THE EFFICIENCY AND EFFECTIVENESS OF DONOR REGISTRY PROMOTION AND THE ORGAN DONATION PROCESS: IMPACT ON THE AVAILABILITY AND THE COST OF PROCURING ORGANS FOR TRANSPLANT

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Submitted to the Graduate Faculty of

Health Policy and Management

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2014

UNIVERSITY OF PITTSBURGH

Graduate School of Public Health

This dissertation was presented

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It was defended on

June 17th, 2014

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ABSTRACT

The remarkable progress of transplant medicine in the latter half of the twentieth century has led to an unprecedented demand for donated organs that have historically remained in short supply. Although a clinically effective procedure, organ transplant's health benefit to the society is seriously limited by the shortage of organs. The resulting tragic and preventable loss of life is therefore a **public health concern**. This dissertation examines the efficiency and the effectiveness of the organ procurement process and its impact on the cost and availability of transplantable organs. Specifically, three issues are examined using data from western Pennsylvania and West Virginia, a region served by the Center for Organ Recovery and Education (CORE).

First, the effect of process breakdown on the availability of transplantable organs is examined using generalized linear model. The principal finding is that for every process breakdown in the care of a potential donor, one less organ is available for transplant. Consequently, 25 organs were lost to process breakdowns over the three-year study period.

Second, the cost of promoting the donor registry and its effect on the supply of organ donors is examined using decision analysis model. The principal finding is that CORE's promotion efforts would generate 4.2 present-day donors at a cost of $726,000 per donor. When compared with previously published estimates of a donor's monetary value to the society, CORE's promotion efforts offer good return on investment.

Third, the impact of donor registry promotion on organ shortage is examined. Our analysis indicates that the impact threshold of registry promotion is reached at 64 donors that yield 73 kidneys, 45 livers, 18 lungs and 15 hearts. The principal finding is that registry promotion alone cannot arrest the growth in transplant waiting list. Although a cost-effective strategy, registry promotion has a significant budget impact.

Living donation and innovations that expand the donor pool or improve the organ acceptance rate may be able to arrest the growth in the waiting list. However, burden of waiting list deaths rests primarily on the causes of end-stage organ failure rather than organ shortage. Prevention and early intervention remain the first line of defense.

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CHAPTER 1: HISTORICAL PERSPECTIVE ON ORGAN DONATION AND TRANSPLANTATION- LITERATURE REVIEW AND CONCEPTUAL FRAMEWORK FOR THE PROPOSED RESEARCH

1.1. INTRODUCTION

The American story of organ donation and transplantation is both remarkable and disappointing. From being an experimental medical procedure only a few decades ago, organ transplantation has evolved as the treatment of choice for end-stage organ disease. Yet thousands of lives are tragically lost to organ failure every year. In 2012 alone, 6,473 people died from end-stage organ disease in spite of abundant financial and technological resources available for organ transplantation [1]. The remarkable progress of transplant medicine in the latter half of the twentieth century has led to an unprecedented demand for donated organs that have historically remained in short supply. As a result, relatively few organs are transplanted, compared to the number of people with end-stage disease. In 2012, more than 116,000 patients were on the waiting list for an organ transplant but only about 28,000 transplants were performed from 14,000 donors [1]. Although a clinically effective procedure, its health benefit to the society is seriously limited by the shortage of organs. The resulting tragic and preventable loss of life is therefore a **public health concern**.

The shortage of transplantable organs in the United States was apparent as early as 1988 when collection of organ transplant data had just begun. Figure 1 presents the widening gap between demand and supply of organs for transplant. In 1988, there were 16,026 people waiting for an organ transplant but only

12,623 organs from 5,909 donors were transplanted with net shortage of at least[1] 3,403 organs [1, 2]. By 2012, the number of organs falling short has increased to over 98,992 [1, 2]. While the number of donors has been increasing at a steady rate, the number of people who are eligible for a transplant has, far out-paced the supply of organs. It is therefore ironical that the benefits of transplant medicine are limited by the consequence of its own success. And it is this great paradox that makes this issue interesting and challenging.

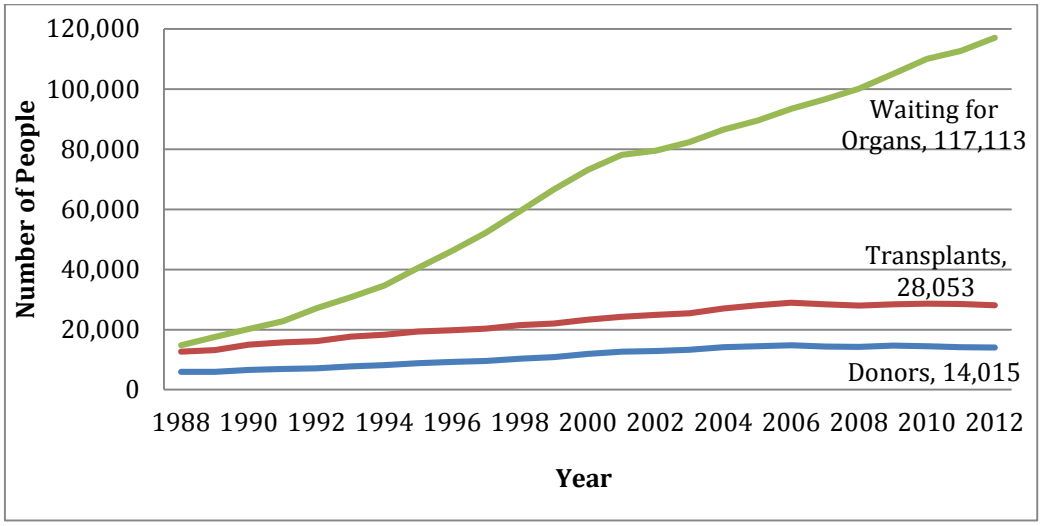


Figure 1: Demand and supply of transplantable organs in the U.S. (1988 thru 2012)

There are three main sections in this chapter. Section 1.2 visits the historical developments that resulted in favorable conditions for the evolution of transplant medicine. Why transplant medicine owes its remarkable progress in the past fifty years to a confluence of technological innovations in varied disciplines

[1] The historical data on transplant waiting list obtained through request to OPTN show the number of candidates and not registrations waiting for a transplant. While each candidate needs at least one organ for transplant, some of these candidates may require multiple organ transplants. Thus in 1988, the 16,026 candidates on the waiting needed at least as many number of organs. Therefore after transplanting 12,623 organs, the organ deficit was at least 3,403. Organ deficit might be greater if there were some multi-organ transplant candidates on the waiting list.

is discussed. The brief history of organ transplantation presented here draws attention to the rapid evolution of transplant medicine and the consequent rapid rise in demand for organs.

Section 1.3 recounts how society has responded to the increasingly evident need for transplantable organs and the ethical issues concerning removal of organs from the human body. Regulatory and legislative breakthroughs since the 1960s and episodic but radical changes to the practice of organ procurement are discussed. Central to this discussion are the laws governing determination of death, creation of a national system for procuring organs, and the role of these developments in structuring the organ donation and transplantation system into its current form.

Section 1.4 details the structure of the organ procurement network with particular emphasis on the activities of organ procurement organizations. Finally, in sections 1.5 through 1.7 the context of the proposed research questions is examined. Motivation for the research questions is discussed under the individual research papers.

1.2. HISTORY OF ORGAN TRANSPLANTATION- FROM EXPERIMENTAL SCIENCE TO CLINICAL MEDICINE

The idea of transplanting body parts to restore bodily function and esthetics is not new. Examples of creatures with body parts from different species- referred to as chimeric beasts- are abundant in Greek mythology. The New Testament also contains several occurrences of auto-transplantation [3]. These occurrences include the story of the Jesus of Nazareth restoring a servant's ear that was sliced off by Simon Peter's sword during a battle. Other recorded accounts detail the stories of St. Peter replanting St. Agatha's breasts and St. Mark restoring a soldier's right hand that was severed in battle. An extraordinary description of a cadaveric allograft can be found in Legenda Aura. In the "miracle of the black leg", two saints replace

Justinian's gangrenous leg with the leg of a recently buried Ethiopian man [4]. The oldest evidence of transplanting body parts dates back to the Bronze Age. Evidence of bone grafts being used to close the cranium post-trephination can be found in the archeological records from this age [5]. Detailed descriptions of using skin grafts to reconstruct amputated nose and damaged ears are found in the ancient Hindu texts dating as far back as 2500-3000 BCE [6, 7].

Between 16th and 20th century, this ancient idea began to evolve into modern day transplant medicine. The few developments that occurred in this era are noted by Hossein Shayan [8]. An upper arm skin graft was used by an Italian surgeon for nose reconstruction in 1590s [8]. In the 17th century, teeth were successfully grafted in humans. A Scottish surgeon, John Hunter, had some success with Achilles tendon allografts [8]. By the beginning of the 18th century, experiments with skin and corneal grafts; thyroid, adrenal and ovarian grafts and other connective tissue grafts were reported [9]. In the 19th century, corneal and skin graft procedures made significant progress. In 1837, Samuel Bigger transplanted a full-thickness corneal graft into the blind eye of a gazelle [7]. In 1898, Winston Churchill was asked to donate some skin from his arm to an injured officer in a famous case of allogenic skin graft. Churchill's description of the incident in his own words alludes to the long-term success of the skin graft [7]:

"A piece of skin and some flesh about the size of a shilling from the inside of my arm. This precious fragment was grafted to my friend's wound. It remains there to this day and did him lasting good in many ways. I for my part keep the scar as a souvenir."

