration of GMP/GTP-manufactured cells/tissues by any stem cell production entity compliant with FDA/CBER guidelines, 3) US-SRTR follow-up of the clinical outcome of distribution of cadaveric and live-donor allogeneic human tissues and implantation of minimally- and more-than-minimally-manipulated autologous cells/tissues, and 4) NVICP-like compensatory mechanisms to accommodate patient health injury/consequences of stem cell therapeutics.
An anticipatory strategy to protect development and implementation of the regenerative medicine "marketplace"

Historically in the U.S., human biological therapies (vaccines, organ transplant and stem cell transplant) have ultimately required federal protections to ensure continued distribution and fair access. Organ and stem cell transplantation have proceeded without inhibitory product liability since the 1950s and 1960s, respectively. Protected under the "stewardship" provided by the Secretary of Health and Human Services, effectively every organ and every unit of stem cells has become a product distributed by the Secretary of HHS. The National Childhood Vaccine Injury Act of 1986 established the NVICP to equitably and expeditiously compensate individuals, or families of individuals, who have been declared injured by vaccines. The NVICP stabilized a once imperiled vaccine supply by substantially reducing the threat of liability for vaccine companies, physicians, and other health care professionals who administer vaccines. The NVICP (in effect since 1988) is a no-fault alternative to the traditional tort system for resolving vaccine injury claims administered jointly by HHS, the U.S. Court of Federal Claims, and the U.S. Department of Justice (DOJ). Efficient resolution of claims is one of the primary objectives of the NVICP and prompt payment of annuities, lump sums, and attorneys’ fees/costs contributed to its success.

Vaccines were the first biologics administered to U.S. citizens en masse (millions of recipients annually). Since stem cell therapies may similarly be administered to millions of Americans, it can logically be anticipated that a Stem Cell Injury Compensation Program (SCICP) will also need to be in place. A SCICP must be able to provide for predictable, rapid and equitable compensation for stem cell therapy injuries because each claim might otherwise require extended, costly, and complex adjudication—a legal process which stem cell patent holders might find economically untenable, thereby forcing them to abandon stem cell therapeutic development. It will be a "sign of good will" by the Regenerative Medicine industry as a whole if a compensation scheme is preemptively established since it demonstrates an intention to do good, an understanding that industry may do well, but that the health care consumer has a right of protection—all recognized from the outset.

Adopting the table of elements composing the NVICP, a similar SCICP strategy can 1) provide a petitioner with a list of anticipated potential injuries, 2) place requirements upon a petitioner which must be proven such that the stem cell intervention significantly aggravated a pre-existing condition, and 3) provide the uniform framework within which a petitioner must prove that the stem cell intervention caused the condition. Risks and benefits associated with FDA/CBER-approved stem cell implantation can be stratified based upon factors such as 1) source of stem cells (EMBRYONIC—autologous or allogeneic and NON-EMBRYONIC—autologous or allogeneic), 2) state of differentiation of the stem cells (terminally differentiated vs non-terminally differentiated), 3) method of delivery (intravenous, percutaneous implantation or surgical implantation), 4) Immunologic Modulation Requirements (none needed, needed for pre-transplant immunosuppression, or needed for immunosuppression post-transplantation), 5) duration of therapeutically anticipated benefit and 6) time to onset of unanticipated effects(s).

With stem cell therapeutic potential we must consider the following characteristics of the intended intervention: 1) the age of the population intended to receive the treatment, 2) the number of cells necessary to provide effective intervention, 3) the source of the cells (EMBRYONIC: autologous or allogeneic, and NON-EMBRYONIC: autologous or allogeneic), 4) the QA/QC-determined rates whereby such cells have been determined to accumulate DNA abnormalities in various phases of the manufacturing process, 5) SAEs encountered and frequency in pre-clinical animal data, and 6) SAEs encountered and frequency in human clinical studies.