With the arrival of the 20th century, a confluence of progressive and parallel developments in the fields of vascular surgery, physiology, immunology and pharmacology revolutionized organ transplantation from a mere subject of Greek legends into clinically effective medicine. Experimental models on animals, influential case studies and clinical trials with organ transplantation are reviewed in detail by Peter K. Linden and Thomas E. Starzl in their respective seminal articles [3, 10]. Following a 1999 conference at the University of California, Los Angeles, a consensus paper identifying important historical milestones in

the evolution of transplant medicine was published in the World Journal of Surgery [11]. The findings of the consensus conference were also summarized by Starzl a year later [12]. We briefly review those developments in science, technology and our understanding of the human body that brought a paradigm shift in transplantation science.

By the twentieth century, what Peter K. Linden refers to as the beginning of the "pre-modern era" (1900-1959), successful skin grafts and corneal transplants were being frequently reported [13, 14]. The logical progression from this point was in the direction of organ transplantation. Animal studies on organ transplantation, failed renal transplantation in humans, innovations in vascular surgery and seminal observations in immunology characterize this era. The main challenge with organ transplantation at the time was that organs are sensitive to ischemia and need major vessel anastomosis for vascular supply as opposed to skin grafts where capillary anastomoses are sufficient. Between 1902 and 1905, French surgeon Alexis Carrel refined the vascular anastomotic suturing methods, vessel reconstruction procedures, and cold preservation techniques [15, 16]. With these innovations, it was now possible to surgically plant organs from one animal into another of the same species. However in ensuing animal transplant models, Carrel discovered that an adverse host response to the foreign graft was a hurdle in realizing clinical transplantation. As he famously observed [9]:

"Should an organ, extirpated from an animal and replanted into its owner by a certain technique, continue to functionate normally, and should it cease to functionate normally when transplanted into another animal by the same technique, the physiological disturbance could not be considered as brought about by the organ but would be due to the influence of the host, that is, the biological factors."

Nevertheless renal transplantation in humans with allografts and xenografts was attempted in Russia and France- albeit with disastrous results [3, 17]. The first breakthrough in the understanding of the host response to allografts came during World War I when the increased need for skin grafts for battle injuries steered Peter Medawar, a British surgeon, into investigating the causes of skin allograft rejection.

He observed that skin grafts between monozygotic twins (identical twins- those who essentially share the same genetic code) were well tolerated [18]. Later in 1954, Joseph Murray and John Merrill reported a successful renal transplant between male monozygotic twins [19]. These findings suggested two things: 1) the host immune system had an important role in graft rejection; and 2) "*Iatrogenic suppression of the recipient's immune system was the keystone to breaking the genetic compatibility barrier*" [3].

Initial attempts at iatrogenic immune suppression employed cytoablative radiation. However it soon became apparent that this method was too crude to achieve meaningful health benefits as vast majority of patients died from the complications of total body irradiation such as infections and malignancy [20]. Development of antileukemic drugs promised a more refined method of suppressing the immune system. Pharmacologic immune suppression with prednisone was first tested on a female kidney recipient in 1960. The patient died after 5 months [21]. Immunosuppression with either azathioprine or 6-mercaptopurine also yielded poor survival rate with only one of the ten transplant recipients surviving to six months post-transplant [22, 23]. The transplant revolution was halted until the early 1960s when Thomas Starzl at the University of Colorado demonstrated that high doses of prednisone with azathioprine could reverse graft rejection and even induce tolerance in the host [24]. Soon after Starzl overcame the genetic compatibility barrier, experimental renal transplants became clinical medicine although complications of lymphocyte depletion remained a problem [25]. A decade later, Borel & Stähelin discovered cyclosporine which was effective in immunosuppression but exhibited little cytotoxicity [26] and till date, combined with Starzl's "cocktail", this drug offers least harmful immune suppression [8].

Parallel to the development of pharmacological immunosuppression, advances in immunology led to the development of immunologic screening. In 1964, guidelines for ABO matching were developed to prevent transplanted organs from infracting due to ABO mismatch and resulting agglutination-related obstruction of microvasculature [27]. A year later, Terasaki et al. introduced the lymphocytotoxic crossmatch test to determine if the recipient's serum was presensitized to donor's lymphocytes [28]. Around the same time, Terasaki et al. also developed the Human Leukocyte Antigen crossmatch (HLA corssmatch)

serum assay to detect preformed anti-graft HLA antibodies [29]. Advances in organ procurement and preservation also contributed to the rapid rise of transplantation as a clinically effective procedure. In the 1980s, “flexible” surgical techniques for rapid removal of multiple organs were developed by Starzl et al. [30, 31]. By 1905, Alexis Carrel had already pioneered the hypothermic preservation technique [16]. Further practicable advancements in organ preservation technology were made several decades later when the innovative yet logistically challenging machine perfusion technique [32] was replaced by the simple flush technique [33].

The remarkable evolution of organ transplantation is not unique. In fact rapid advancements in basic biomedical sciences and engineering and technology that were fundamental to the rise of organ transplantation also revolutionized medicine in general. However dependence on donated organs for transplants poses a challenge that is unique to this field of medicine. Indeed shortage of donated organs is proving to be an insurmountable barrier for the transplantation community. Consequently, the organ donation community continues to evolve as the demand for organs ever increases.

1.3. HISTORY OF ORGAN DONATION- MAKING OF A NEW HEALTHCARE SUB-SECTOR

In the early sixties when critical care medicine and organ preservation were a fledgling science, organ transplants were limited to kidneys donated by living relatives and friends. Laws premised on the ethical principle of non-maleficence barred donation of other vital organs by living donors. The colloquial “dead-donor rule” was based on the ethical expectation that organs that were necessary to sustain life could be removed only after a donor is declared dead [34-36]. The problem was that without modern intensive care, organ health in critically ill individuals was already compromised. Furthermore, ischemic insult from circulatory failure at death meant that cadaveric organs readily became unfit for transplantation. Without

modern critical care and effective organ preservation, the dead-donor rule seriously limited the scope of transplant medicine.

Advancements in critical care created what Linden describes as the "patient-donor substrate" of viable cadaveric organs [3]. Contemporaneous innovations in organ preservation allowed removal and transportation of cadaveric organs with minimal ischemic insult making cadaveric organ transplants a real possibility. Ironically, advancements in intensive care also made it difficult to determine when a critically ill individual had passed away. Prior to the development of modern critical care, an individual was deemed to have died after cessation of heartbeat and breathing [37]. Loss of neurologic function inevitably led to the same result and therefore death, regardless of the cause, could be certainly determined. With advancements in perfusion and oxygenation technology in the 1960s, circulation and respiration could be maintained even when there was no neurologic function. Consequently, cessation of heartbeat and breathing was of no value in determining death in patients who had suffered serious, irreversible brain injury but who were on mechanical ventilation.

In 1968, the *Ad Hoc Committee of the Harvard Medical School* proposed irreversible coma as a criterion for determining death[2] [38]. According to the committee's report, individuals in irreversible coma are unreceptive and unresponsive to even the most noxious stimuli; they lack spontaneous breathing and other movements; no reflexes including pupillary, corneal, pharyngeal and stretch tendon reflexes or ocular movements can be detected; and the electroencephalogram shows no brain activity [38]. The concept of brain death thence introduced offered an alternative definition of death that was independent of circulation and respiration. This new development was of great import. First, it expedited substitution of mechanical ventilation with care that more befitted the dead. Second, it freed the scarce intensive care resource for those who might benefit from its use. Last, precious time saved in identifying brain-dead donors greatly improved prospects of a successful cadaveric organ transplant.

[2] Also referred to as the "Harvard Criteria"

The year of 1968 saw other important developments. The New England Organ Bank, the first ever organ procurement organization that was independent of a transplant center was established in Boston, Massachusetts [39]. In the same year, the Uniform Law Commission[3] formally recognized the power of individuals to donate organs and tissues for transplantation through the Uniform Anatomical Gift Act (UAGA) [39]. To address the significant variation in organ procurement policies across the country the UAGA, in 1972, mandated that donor card be recognized as a legally binding document in all 50 states [40]. The irreversible coma criteria and the UAGA provided the initial framework within which organ donation was handled in the 70s. Nevertheless there was wide variation in the adoption of the neurologic criteria across the country since many states, through statutory law, continued to recognize the cessation of circulation and respiration as the sole criterion for determining death.

The Uniform Law Commission attempted to address this variation by drafting the Uniform Brain Death Act in 1978. Based on the rationale that, "*brain, as the center of the human body, is its most important organ. Its irreversible functioning should be accepted as death*", the legislation deemed an individual to have died when there was "*irreversible cessation of all functioning of the brain, including the brain stem*" [41]. The actual determination of death was based on "*reasonable medical standards*." Cessation of circulation and respiration was assumed to automatically conform to the neurologic criteria and was omitted from the act itself, which proved confusing for the states that were trying to adopt the legislation.

To address this legal ambiguity, the *President's Commission*[4] in 1981 published a report[5] making several influential observations [42].

"That recent developments in medical treatment necessitate a restatement of the standards traditionally recognized for determining that death has occurred."

"That such a restatement ought preferably to be a matter of statutory law."

[3] The National Conference of Commissioners on Uniform State Laws. http://www.uniformlaws.org
[4] President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research
[5] Defining Death: A Report on the Medical, Legal and Ethical Issues in Determination of Death

"That the statutory law ought to be uniform among the several states."

"That the definition contained in the statute ought to address general physiological standards rather than medical criteria and tests, which will change with advances in biomedical knowledge and refinements in technique."

Working closely with the Uniform Law Commission and with input from the American Medical Association[6] and the American Bar Association[7], the President's Commission proposed a revised draft of the Uniform Brain Death Act. This act known as Uniform Determination of Death Act was set forth as follows [42]:

§ 1. [Determination of Death.] An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead. A determination of death must be made in accordance with accepted medical standards.