Development of regenerative medicine and the Federal Tort Claims Act

The Federal Tort Claims Act (FTCA) addresses liability claims via the Executive, Judicial and Legislative branches, the Military, as well as independent establishments of the United States, and corporations primarily acting as instrumentalities or agencies of the United States. Federal employees are protected from liability claims "...any claim for money damages against the United States for injury or loss of property or personal injury or death caused by the negligent or wrongful act or omission of any employee of the agency while acting within the scope of his office or employment, under circumstances where the United States, if a private person, would be liable to the claimant in accordance with the law of the place where the act or omission occurred: Provided, That any award, compromise, or settlement in excess of $25,000 shall be effected only with the prior written approval of the Attorney General or his designee." Safeguards in the adjudicative process ensure that petitioners will not be impermissibly rewarded by an unacceptably lenient standard as respondent fears. These safeguards include the fact that petitioners must prove all five prongs proposed: first, a theory for their alleged injury; second, support for that theory; third, the suffering of a relevant injury; fourth, the onset of the injury within a medically accepted time frame; and fifth, that other causes were eliminated. This court has seen many cases fail each of these five prongs.

Transplantable human organs/cells/tissues developed for Regenerative Medicine can potentially receive the same protections that organs/cells/tissues currently receive. Given the Federal mandate creating the C.W. Bill Young Cell Transplant Program (S1317 and HR2520) and the appropriation of $79 million specifically to build the 150,000 stem cell unit repository, U.S. government participation in the “chain of custody” of these stem cell products supplied by HHS/HRSA is established. This reality may provide an umbrella of liability protection to other participants in the stem cell unit “chain of custody” under the FTCA—similar to the
protection from product liability seen in organ and stem cell transplantation for the past 40-50 years.

Unaddressed, the issue of Regenerative Medicine product liability has the potential to negatively impact the advancement of stem cell therapeutic delivery much as the “Swine Flu” Vaccine experience began a cascade of events which has resulted in the decimation of the vaccine manufacturing industry and the exorbitant growth in cost associated with vaccinations. The occurrence of similar developments in the nascent stem cell/parenchymal cell therapeutic delivery industry could result in abandonment of a promising therapeutic.

**HRSA “stewardship” of human organs, cells and tissues**

Transplantation of organs/cells/tissues has proceeded safely and effectively in the U.S. with HRSA taking “stewardship” (if not actual custody) of the donor organs/cells/tissues. Currently, there are more than 1970 companies or entities which have registered cell-base therapy INDs with FDA/CBER. The functions fulfilled by DoT’s OPTN, NBMDR and SRTR can directly translate into the arena of stem cell/parenchymal cell matching and equitable distribution. Stem cell/parenchymal cell “manufacturers” currently can chose from the “marketing” scenarios visualized in Figure 2.

**Making patient safety and clinical candor the hallmark of the development of regenerative medicine clinical trials: a proposal for the pre-emptive formation of the Stem Cell Injury Compensation Program (SCICP)**

The establishment within HHS/HRSA’s Bureau of Special Programs (BSP) of an Office of Patient Safety and Health Care Quality and MEDIc Program was recently communicated by Sen. Barack Obama & Sen. Hillary Clinton in the *New England Journal of Medicine.* It provides a formalized and generalizable structure for patients and physicians to have open communication regarding sharing of “up to the minute” data and information—matters that may have far-reaching benefits in regard to the development of Regenerative Medicine. Such a program could be the impetus to ensure that “current information” on stem cell lines, which patients might receive in the course of FDA-monitored human clinical stem cell trials, be definable and available to patients and physicians simultaneously. This would be in keeping with patient advocacy aspects already inherent in the mandates for UNOs and the C.W. Bill Young Cell Transplant Program. The existing US-SRTR and any future proposals for patient access to up-to-date information from HHS/HRSA can provide Regenerative Medicine an atmosphere of candor, collaboration and collegiality between
potential patients, treating physicians and regulatory bodies. Simultaneously, the adoption of a federal stewardship model of FDA/CBER-approved stem cell units by academic, entrepreneurial and other stem cell product developers may facilitate product liability protections afforded by the FTCA. This combination may represent a proposed solution for successful advancement of stem cell therapeutics with far-reaching implications.