§ 2. [Uniformity of Construction and Application.] This act shall be applied and construed to effectuate its general purpose to make uniform the law with respect to the subject of this Act among states enacting it.

The Uniform Determination of Death Act served several purposes. First, the legislation established the legality of brain death as an alternative criterion for determining death where mechanical ventilation precluded the use of traditional criterion. Second, it provided a uniform basis for determining death across the country. Third, by using physiological standards instead of diagnostic tests as the basis for determination, the proposed legislation was immune to becoming obsolete when medical science advanced.

[6] http://www.ama-assn.org/ama
[7] http://www.americanbar.org/aba.html

The draft legislation was adopted by the 50 states and having settled this issue, the focus shifted towards increasing the availability of cadaveric organs.

In 1983, Surgeon General C. Everett Koop convened the first workshop on solid organ procurement for transplant [43]. The workshop culminated with the formation of the American Council on Transplantation. With the goal to *"increase availability of organs and tissues for transplantation through post mortem donation and surgical procurement",* the newly formed council identified "*promoting effective use of multiple organs*" as an important objective [43]. At that time transplant centers typically relied on the local network of donor hospitals for cadaveric organs. Specificity of the donor-recipient match meant that wastage of organs was rampant. It was increasingly evident that only a national network that offered a large donor-recipient pool would ensure that all viable cadaveric organs are matched to recipients and transplanted.

In 1984, the National Organ Transplant Act (Public Law 98-507, 98th Congress) came into effect with four important provisions. Title I created a *Task Force on Organ Procurement and Transplantation* comprising of physicians, lawyers, representatives from healthcare organizations and lay people to study and recommend improvements in the structure and practice of organ procurement and transplantation. Title II established the Organ Procurement and Transplantation Network (OPTN) as a national, integrated network of donor hospitals, transplant centers and bridging organizations. In addition, title II outlined the creation of the organ procurement organizations (OPO) that would act as the bridge between procurement and transplantation. This title also provided for the creation of a scientific registry[8]. Title III prohibited sale and purchase of human organs. Title IV provided for a demonstration project on a national bone marrow registry. The National Organ Transplant Act (NOTA) would be amended in 1990 to permanently establish and maintain the National Bone Marrow Donor Registry [41].

[8] It is now called the Scientific Registry of Transplant Recipients

When the OPTN was first established, membership in the network was voluntary and only few OPOs and transplant hospitals participated. Without participation of all OPOs and hospitals, a nationally integrated network as envisioned under NOTA, could not be realized. Without a nationally integrated network, a large donor-recipient matching pool would not be available and all donated organs would not be transplanted. To address this issue, the Social Security Act was amended through the Omnibus Budget Reconciliation Act of 1986 (Public Law 99–509) to require "*hospitals that perform organ transplants to be members of and abide by the rules and requirements of the OPTN as a condition for participation in the Medicare and Medicaid programs*" (Public Law 99–509). The amendment also required that "*to be eligible for reimbursement of organ procurement costs by Medicare or Medicaid an OPO must be a member of and abide by the rules and requirements of the OPTN*" (Public Law 99–509).

In 1987, the Uniform Law Commission revised the Uniform Anatomical Gift Act to address the changes in circumstance and practice of organ procurement and transplantation since the 1968 law [40]. Specifically, this version of the law reaffirmed the prohibition on sale of organs; guaranteed priority of the donor's wishes over the wishes of family members; required that hospitals make routine inquiry regarding the intention to donate; and permitted medical examiners to authorize organ recovery from decedents in their custody who didn't have next-of-kin [44]. The last provision was contentious leading to considerable resistance from several states. Only 26 states adopted the 1987 legislation and the remaining states enacted only parts of this legislation (especially pertaining to routine inquiry) leading to significant dissimilarities in the practice of organ procurement across the country [44].

By this time, it had also become apparent that there was a need to clarify the "*rules and requirements of the OPTN*" as set forth in the Omnibus Budget Reconciliation Act of 1986. In 1989, the Health Care Financing Administration[9] (HCFA) published an administrative rule in the Federal Register (54 FR 51802) clarifying that OPTN policies (42 CFR Part 121) must be formally approved by the Secretary

[9] Now called the Centers for Medicare and Medicaid Services (CMS)

of Health and Human Services (HHS) to be considered "*rules and requirements*" under the above mentioned amendment to the Social Security Act. Thus OPOs and hospitals in violation of OPTN's policies not approved by the Secretary as *rules and requirements* did not fall out of compliance under the Social Security Act for reimbursement of organ procurement and transplantation costs. In essence, the new administrative rule trimmed down OPTN's power to enforce compliance with its policies.

In 1991, a national workshop on increasing organ donation convened by Surgeon General Antonia Novella concluded that "*stronger efforts were needed to ensure compliance with existing routine inquiry and required request laws….. Unfortunately, most State laws contain neither provisions nor monies to assure adequate compliance*" [45]. In 1998, HCFA published a final rule for organ, tissue and eye donation (63 Federal Register 33875) as part of the revised Medicare and Medicaid Conditions of Participation for Hospitals (42 CFR Part 482). To facilitate best practices for increasing organ donation, two key requirements were added to the conditions of participation. First, hospitals must refer imminent death and deceased patients to their OPO in a timely manner. Second, only OPO staff or a trained hospital staff may approach families about organ donation. For the critical care staff, the new requirements were a departure from their traditional role. Lacking experience on this front, many hospitals struggled to implement the referral and request requirements.

In 2000, to facilitate compliance with the new rules, Health Resources and Services Administration (HRSA) published a resource guide to aid hospitals in developing training programs for referral and request procedures [46]. In the same year, the Organ Procurement Organization Certification Act of 2000 (Public Law 106-505 Sec. 701) established requirements for certification of the OPOs to receive grants from the Secretary of HHS and participate in Medicare and Medicaid programs.

In 2001, Secretary Tommy G. Thompson of Health and Human Services launched the Gift of Life Donation Initiative with a focus on increasing organ donation rates across the country. Noteworthy programs in the initiative included "Workplace Partnership for Life", "National Forum on Donor

Registries", "National Gift of Life Medal", "Driver's Education Curriculum", and "Model Donor Card" [47]. The initiative also enjoyed broad support in the community with the Coalition on Donation, the Advertising Council, the American Medical Association, state law associations, several educational and religious organizations, and donor and recipient groups actively partnering in the initiative [47].

A more recent and perhaps the most popular component of Secretary Thompson's initiative is the Organ Donation Breakthrough Collaborative. The Collaborative is modelled on the Institute for Healthcare Improvement's [10] breakthrough series. This approach expedites acquisition of new knowledge, its dissemination and widespread replication across organizations participating in the collaborative [48]. The Collaborative began in September 2003 with the primary goal of increasing the average conversion rate[11] from the then current average of 43% to 75% [49]. Through site visits and interviewing professionals from 6 OPOs and 16 hospitals known to have highest donation rates, 15 best practices were identified and disseminated to other participating OPOs and hospitals. By sharing experiences, collective problem-solving exercises and celebrating success together, a community of OPOs and hospitals committed to quality improvement has emerged. As a result, considerable increase in the number of organs available for transplantation has been realized since the collaborative began [50]. From October 2003 to September 2006, the number of organ donors increased by 22%, four times faster than preceding three years [51]. Hospitals that participated in the collaborative experienced an eight percentage point increase in donation rates from 52% to 60% while donation rates at non-participating hospitals remained unchanged at 51% [52]. Out of the 95 participating hospitals, 36 achieved a 75% conversion rate by April 2005 [53]. Some OPOs experienced increase in consent rates, albeit at one or two hospitals [54].

In 2006 after the collaborative ended, the Organ Donation and Transplantation Alliance[12] was established as a non-profit, independent organization to further capitalize on the gains realized through the

[10] www.ihi.org
[11] Conversion rate is defined as the proportion of eligible decedents that become actual donors. This metric is discussed in greater detail in the next section.
[12] http://www.organdonationalliance.org

collaborative [55]. U.S. Department of Health and Human Services' Health Resources and Services Administration (HRSA) partners with the alliance to disseminate best practices through the Donation and Transplantation Community of Practice (DTCP) [7]. The goal of the DTCP is to help OPOs and hospitals institutionalize the identified best practices. This is accomplished through web-based education[13] and interactive approaches like *Donation Service Area Teams* and *Regional Collaborative Teams* [7]. In addition, HRSA also organizes leadership meetings involving hospital CEOs and OPO presidents, task forces and national events like the National Learning Congress to sustain the quality improvement work [7].

In 2006, the Uniform Law Commission approved a new version of the Uniform Anatomical Gift Act to address the uneven adoption of the 1987 version and to harmonize it with the federal and state regulations governing the organ procurement system. The 2006 version underscored the finality of donor's anatomical gift by barring others from overriding the individual's decision to donate [56]. The legislation also recognized organ donor designation on driver's licenses, donor registration cards, and those listed in living wills as legally binding first-person authorizations. It further clarified the priority list of individuals who can authorize donation on behalf of the deceased. Importantly, the 2006 UAGA prohibited the coroners and the medical examiners from making anatomical gifts unless the authority to dispose of the decedent's body rests in them [56]. At present, all states except Delaware, Florida, New York and Pennsylvania have adopted the 2006 version. The Act is under review for adoption in Pennsylvania (2014) where the 1987 version is in effect at present [56].