For purposes of this discussion, only human stem cells that conform to FDA/CBER HCT/P practices will be considered. Non-conforming cells, transfected cells, cells delivered via nanotechnologies (current and anticipated) and xenogeneic cells/tissues will not be considered due to their inherently compounded risks. Currently stem cell unit risk/benefit modeling can be defined in accordance with the following data points depending upon whether the unit is derived from FDA/CBER-approved sources (non-embryonic) or from not-yet-FDA/CBER-approved sources (embryonic cells): 1) existing pre-clinical animal safety/efficacy data with a particular source of stem cells; 2) existing pre-clinical animal serious adverse event (SAE) data with a particular source of stem cells; 3) existing human clinical safety/efficacy data with a particular source of stem cells; and 4) existing human clinical serious adverse event (SAE) data with a particular source of stem cells.

**Stem cell line risk assessment algorithm proposal**

Risk assignment and thus potential for liability could be assessed by the developers of stem cell therapeutics according to the following 8 quadrants (I.0 through I.3) as shown in Figure 3.

![Risk assessment algorithm](image)

**Fig. 3. Risk assignment and liability assessment**

Based upon such a theoretical breakthrough of pre-clinical and clinical data, stakeholders in the therapeutic development of stem cell lines would be able to begin to stratify their level of anticipated product liability risk and medical malpractice risk as follows:

**Stem Cell Lines no longer progressing from I.0:**

**HIGHEST RISK**

(example: Hu-ESCs implanted into human CNS yielding teratomas/teratocarcinomas)

**Stem Cell Lines progressing from I.0 to I.1, I.2:**

**HIGHEST RISK**

(example: none known to date)

**Stem Cell Lines progressing from I.0 to I.1, I.2, I.3:**

**LOWEST RISK**

(example: Allogeneic human bone marrow/cord blood transplant for leukemia)

**Stem Cell Lines progressing from I.0 to I.1, I.2, I.3:**

**LOW RISK**

(example: Allogeneic human bone marrow or umbilical cord blood transplant for treatment of solid tumor)

**Stem Cell Lines progressing from I.0 to I.1, I.2, I.3:**

**LOW RISK**

(example: Allogeneic human bone marrow or umbilical cord blood transplant for leukemia/lymphoma)

**Stem Cell Lines progressing from I.0 to I.1, I.2, I.3:**

**LOW RISK**

(example: Allogeneic human bone marrow or umbilical cord blood transplant for treatment of solid tumor)

**Stem Cell Lines progressing from I.0 to I.1, I.2:**

**HIGHEST RISK**

(example: Hu-ESCs implanted into human CNS yielding teratomas/teratocarcinomas)

For patients considering entry into Phase I clinical trials, preclinical data from a defined list of peer-reviewed clinical transplant journals (e.g., Transplantation, American Journal of Transplantation, Journal of Clinical Investigation) can be compiled in meta-analysis format to enhance the informed consent process. Additionally, data being generated by human clinical trials (see Stem Cell Clinical Trials on NIH website) can be progressively compiled and continuously updated and made available to the public allowing patients access to up-to-date clinical data. This can facilitate the process of informed consent and patient advocacy mandated by the C.W. Bill Young Cell Transplant Program and the United Network for Organ Sharing.

**Diabetes transplantation/regenerative medicine model**

Translating the above issues into existing human clinical experience is necessary and instructive. The existing human clinical transplantation therapeutic model that anticipates the expansion of Regenerative Medicine is the insulin dependent diabetes mellitus (IDDM) patient. For IDDM patients, current Medicare-reimbursable treatment options (Fig. 4) include:

1) Intensive insulin therapy—requires outpatient treatment

2) Whole-organ pancreas transplantation—requires 7-10 days hospitalization

3) Parenchymal cell (pancreatic islet) implantation—requires < 5 days hospitalization

The Regenerative Medicine paradigm is intended to broaden the therapeutic options to include:

1) Immunologic tolerance protocols designed to prevent IDDM—inpatient duration not yet determined

2) Implantation of Pancreatic Islets created from stem cells—if autologously derived will require < 3 day hospitalization
Heart failure is diagnosed in more than 500,000 Americans annually. Of those diagnosed, approximately 10,000 are listed for heart transplantation with UNOS but only 1,000 will actually undergo transplantation. Patients over the age of 55 with progressive clinical heart failure may fail to qualify for listing for heart transplant; thus they are relegated to long-term medical therapies, recurrent hospitalizations and a progressively dependent existence. Since patients “not listable” for transplant are unlikely to achieve long-term improvement in performance status from mechanical assist devices (LVAD) or mechanical replacement, a potential gap exists in this population’s treatment armamentarium.