In May 2006, the Centers for Medicare and Medicaid Services published the final rule (71 Federal Register 30928) on Conditions for Coverage for Organ Procurement Organizations (42 CFR Parts 413, 441, 486 & 498). The final rule set following process requirements for the OPOs as conditions for coverage under the Medicare and Medicaid programs. First, OPOs have written agreement with hospitals defining the roles and

[13] www.healthcarecommunities.org

responsibilities of each in the organ procurement process (§486.322). Second, OPOs make cooperative arrangements with tissue banks that have agreement with hospitals with which the OPO also has an agreement (§486.322). Third, OPOs provide individually-identifiable hospital specific data on organ donation and transplantation to the OPTN (§486.328), Scientific Registry of Transplant Recipients and HHS. Fourth, the OPOs assume responsibility for identification of potential donors, requesting authorization (§486.342), evaluating and managing potential donors (§486.344), organ recovery (§486.344), organ preservation and transport (§486.346), and organ allocation (§486.344). Thence the role of the OPO as a bridge between donor hospitals and transplant centers was well established through the final rule.

The U.S. organ procurement system is balanced on three fundamental legislative pillars- the Uniform Anatomical Gift Act, the Uniform Determination of Death Act and the National Organ Transplant Act. Numerous amendments, and DHHS rules and regulations (e.g., CMS Conditions of Participation) have refined these laws and facilitate compliance. In section 1.4, we describe the current form of the organ procurement system and the central role that organ procurement organizations play in this system. Two core activities of the organ procurement organizations, clinical services and public education, serve as the conceptual framework for studies 1 and 2. Study 3 will build on the results of study 2.

1.4. THE ORGAN PROCUREMENT AND TRANSPLANTATION NETWORK

The health benefit from organ transplants is a function of two processes. The more conspicuous process at the "front end" is where organs are **surgically transplanted** into patients suffering from end-stage organ failure. The surgical procedure is carried out at hospitals with specialized transplant programs and by highly skilled surgeons. Less noticeable, at the "back end" is the **organ procurement** process that involves making viable organs available for transplantation. While any hospital may have a potential donor, specialized hospitals with emergency and critical care facilities that see patients with traumatic head injuries

or terminally ill patients are the most likely source of organ donors. Most transplant centers also care for such patients and are a source of donated organs but the need to match organs with recipients necessitates dependence on other “donor hospitals”. It is for this reason that many transplant centers operated in-house organ procurement centers before the OPTN came into existence. Nevertheless the supply of viable organs through these procurement centers has been limited by the small network of regional donor hospitals that have had no incentives to make organs available for transplants.

In 1984, the National Organ Transplant Act established the OPTN as a nationally integrated system to overcome the “regional” network barrier. In addition, the CMS Conditions of Participation (42 CFR 482.5) required hospitals to identify donors and help procure organs for transplant centers. Also established under NOTA, organ procurement organizations assumed the role of procurement centers to facilitate the flow of viable organs from donor hospitals to transplant centers. The CMS Conditions for Coverage for the OPOs (42 CFR Parts 413, 441, 486 & 498,) and Conditions of Participation for the Hospitals (42 CFR Part 482) govern the OPTN activities of the respective organizations for compliance with public laws. These final rules that set forth the conditions for reimbursement under the Medicare and Medicaid programs form the “regulatory backbone” of the whole OPTN operation.

The OPTN is a public-private partnership that enables all professionals involved in the donation and transplantation system to interact and coordinate organ sharing 24 hours a day. By facilitating communication across a large geographic area, the OPTN serves to improve effectiveness, efficiency, and equity in organ sharing nationwide and consequently increase the supply of donated organs. The OPTN operates the national database of all patients in the U.S. waiting for a transplant. In addition, the OPTN develops policies and procedures for organ recovery and allocation, and evaluates the OPOs and transplant centers for compliance.

The contract for the operation of the OPTN was awarded in 1986 [39] to Richmond-based private, not-for-profit organization called the United Network for Organ Sharing[14] [47]. As a move towards a "*fast, reliable system to match organs to patient*" UNOS started using an internet-based system called UNet in 1999 to connect transplant hospitals and OPOs together [57]. UNet allows transplant hospitals to list patients on the transplant waiting list, complete and submit OPTN data forms, status justification forms and access reports in a real-time, secure, and a confidential environment. The OPOs use UNet to add donors and run donor-recipient matching lists. Donated organs are also offered to transplant centers through UNet.

1.5. ORGAN PROCURMEENT ORGANIZATIONS

OPOs are federally designated, not-for-profit organizations established under the NOTA as bridging organizations between donor hospitals and transplant centers. At present, there are 58 OPOs throughout the United States [58]. Eight of these OPOs are hospital-based with the remainder being independent [58]. Each OPO serves an exclusive geographical region known as a donation service area (DSA). The size of the DSA depends on the geography, population and rural-urban character of the region and varies greatly among the OPOs. LifeCenter Northwest, for instance, has the largest DSA in the country spanning across all of Alaska and Montana, almost all of Washington and parts of Idaho serving an area of over 800,000 square miles [59]. LifeLink of Puerto Rico, on the other hand, has the smallest DSA in the country with an area of 3,557 square miles [60].

In addition to recovery of solid organs, most OPOs are involved in tissue and cornea recovery. OPOs employ variable staffing approach to address the unique challenges that their DSA's geography and healthcare system pose. OPOs with a smaller DSA typically carry out their operations from one center.

[14] www.unos.org

Those with DSAs spanning multiple states may also have regional offices. While most donor hospitals are served by OPO professionals operating from the OPO's office, OPOs maintain permanent presence at Level 1 trauma centers through in-house coordinators. Number of employees at any OPO is largely determined by the population it serves and the number of hospitals in its DSA [61]. Due to inherent demographic differences among DSA's, the donation and organ recovery rates vary widely across the OPOs. In 2004, the donation rate varied from 34.3 percent of eligible deaths to 77.9 percent of eligible deaths [61]. In 2011, organs recovered per donor ranged from 2.91 to 4.19 [62].

1.5.1. The Center for Organ Recovery and Education

The Center for Organ Recovery and Education (CORE) is the OPO that serves western Pennsylvania and almost all of West Virginia. Founded in 1977, CORE is headquartered in Pittsburgh, PA with a regional office in Charleston, WV. Its region encompasses 155 hospitals serving 5.5 million people across 32 counties in Pennsylvania, 50 counties in West Virginia and Chemung County in New York [63]. CORE's DSA covers 45,905 square miles and is the 22nd largest in the country [64]. Each hospital in CORE's DSA serves as a source of organ donors. In addition, five of these hospitals also have transplant program: Children's Hospital of Pittsburgh, UPMC Presbyterian, Veterans Administration Medical Center; Allegheny General Hospital, and Charleston Area Medical Center in West Virginia. UPMC Presbyterian and Allegheny General Hospitals also have the highest donation potential in CORE's DSA. CORE maintains permanent presence in these hospitals through in-house coordinators [65]. While most organs are transplanted locally, organs recovered by CORE are transplanted regionally and nationally. In 2013, one liver recovered by CORE was transplanted as far away as San Francisco, California [64].

1.5.2. OPO Performance Assessment and Certification

In addition to the process requirements, the Organ Procurement Organization Certification Act of 2000 (Public Law 106-505 Sec. 701) also establishes performance requirements for certification of the OPOs to receive grants from the Secretary of HHS and participate in Medicare and Medicaid programs. OPOs are certified every four years. The certification process relies on multiple outcome measures set forth in the CMS Conditions for Coverage for OPOs (42 CFR §486.318). OPOs are assessed on three outcome measures: 1) donation rate; 2) observed over expected donation rate; and 3) organs transplanted per donor, and organs used for research per donor.

Donation Rate. Donation rate is the number of eligible donors (actual donors) divided by the number of eligible deaths. An eligible death for organ donation is defined as a patient 70 years old or younger, who is legally declared brain dead, and who does not exhibit any of the exclusionary conditions listed in 42 CFR §486.302. These conditions are also listed in Appendix A of this dissertation. This outcome measure allows CMS to assess how well has an OPO performed with regard to the donation potential of its service area, as well as, how well it has performed when compared to other OPOs. When comparing an OPO's donation rate to other OPOs (the national average), only the standard criteria donors[15] are considered in the assessment. In this case, the donate rate is defined as the number of SCDs divided by the number of eligible deaths. When an OPO's performance is assessed with regard to the donation potential of its service area, donors after cardiac death[16] and expanded criteria donors[17] are also considered. In this case, the number of DCDs and ECDs are added to the number of SCDs in the numerator and to the number of eligible deaths in the denominator. The two separate definitions of the donation rate serve two goals. First, for

[15] Standard criteria donors (SCD) are actual donors who meet the eligible death criteria.
[16] Donors after cardiac death (DCD) are declared dead using the circulatory determination of death criteria. According to the Uniform Determination of Death Act, death can be declared using the neurologic criteria (SCD or ECD) or the cardiorespiratory criteria (DCD).
[17] Expanded criteria donors (ECD) are donors that do not fit either the SCD or DCD definition of donors. CMS purposely uses a broad definition of ECD since technological advancements in transplantation field can make narrower definition obsolete.

comparison with national average, OPOs with a limited potential for DCD and ECD are not penalized. Second, all OPOs are nevertheless incentivized to improve DCD and ECD donation rates and expand the donor pool.

Observed over Expected Donation Rate. The second outcome measure provides an independent statistical assessment of each OPO's performance by calculating an expected donation rate using the statistical methodology developed by the SRTR. SRTR methodology uses hospital characteristics to determine the expected donation rate for each OPO: Level I or Level II trauma center, size of the metropolitan statistical area, CMS case-mix index, total number of all beds, number of ICU beds, primary service, availability of neurosurgical services, and hospital control or ownership [66, 67]. The expected referral rate[18] for each OPO is also adjusted for its area-specific hospital characteristics and is used to calculate the expected number of eligible deaths. A ratio of the observed over expected donation rate is calculated with a ratio greater than 1 signifying better than expected performance and vice versa. To meet this performance standard the observed donation rate of an OPO must not be significantly less than the expected donation rate for its service area at a probability level of 0.05.