Current heart failure treatment regimens include (Fig.5):
1) IV inotrope/afterload reduction therapy—requires inpatient treatment for up to 14 days and may require frequent re-treatment;
2) Mechanical assist devices—require initial inpatient treatment for up to 21 days and may require frequent readmissions with or without frequent outpatient follow-up;
3) Heart transplantation—requires 14-21 days hospitalization.

The stem cell research literature is replete with existing abilities to harvest stem cell or parenchymal precursors of muscle cells from bone marrow, umbilical cord blood or skeletal myoblasts. The patented technologies to \textit{ex vivo} expand these cells and ultimately clinically deliver them \textit{in situ} in viable areas of existing myocardium via percutaneous interventions or minimally-invasive surgery are intended to enable patients to minimize or avoid periods of debilitation and disability. As the clinical design of such interventions is rationally and economically developed, the clinical goals will include: 1) increased work productivity, 2) reduced expenditures on chronic medication use, 3) reduced long-term care expenditures and 4) ultimately less GDP expenditure in the more than 5 million Americans with chronic heart failure. Myoblast or myocardial stem cell implantation requires approximately no more than 7 days hospitalization.

Cell-based therapies to regenerate myocardial contractility could fill an existing void and be delivered in conjunction with and consistent with existing distribution of organs and tissues via HRSA/Department of Transplantation.

**Extending the IDDM regenerative medicine model to heart failure**

**Current treatment options for IDDM patients**

**Fig. 4. Current treatment options for IDDM patients**

**Fig. 5. Treatment strategy for patients with progressive class III/IV NYHA heart failure**

**Current U.S. stem cell patients and the development of cardiovascular regenerative medicine interventions**

All human tissues can be recapitulated by human embryonic (Hu-ESCs) and non-embryonic stem cells (Hu-nonESCs). Key patent holders already exist in both Hu-ESC and Hu-nonESC sectors. Regenerative Medicine therapeutics with either Hu-ESCs or Hu-nonESCs can be developed in the private sector alone, in academia alone, or conjointly by academia and the private sector. Outlet or distribution of “more-than-minimally-manipulated stem cell units” as an IND approved under FDA/CBER guidelines can be accomplished via the current HHS/HRSA/Dept of Transplant methodology.

Distribution of Hu-nonESCs for clinical treatment outside of the above methodology potentially violates the National Organ Transplant Act. Distribution of Hu-ESC-derived products for clinical treatment outside of the HHS/HRSA/Dept of Transplant methodologies may incur federal penalties in addition to product liability risks—thereby reducing the likelihood that medical/surgical practitioners would be unwilling to participate in the delivery of such therapeutics from a malpractice point of view.

As cardiovascular stem cell researchers develop human therapeutics utilizing more-than-minimally-manipulated stem cell products, they could be afforded protections from product liability historically enjoyed by the transplant community. The quid pro quo will of necessity be adoption of the movement of “more than minimally-manipulated” cell products via the HRSA/DoT donor-recipient matching system to ensure equal and systematic access to such therapeutics with uniform oversight of their therapeutic outcomes via the HRSA/STRTR database and the C.W. Bill Young Cell
Transplant Program. If HRSA/DoT oversight affords these "manufacturers" the necessary product liability protections, access to the same health care insurer reimbursement path currently available to suppliers of cord blood-, bone marrow- and peripheral blood-derived stem cell units can also apply.