Organs Transplanted per Donor. This outcome measure provides an assessment of the extent to which OPOs are able to achieve the ultimate goal of providing organs for transplantation. To be recertified, CMS requires that OPOs do not fall 1 standard deviation below the national mean, averaged over 3 years during the recertification cycle, on at least two of the following three measures: 1) number of organs transplanted per standard criteria donor; 2) number of organs transplanted per expanded criteria donor; and 3) number of organs used for research per donor.

If an OPO fails to meet the performance standards, the OPO is required to file a corrective action plan with a three-year grace period to implement the plan. During the grace period, the OPO does not risk decertification. However, if the OPO still fails to meet the performance standards, the OPO loses

[18] Referral rate is the percentage of deaths that are referred to the OPO.

certification and its service area is opened to auction for other OPOs. The affected OPO can appeal the decertification to the Secretary on substantive and procedural grounds.

1.5.3. Functions of OPOs

The *Association of Organ Procurement Organizations* identifies four core functions of an OPO [58]. Under clinical services, OPO professionals provide support to potential donors' families throughout the dying process. These professionals are available at all times to ensure that patients' donation decisions are honored. In addition, these professionals collaborate with the hospital's staff to maintain the donor's organ function, evaluate the medical suitability of the potential donor, offer families the opportunity for organ donation, match organs with recipients through the OPTN and coordinate surgical recovery of donated organs.

Hospital development involves professionals who act as a liaison with the hospitals in the OPOs service area. These "professional services liaisons" (PSLs) provide education and training to the hospital personnel who are involved in the donation process. Training programs are tailored to the role that each hospital employee plays in the donation process. In addition, these professionals are responsible for developing effective communication plans and strong relationship with their hospitals. The goal of these activities is to build strong partnership with the donor hospitals and eliminate errors that may jeopardize potential for donation.

Under donor family services, OPOs offer bereavement services to the families of donors including a library of resources available to the family members; and a quiet room to meditate, read and create memory quilt squares, scrapbooks or photo albums. Many OPOs hold annual remembrance events for the donor families or make their staff available to listen to and support donor families throughout the bereavement process. These activities aim to honor the donors and build public trust. OPOs also connect

donor families with recipients of organ transplants through letters or in some circumstances through in-person meetings.

Through public education efforts, OPOs strive to increase awareness about organ donation. These efforts include mass media campaigns on radio, TV and print; and interpersonal campaigns at faith-based events, youth festivals, sporting events, driver's license bureaus, workplaces and other community events. The goal of the outreach is to encourage people in the communities they serve to join the state donor registry.

1.5.4. Clinical Services- the Organ Donation Process

Clinical services include all OPO interactions with a donor hospital that directly result in procurement of organs for transplant. Before organs can be recovered, a complex set of procedures must be executed to ensure that patients who have the potential to donate organs become donors on death. This set of procedures is known as the organ donation process. The organ donation process is typically housed in the critical care unit where patients with catastrophic brain injuries or who are terminally ill, are cared for. This process is the single most important determinant of whether organs will be recovered from a potential donor. Consequently, this process has received most attention from policymakers.

"*[E]very system is perfectly designed to achieve the results it achieves*" [68]. Thus the system must be redesigned if different results are desired. Critical care units have historically operated with the goal of caring for the sickest patients rather than procuring organs. Since the organ donation process essentially begins with the critical care staff notifying the OPO, lack of attention to prompt identification of potential donors and referral has resulted in numerous opportunities for donation being lost over the years. For instance in 1990, Gortmarker et al. estimated that 27 percent of donors were lost because they were not identified [69]. Sheehy et al. estimated that between 1997 and 1999, 20 percent of patients with catastrophic

brain injuries (those best suited for organ donation) were not referred to the OPOs [70]. To address this problem, the breakthrough collaborative in 2003 recommended that the critical care system be redesigned to incorporate the organ donation process into the routine roles and responsibilities of the critical care staff [49]. Observing that the organ donation process and end-of-life care share a common framework of respect and compassion for patients and their families, the Institute of Medicine has reaffirmed that the organ donation process should be seamlessly integrated into end-of-life care [71].

The organ donation process is initiated when a terminally ill patient is identified to be at risk of imminent death. Figure 2 presents a schematic of the organ donation process employed in all hospitals that fall in CORE's service area. As the schematic suggests, the process is not strictly linear as several components of the process overlap in time. For convenience, the organ donation process is described under six topic areas: 1) identification and referral; 2) evaluating medical suitability; 3) authorization for donation; 4) determination of death; 5) donor management; and 6) recovery and allocation.

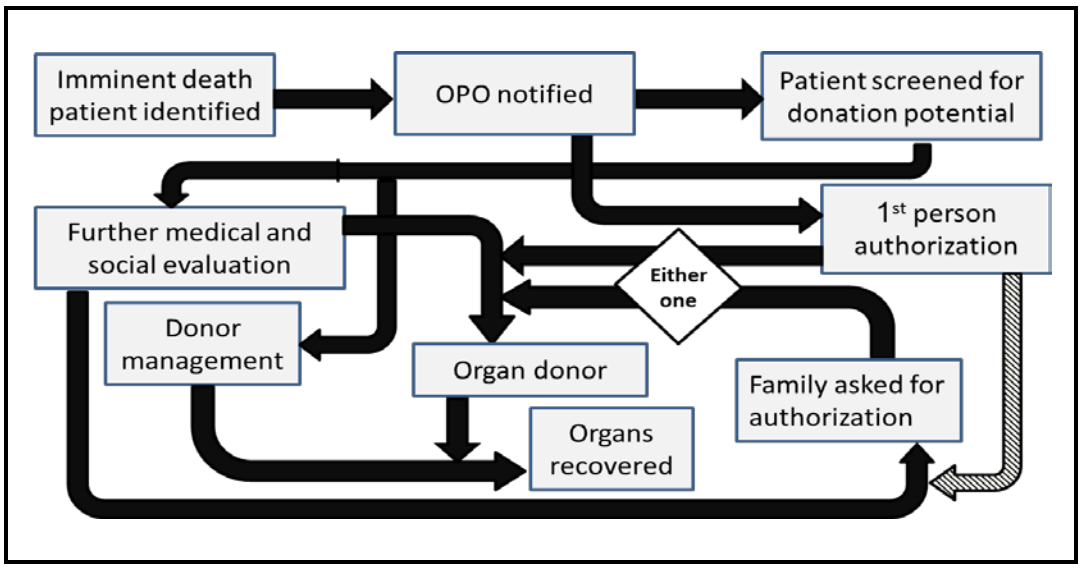


Figure 2: The organ donation process

1.5.4.1. Identification of Imminent Death and Timely Referral to the OPO

In compliance with the CMS Conditions of Participation, all hospitals in the U.S. are required to identify patients whose death is "imminent" or have died and report them to the regional OPO within 1 hour of determination. The purpose of this regulation and associated state and federal laws is to maximize success of organ transplantation by timely identification and referral of the potential donor, which allows for appropriate donor family support and optimum donor management.

The *Advisory Committee on Organ Transplantation* recommends following guidelines for diagnosis of imminent death [72]:

A patient with severe, acute brain injury:

Who requires mechanical ventilation; AND

Is in an Intensive Care Unit or Emergency Department; AND

Has clinical findings consistent with a Glasgow Coma Score (GCS) that is less than or equal to a mutually-agreed-upon threshold; OR

For whom physicians are evaluating a diagnosis of brain death; OR

For whom a physician has ordered that life sustaining therapies be withdrawn, pursuant to the family's decision.

The Glasgow Coma Scale is provided in Appendix B. In CORE's service area, these guidelines are operationalized through the use of trigger cards. CORE emphasizes that all hospitals anticipate imminent death and promptly refer the patient to CORE. In CORE's donation service area, a patient meeting any of the criteria presented in Table 1 will trigger a referral.

Table 1: Imminent death criteria used by CORE

- *Death expected within 24 to 48 hours.*
- *Patient has suffered severe, irreversible brain injury.*
- *A Glasgow Coma Scale score of 5 or less.*
- *Anoxia secondary to cardiac arrest.*
- *Change in medical care protocol from active treatment to "Do Not Resuscitate" or "Comfort Only" or "De-escalation of Care" being considered.*

Referrals are generally made through a phone call to CORE's donor referral center that operates 24-hours a day. When CORE receives a phone call, a set of standard procedures is initiated. First, the identities of the referring organization and the potential donor are established and verified. Next, the referral center executive queries the state donor registry to determine if the patient has registered as an organ donor. At the same time, the patient is preliminarily screened for conditions that might rule out prospects of organ donation and at the same time determine if the potential donor will be a standard, cardiac death or expanded criteria donor. The exclusionary conditions are listed in CMS Conditions of Coverage for the OPOs as well as Appendix A of this dissertation. If the patient clears preliminary screening, an organ procurement coordinator (OPC), who is a highly trained medical representative from CORE is assigned to the case. While the procurement coordinator is not involved in patient's care, this person is responsible for all procedures that must be carried out to preserve the opportunity for organ donation. These procedures include detailed medical evaluation of the potential donor, offering support to the family, requesting the family to authorize donation (if the patient is not already on the donor registry), and donor management. In addition, the procurement coordinator is also responsible for coordinating with the organ recovery team, organ preservation and allocation.

1.5.4.2. Evaluating Medical Suitability

All activities to determine medical suitability of the donor are governed by the OPTN Policies (42 CFR 121) [73]. Each OPO must establish acceptance criteria for deceased donors and organs, and evaluate potential donors for fulfillment of those criteria. Once the OPC is assigned the case, the process of evaluating the patient's medical suitability for donating organs is initiated. The goals of the medical suitability evaluation are: 1) to identify conditions that may make the potential donor ineligible; 2) to determine risk of infections and employ strategies to alleviate that risk by treating the donor for the infection; and 3) to implement preventive measures including vaccination in the potential recipient [74].

Medical and Behavioral History. OPTN requires that the medical history includes each of the following: 1) laboratory tests and results used to identify transmissible disease, treated and untreated, that if transmitted will adversely impact the recipient; 2) factors that are associated with increased risk of infectious disease transmission including HIV, HBV and HCV; and 3) prior exposure to Human Pituitary Derived Growth Hormone to determine the risk of prion disease. In addition, obtaining information on vaccination status, residence or travel to disease endemic areas, drug use, risky sexual behavior and incarceration are also recommended [75]. Identified infections, if any, do not automatically preclude transplantation in all cases and in all infections. The urgency of the recipient's need and the recipient's infection status are also factored in while making a decision to accept or reject the organ. For instance, if the donor is HCV positive and the recipient is negative, the organ is rejected. But if the donor and recipient are HCV positive, the organ can be accepted for transplant. The medical and behavioral history is obtained from the patient's medical records and from interviewing close associates. For donors less than 18 months old, history of the potential donor and the mother is recorded.

Hemodilution Assessment. All donor serological screening tests must be performed on non-hemodiluted samples to preclude altered serological test results. The extent of hemodilution is determined from the medical record detailing all blood products and intravenous fluid transfusions that the potential

donor has received since admission. In addition, the OPO assesses all blood samples obtained for serology screening for the extent of hemodilution using a U.S. Food and Drug Administration (FDA) approved hemodilution calculation. For infants younger than 3 months old with diluted blood, serology tests can be performed using the blood from the biological mother.

Serology Screening and Blood Typing. Most OPOs operate an in-house laboratory to run serology tests and blood typing on potential donors. Given the uncertainty about when a potential donor may become available and the short timeframe within which medical evaluation must be completed, laboratories involved in potential donor serological screening are operated 24 hours. Blood samples from the potential donor are tested for blood type and subtype. In order to prevent donor-recipient blood type mismatch, OPTN employs stringent reporting requirements on blood typing. These include primary reporting and secondary reporting (by an individual other than the one who entered the primary reports) to UNet. There is consensus among the transplantation community that routine serological screening of potential organ donors should include testing for HIV, human T lymphotropic virus, hepatitis B virus, hepatitis C virus, and cytomegalovirus [76].

1.5.4.3. Authorization for Donation

Authorization for organ donation is governed by the Uniform Anatomical Gift Act of 1968 (revised 1987, 2006). According to this act, organs can be donated either through first-person authorization or next-of-kin authorization.

First-person Authorization

First-person authorization for donation (authorization by the donor himself or herself) documents an individual's desire to make the anatomical gift and requires no further confirmation from the next-of-kin. The Uniform Anatomical Gift Act protects the right of individuals to donate their organs and requires that OPOs and hospitals honor the decedent's wishes. An individual can authorize organ donation either through filling a donor card, registering online, designation on driver's license or state ID, or by executing a living will. The most common method is to join a state donor registry when renewing a driver's license or state ID. While the driver's license/state ID may display an individual's designation status, the actual registration is in a state operated secure database. According to the Donor Designation Collaborative, the design of the registry plays an important role in its effectiveness [77]. Several design factors have been identified that determine whether a donor registry is effective. These criteria are listed in Appendix C. When an imminent death patient is referred to the OPO, the donor referral coordinator queries the state donor registry to determine the patient's donor designation status. If the patient is a designated donor and medically suitable for donation, the OPO is legally obligated to honor the donor's wish.

Next-of-kin Authorization

Next-of-kin authorization is only considered if the potential donor is medically suitable to donate and if there is no evidence of first-person authorization. While requesting authorization, the procurement coordinator provides all possible donation options; discusses the impact of donation on funeral arrangements; gives a general description of the recovery process; and explains that the family will not incur any cost for donation. Institutional support personnel including social workers, a chaplain and nursing staff are involved as appropriate. Two important considerations for this type of authorization are: 1) the individual to be approached for authorization; and 2) the timing of the request for donation.

Individual to be approached for authorization: The Uniform Anatomical Gift Act (UAGA) establishes the order of priority in which the next-of-kin are approached for organ donation conversation. According to UAGA, *"an anatomical gift of a decedent's body or part for purpose of transplantation, therapy, research, or education may be made by any member of the following classes of persons who is reasonably available, in the order of priority listed:*

> *(1) an agent of the decedent at the time of death who could have made an anatomical gift immediately before the decedent's death;*
> *(2) the spouse of the decedent;*
> *(3) adult children of the decedent;*
> *(4) parents of the decedent;*
> *(5) adult siblings of the decedent;*
> *(6) adult grandchildren of the decedent;*
> *(7) grandparents of the decedent;*
> *(8) an adult who exhibited special care and concern for the decedent;*
> *(9) the persons who were acting as the [guardians] of the person of the decedent at the time of death; and*
> *(10) any other person having the authority to dispose of the decedent's body."*

UAGA requires OPOs to make reasonable efforts to approach the highest order next-of-kin, and if not available, move down the order to the next available next-of-kin. Further, *"A person may not make an anatomical gift if, at the time of the decedent's death, a person in a prior class under subsection (a) is reasonably available to make or to object to the making of an anatomical gift."* If two or more individuals are in the same class, consensus of the absolute majority is required for authorization.

Timing of the authorization request: The OPO community believes that timing of the organ donation request is crucial and that the request for authorization should be "decoupled" from the news that the family's loved one has died. Decoupling refers to the temporal separation of pronouncement of death

from the request for donation. Bartucci and Bishop recommend that request for organ donation to be made only after the family has had sufficient time to accept the death of their loved one [78]. Rudy et al. also suggest similar disconnect in the pronouncement of death and request for donation [79]. Empirical evidence testing this notion however is mixed but suggestive of a weak effect of timing on authorization. Garrison et al. have found that the family authorization rate increased from 18% to 61% when the request for donation was made separate from the time of explanation of death [80]. Cutler et al. also found that authorization was more likely if the request was made after death was pronounced (78%) than if the request for donation was made either before (60%) or at the time of pronouncement of death (58%) [81]. Morris et al. however have found no difference in the authorization rate whether the request for donation was made immediately after, within 12 hours, or after 12 hours of pronouncement of death [82]. Niles and Mattice found that authorization rates were similar when the request for donation was made either before (62%) or after (57%) the pronouncement of death but they differed significantly from request made at the time of pronouncement of death (25%) [83]. In a multivariate analysis, Siminoff et al. found that donation rates did not differ significantly regardless of whether the request was made before (51%), concurrently (63%), or after (57%) death was pronounced [84]. Nevertheless, it is a common practice among the OPOs to decouple the request for donation from pronouncement of death.

1.5.4.4. Determining Death

A fundamental premise of organ donation is the dead-donor rule that requires that donors must be dead before their vital organs can be recovered. The Uniform Determination of Death Act sets forth a broad physiologic definition of death: *An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead* [42]. Because protocols and procedures to recover organs from individuals declared dead using the two criteria are different, the *Institute of Medicine* has recommended the use of "donation after neurologic determination of death" and "donation after circulatory determination of death"

respectively to distinguish between the two in context of organ donation [71]. Brain death testing and neurologic determination of death are used interchangeably for convenience.

Neurologic Determination of Death

In the United States, the Uniform Determination of Death Act sets the general legal standard for neurologic determination of death but the law does not establish the clinical criteria for this determination. The *Quality Standards Subcommittee of the American Academy of Neurology* has developed the clinical criteria for neurologic determination of death, which are detailed in the *1995 American Academy of Neurology Practice Parameters* [85]. Brain death is defined as the "irreversible loss of all brain functions including brain stem reflexes" [85]. Brain death is frequently a result of severe head injury or aneurysmal subarachnoid hemorrhage [85].

Since declaration of death is irrevocable, brain death determination involves a rigorous examination to see if the patient meets the clinical criteria for brain death diagnosis. Determining death using the neurologic criteria involves at least one comprehensive neurologic exam after a prolonged observation period, to exclude any possibility of neurologic recovery. There is extensive variation in the recommended length of observation period worldwide and evidence on minimally acceptable observation period is insufficient [86]. While the observation period can vary on case-by-case basis, a period of at least 24 hours is recommended when the cause of coma is undetermined [87]. Brain death diagnosis is made by physicians who have evaluated the medical history of the patient and completed the neurologic examination. Some states including Pennsylvania and West Virginia require a second comprehensive neurologic examination. Although the same physician may do both exams, hospitals often require different physicians to conduct the two exams. The importance of the second neurologic exam lies in establishing the irreversibility of the condition determined during the first exam. While the intervening period between the two exams is arbitrary, a period of 6 hours is considered reasonable [85]. In children (37 weeks to 18 years), the

recommended observation period is longer (12 hours for 1 year or older to 48 hours for 7 days to 2 months old) [88]. The clinical criteria are listed in Appendix D.