**Focusing upon regenerative medicine and cardiovascular disease**

The clinical scenarios of chronic heart failure and acute myocardial infarction comprise the largest populations of interest in the realm of potential cardiology stem cell interventions. Chronic heart failure stem cell intervention presents a "golden opportunity" to begin to strategically prepare for Regenerative Medicine interventions and its incumbent steps (Table 1).

Of the 5 million Americans with chronic heart failure who are currently listed with UNOS for heart transplantation, annually about 1,000 will undergo heart transplantation, less than 500 will receive an LVAD, and the majority who die will do so without undergoing either intervention. Thus, the gap patient population to consider for Regenerative Medicine interventions (likely numbering in the tens of thousands) would include those with the following characteristics: 1) unable to qualify for heart transplantation; 2) statistically unlikely to benefit from use of mechanical assist devices; 3) 6-month mortality rate > 50%; 4) willingness to enter autologous vs allogeneic stem cell intervention protocol with consent to use of chronic immunosuppression (calcineurin inhibition only), autologous stem cell retrieval procedure, or randomization to PCI vs thoracotomy.

The selection of such a population will enhance the discernable benefit of autologous vs allogeneic stem cell/myocardial interventions, facilitate the merging of UNOS- and NBMDR-specific data collection and SRTR-specific data follow-up, thereby providing a tangible expression of the intent of S1317's C.W. Bill Young Cell Transplant Program.

As the U.S. heart failure population ranks swell and as researchers demonstrate ability to increase ejection fraction utilizing delivery of intra-myocardial stem cell/cell-based therapeutics, clinicians may increasingly consider these Regenerative Medicine alternatives to provide meaningful alternatives to heart transplantation and mechanical assist devices for patients no longer responding to medical therapies. Since the potential liabilities associated with novel cell-based therapeutic delivery could dissuade investment and development of such therapeutics, and since failure to develop such therapeutic alternatives could have catastrophic implications for U.S. health care dollar expenditures over the next 25 years, the federal protections afforded by HHS/HRSA "stewardship" of organs/tissues/stem cells to date may provide that vehicle which ensures that the Regenerative Medicine industry does not suffer the fate of U.S. vaccine manufacturers.

The current FDA/CBER pathway/HRSA/Dept of Transplantation pathways offer a hybrid that can permit entrepreneurial investment in the fledgling Regenerative Medicine industry, uniform oversight of all sources of GMP/GTP compliant human cell-based therapeutics and rigorous pre- and post- transplant/implant monitoring to ensure meaningful comparisons and conclusions are facilitated in the same vein as the HHS/HRSA Scientific Registry of Transplant Recipients. Additionally, it is our position that novel proposals which emphasize constructive partnering between patients, medical community, legal community, legislators and health care insurers (e.g. the recently proposed MEDiC Program) can further enable the development of Regenerative Medicine by ensuring the prompt sharing of up-to-date scientific data—thereby allowing meaningful informed consent for all involved in this potential revolution in health care delivery.

**Table 1. Algorithm for the regenerative medicine interventions**

<table>
<thead>
<tr>
<th>Patient identification</th>
<th>Transplant candidacy exclusion</th>
<th>Myocardial viability testing</th>
<th>Coronary angiography</th>
<th>Stem cell harvest and ex vivo expansion</th>
<th>Same day surgery admission</th>
<th>Potential methods of delivery</th>
<th>Post-procedure monitoring</th>
<th>Outpatient follow-up</th>
<th>Medication</th>
<th>Change</th>
<th>Reduction/Elimination</th>
<th>Testing</th>
<th>Radiology</th>
<th>Nuclear</th>
<th>Ultrasound</th>
<th>Serologic</th>
<th>Evaluation of patient quality of life</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Percutaneous: Cardiac catheterization lab equipment/timeslot</td>
<td>Surgical: Mini-thoracotomy, video-assisted thacoscope, open thoracotomy</td>
<td>Cardiac telemetry</td>
<td>Cardiothoracic ICU</td>
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<td>Testing</td>
<td>Nuclear</td>
<td>Ultrasound</td>
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<td>Level of function: Improved/Stable/Worsened</td>
<td>Employment</td>
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References