Circulatory Determination of Death

Donation after circulatory determination of death (DCDD) is considered in cases where: 1) the neurologic criteria cannot be fulfilled in spite of the presence of catastrophic brain injury and the patient's family has requested withdrawal of life support; or 2) when neurologic determination of death cannot be made due to severe hemodynamic instability [71, 89]. In either case, there is no expectation of meaningful survival in patients being considered for circulatory determination of death [90, 91]. At this time, the OPC talks to the family about the process of withdrawing life-support and the opportunity for organ donation. If the patient is a designated organ donor or if the family authorizes donation, the patient is evaluated for the likelihood of passing away within 60 minutes. This evaluation involves several assessments including the T-piece trail.

In general, the exact set of procedures to be followed during the withdrawal of ventilator support is governed by individual hospital policies. CORE gets involved only if donation is anticipated. In CORE's DSA, hospitals follow the *Pittsburgh Protocol*[19] for donation after circulatory determination of death [92]. The patient is taken to the operating room and comfort measures are provided. The attending physician from the hospital is in charge of withdrawal of support. Once the physician deems that the patient is comfortable, ventilator and oxygen perfusion support is withdrawn. Death is pronounced two minutes after loss of pulse, apnea, and unresponsiveness to noxious stimuli.

[19] University of Pittsburgh Medical Center policy and procedure manual. Management of terminally ill patients who may become organ donors after death.

The two minute period has invited mixed reactions. Critics argue that some patients can be resuscitated even at two minutes after cardiorespiratory arrest, thus the cessation of cardiopulmonary function is not irreversible and the patient is not dead by the legal definition [93]. However, those in support of the protocol have argued that resuscitation in such patients is contrary to patients' wishes since the patients (or their surrogate decision makers) have requested withdrawal of life support [94]. For this reason, the *Council on Ethical and Judicial Affairs*[20] views the loss of cardiopulmonary function in these patients as irreversible [95]. The *Institute of Medicine* has recommended that death should be pronounced 5 minutes after cardiorespiratory arrest [90]. The disadvantage of waiting this long is that organs begin to rapidly lose viability once oxygenation is lost after cardiopulmonary failure. Since there is no evidence that patients can auto-resuscitate after 2 minutes [23, 28], the *Society of Critical Care Medicine* and the *American Society of Transplant Surgeons* (ASTS) agree with a waiting period of two minutes to minimize warm ischemic insult to the organs and maximize their transplant potential [89, 96].

Until the attending physician declares the patient dead, patient management continues to be under the control of the hospital and the recovery surgeon or team has no contact with the patient. When conflicting interests arise, as when a member of the transplant team shares patient care duties, the ASTS recommends that the transplant team member in such cases shall cede patient care responsibilities to someone who is not involved in the organ recovery/transplant process [89]. In some cases, the patient does not pass away in the expected time period after removal of ventilator support. In such cases, the donation process is aborted and the patient is returned to the intensive care unit or the ward and made comfortable [23, 90].

[20] The American Medical Association Council on Ethical and Judicial Affairs

1.5.4.5. Donor Management

Once the potential donor is declared dead, the OPC begins medical management of the potential donor to preserve organ viability. Systemic physiologic changes that accompany brain death occur as different parts of the brain undergo ischemic injury. Most common pathophysiologic conditions observed after brain death are hypotension, diabetes insipidus, disseminated intravascular coagulation, cardiac arrhythmias, pulmonary edema and metabolic acidosis [97]. These conditions are a result of a complex interaction of neural, hormonal and immunologic derangements that begin to precipitate as soon as the central nervous system activity ceases. Donor management ensures the viability of organs by minimizing the insult to the organs. In addition to delayed and poor graft function, cadaveric organs transplanted from improperly managed donor are more likely to fail due to increased and severe acute rejection by the host [98]. Evidence also suggests that long-term graft function may be determined by changes that occur early in death [98]. For these reasons, many OPOs and hospitals employ a more aggressive donor management protocol. In addition to early identification of a potential donor, and intensive care unit admission and management, donor management procedures are initiated regardless of authorization status of the donor [99]. For donation after circulatory determination of death, medications that improve quality of organs may be administered prior to death. The Institute of Medicine notes that while myths about these medications hastening or even causing death exist, these medications are considered to be safe by experts in the field [71].

OPTN requires OPOs to make reasonable efforts to maintain adequate blood pressure for perfusion of organs; monitor the potential donor's vital signs; administer IV therapy or drugs as required; administer antibiotic therapy when required; and administer and monitor fluid intake and output [73]. CORE uses a standard order set for donor management for the 155 hospitals in its DSA. Structured donor management protocols improve adherence to quality care and significantly increase the number of organs transplanted without compromising the quality of the organ [100]. The exact donor management guidelines and critical

care endpoints vary by the OPO, the hospital as well as the specific organs being recovered [101]. The goals of CORE's donor management order set are to achieve a set of specific critical care endpoints. Specific donor management and the critical care endpoints that CORE uses are listed in Appendix E.

1.5.4.6. Organ Recovery and Allocation

Almost all organs have already been designated for transplant to a specific recipient before organs are removed. Organs can be recovered only after authorization (either first-person or next-of-kin) has been obtained. For donors less than 18 years old, authorization from the parents must be obtained even if the potential donor is listed on the donor registry. OPTN prohibits the attending physician or the physician who declares the time of potential donor's death from recovering the organs [73]. Organs are typically recovered by the transplant team in accordance with any specific requests for authorization including which organs may be recovered. Although specific processes in organ recovery may vary by the OPO, all organs are recovered using standard surgical techniques in a sterile environment. Flush solutions, additives and preservation media are made available for immediate extra-corporeal preservation. CORE maintains detailed operative notes on the recovery procedure. The organs are placed in sterile packaging and transported to the recipient's transplant hospital. Organ abnormalities and surgical damage, if any, are also documented at this stage.

The allocation process typically begins before organs are recovered to minimize the warm ischemic insult. Once an organ is deemed medically suitable for donation, the potential donor's information is entered into UNet to match the donor's organs with recipients on the transplant waiting list. Specific queries are run for each eligible organ. UNet then generates a priority list of waitlisted patients based on a number of suitability factors. These factors include geographical proximity of the recipient to the donor, time spent on the waiting list, potential recipient's health status; and medical factors like physical characteristics of the donor and the recipient, HLA crossmatch, blood type and subtype. In addition, for each organ, allocation

policies differ in the impact that each factor has on where the potential recipients are placed on the priority match list. The most recent allocation policies in effect as of March 2012 are described in detail by Smith et al. for kidneys, pancreas and liver [102]; and Colvin-Adams et al. for lungs and heart [103]. Once the list is generated for each individual organ, the OPO offers the organ to the transplant program of the top-listed waiting list candidate. After the recipient's transplant surgeon accepts the organ, an organ recovery surgery is arranged at the donor's hospital.

1.6. THE ORGAN DONATION CRITICAL PATHWAY

Since the recommendations of the breakthrough collaborative, critical pathways for organ donation have evolved to maximize the quality of end-of-life care while preserving the opportunity for donation. Critical pathways help improve quality of care in high volume and high risk procedures [104]. In the context of organ donation, "high volume" means the organ donation process must be initiated every time a patient nears death. "High risk" signifies the high likelihood of losing viable organs if the donation process is not optimally timed and sequenced. Consistent with the definition of critical pathway set forth by Coffey et al. [104], the organ donation process involves comprehensive decision making by the healthcare team and the patient's family, timely execution of interventions, collaboration between hospital and OPO staff, and case management of the donation aspect of patient care by the procurement coordinator.

Adopted from the industry, the critical pathway approach was first employed in the U.S. healthcare in the 1980s during the time when prospective payment system was being implemented [104]. There is growing consensus worldwide that a standard critical pathway for organ donation can improve organ donation outcomes. In 2010, the *Madrid Resolution on Organ Donation and Transplantation* [21]

[21] The Third World Health Organization Global Consultation on Organ Donation and Transplantation: Striving to Achieve Self-Sufficiency held in Madrid, Spain, on March 23–25, 2010.

recommended that the organ donation critical pathway be used internationally to facilitate donation in as many situations as possible [105]. In 2011, standardized critical pathways for organ donation were developed that could be used in healthcare settings worldwide [106].

In the U.S., standardized protocols for organ donation have been jointly developed by the OPOs and their partnering hospitals. These protocols incorporate the best practices that are being continually identified and disseminated through the Donation and Transplantation Community of Practice and the National Learning Congress. Although OPOs and the critical care staff in the hospitals served by the OPOs work closely to adhere to the best practices, the complexity of critical care can sometimes lead to deviations from best practices. OPOs identify these deviations from best practices by different names including "process breakdown", "deviation", "process improvement area" etc. [107] and spend considerable resources in identifying and addressing them. This dissertation makes use of the term "process breakdown" to identify the deviation from best practice since this term is indicative of both, a disruption in the donation process as well as a breakdown in the OPO-hospital coordination. Process breakdown is a generic term applied to a set of failures in the donation process that can jeopardize the opportunity for donation. Table 2 presents a list of process breakdowns that CORE identifies, records and resolves on a day-to-day basis as well as their consequence. While many process breakdowns including untimely referral, suboptimal request for donation, and early extubation are readily and objectively identifiable, others like inadequate donor management require some amount of subjective assessment.

While several studies[22] have identified a relationship between process breakdowns and conversion rate[23], it is unclear how process breakdowns affect the supply of viable organs. In addition, existing literature does not account for other factors that affect donation rates. Chapter 2 examines these relationships while controlling for other factors that are known to affect organ donation.

[22] The studies are reviewed in the Discussion section of chapter 2 of this dissertation.
[23] Conversion rate is defined as the number of organ donors divided by the number of eligible deaths. This is discussed in detail in chapter 2 of the dissertation.

What is the effect of process breakdowns on availability of transplantable organs?

…..***Question 1***

Table 2: Process breakdowns and their consequences

Name	Description	Consequences
Missed Referral	The OPO was never notified about the deceased. Unaccounted patient deaths are found during medical/death record review.	Any opportunity for donation is lost.
Untimely Referral	The OPO was not notified about the imminent death patient within 1 hour of determination.	OPO gets less time to evaluate the donation potential and provide support to the donor family. Increases the risk of deceleration of care or early extubation (discussed in the table).
Suboptimal Request for Donation	Either the timing of the request is poor or the requestor is not the designated requestor. Poor timing of request include before or soon after the family is informed about patient's death.	The risk of family refusing to donate is significantly increased.
Inadequate Donor Management	Lack of hospital staff support in donor management. Potential donor's metabolic derangement is not controlled.	Organ viability is compromised. May potentially lead to less number of organs being transplanted from the donor.
Deceleration of Care	The referral is made timey but medical care is decelerated before the organ procurement coordinator becomes involved in the case.	Either organ viability is compromised or donation opportunity is totally lost.
Early Extubation	Initial referral is made on time but the patient is withdrawn from the ventilator before the family is offered the opportunity to donate.	Opportunity for donation is lost.
Body released to funeral home	The body is released to the funeral home without informing the OPO.	Opportunity for tissue donation is lost.

1.7. PUBLIC EDUCATION- ENCOURAGING DONOR DESIGNATION

Evidence on the inefficiency of the national organ procurement system began to emerge as far back as in 1992. That year, Evans et al. estimated the efficiency of the organ procurement efforts between 37 percent and 59 percent [108]. Recent evidence also suggests that the current shortage of organs is more likely due to the inefficiency in the procurement system rather than a limited potential donor pool. In each year between 1997 through 1999, there were an estimated 10,500 to 13,800 brain dead potential donors [70]. Yet there were no more than 5,824 deceased donors in any of these years [1]. The attrition in the potential donor pool is a result of successive loss of individuals at two stages in the organ donation process. First, there is a failure to identify patients at imminent risk of death or decedents with potential for donation. Second, potential donors are identified, referred, evaluated and managed appropriately but the family refuses to authorize donation.

In 1990, Gortmarker et al. estimated that 27 percent of donors were lost because they were not identified and 52 percent of identified donors were lost because the family refused to donate organs [69]. To tackle this problem, in 1998, CMS Conditions of Participation (42 CFR Part 482.5) required that hospitals refer **ALL** imminent deaths and deceased patients to their OPO; and only OPO staff or a trained hospital staff may approach families about organ donation. Since the new requirements came into effect, the loss of donors because of missed identification has witnessed a 40 percent reduction from 27 percent in 1990 to 16 percent in 1997-99 [69, 70]. However, the loss of donors because of family refusal has proven to be more resistant. Family authorization rate[24] had only marginally improved from 48 percent in 1990 to 54 percent in 1997-99 [69, 70]. Studies on interventions designed to improve authorization rates have reported mixed results. Beasley et al. reported no improvement in authorization rate after a 2-year intervention [109]. After placing an in-house coordinator in one hospital, Salim et al. observed an improvement in authorization rate from 35 percent to 52 percent [110]. Siminoff et al. reported a smaller

[24] Authorization rate is referred to as consent rate in the studies we cite.

improvement in authorization rate from 47 percent to 56 percent after educating OPCs in appropriate communication techniques [111]. Although these studies are not nationally representative, they consistently demonstrate that increasing authorization rate is a major challenge. In addition, Koh et al. in their evaluation of the *Massachusetts Organ Donation Initiative* have demonstrated the obstinate nature of family authorization rate [112]. Prior to the initiative in 1999, the authorization rate across 9 medical centers in Massachusetts was 59 percent [112]. In the second year of the initiative in 2001, the authorization rate increased to 67 percent. In 2003, two years after the initiative ended, the authorization rate dropped to 46 percent [112].

There is considerable amount of evidence on the factors that influence a family's decision to authorize donation [113-120]. These factors are listed as 'barriers' to family authorization along with the relevant studies in Table 3. Driven by the findings of the collaborative, the critical pathway approach was developed to address many of these barriers[25]. As a result, the family authorization rates have shown considerable imporvement in the last decade. Between November 2012 and October 2013, the national authorization rate was 74% [121]. Nevertheless, there remain several other barriers[26] to authorization that cannot be addressed through the critical pathway approach. In fact these barriers are largely beyond the control of the hospital and the OPOs, and they continue to erode the organ donor pool.

The Uniform Anatomical Gift Act is an effort to protect the donor pool from the effects of family refusal. According to this law, the document of anatomical gift is irrevocable other than by the individual. In addition, OPOs are under legal obligation to honor the donor's wishes. Thus if a potential donor has executed the document of anatomical gift, the OPO does not need authorization for donation from the family. Donor designations are therefore crucial in reducing the shortage of organs. "*A Donor Designation*

[25] These barriers include perceived poor quality of care, poor explanation of brain death, suboptimal request for donation, perceived lack of support from the OPC and hospital staff, and poor understanding of organ donation process.

[26] These barriers include patient demographics, religious beliefs, no prior knowledge of the patient's wishes, fear of mutilation, negative organ donation attitude, death from medical cause rather than trauma, family disagreement regarding donation decision, and family's emotional state. These barriers are presented in Table 3.

is a documented, legally authorized commitment by an individual to make an anatomical gift that cannot be revoked by anyone other than the registered donor" [77]. While there are several mechanisms to register as an organ donor, only joining the state donor registry can guarantee that the designated donor's wishes will be honored. A donor registry is a database of all individuals who have designated themselves as organ donors. Individuals can join the registry either online or through the department of motor vehicles during issuance/renewal of their state ID or driver's license. State donor registries are secure databases typically maintained by the motor vehicle departments. To ensure security, registries can be accessed only by the state OPOs and only for imminent death patients or decedents who have been referred to the OPO.

In spite of concerted efforts of the organ donation community to promote state donor registries, less than half of all Americans have signed up as organ donors. In 2012, there were only 108 million individuals on state donor registries nationwide, that is only 45 percent of all individuals 18 years and older [77]. While Pennsylvania is slightly better than the national average (46 percent), only 35 percent of individuals 18 years and older are designated donors in West Virginia [77]. Thus there is a need to step up efforts to promote state donor registries nationally. DLA is actively involved in the promotion of donor registries and sets national goals for total designations. In recent years, HRSA has funded a large portfolio of research on innovative approaches to adding donors to the state registries. Both efforts are based on the premise that more donor designations will result in more organ donors. However, the question of how additional designations translate into additional donors is difficult to answer. First donor designation does not guarantee actual donation since only a very small fraction of decedents actually become eligible to be organ donors. Estimates of eligible decedents range between 10,500 and 13,800 [70] compared with over 2.4 million deaths countrywide [122]. Second, even if a designated donor becomes an actual donor, organ donation generally happens many years after the individual joined the registry. Given the fuzzy relationship between designations and donors, it is difficult to determine if the number of designations generated is worth the money spent on promoting donor registries. Chapter 3 will investigate this connection between

designations and donors, and examine the cost-effectiveness of public education programs to promote donor registries.

How much does CORE spend to get one additional designation? What does one additional designation mean in terms of organ donors?

……Question 2

Table 3: Barriers to family authorization for organ donation

Author	Year	Barriers to Family Authorization
McNamara et al. [113]	1997	Perceived poor quality of care Poor explanation of brain death Suboptimal request for donation
Guadagnoli et al. [114]	1999	Race (Caucasians more likey to donate)
Siminoff et al. [116]	2001	Family and patient demographics No prior knowledge of patient's wishes Less time spent with the OPC Suboptimal request pattern experienced
Rocheleau [115]	2001	Donor demographics Distrust of the medical community Religious beliefs Fear of mutilation Concern regarding use of organs Lack of knowledge about deceased's wishes Misunderstanding of brain death Bereaved family's emotional state
Rodrigue et al. [117]	2006	Patient's donation intentions known Older decedent Family's organ donation beliefs Family approach not timely Perceived insensitivity of the OPC
Rodrigue et al. [118]	2008	Family disagreement regarding donation decision
Brown et al. [119]	2010	Race Old age Death from a medical cause Untimely request
Jacoby et al. [120]	2010	Lack of support from the OPC and hospital staff Percieved quality of care Organ donation not understood

1.8. IMPACT OF REGISTRY PROMOTION ON ORGAN SHORTAGE AND THE COST OF ORGAN SECURITY

In this study we extend the analysis in study 2 to the level of the organ. The extent to which registry promotion can impact the organ shortage, and its financial impact on the society have not been previously quantified. These relationships warrant examination for several reasons. For one, the transplant waiting list is a composite list of individuals who are waiting for one or more organs and the demand for some organs is more than others. Second, donors do not yield all organs equally. Some organs such as kidney are more frequently recovered than other organs. The interaction between these two factors has important implications on the extent to which shortage of specific organs is addressed as well as the costs incurred.

The objective of this study is to analyze the cost and potential impact of donor registry promotion in relation to organ shortage. Specifically, we examine two key issues: 1) what is the maximum potential effect on organ shortage that we can achieve through registry promotion (we refer to this as "impact threshold"); and 2) what are the costs associated with securing each type of solid organ and reaching the impact threshold? Later these issues are analyzed in the context of arresting the growth of the transplant waiting list. At present, the prospects of supplying enough organs to clear the waiting list are gloomy. A more reasonable goal for the society would be to arrest the growth of the transplant waiting list. Our intent in this study is to initiate a discussion on whether donor registry promotion has the potential to address the organ shortage in a meaningful manner and if the associated costs are affordable. Later we discuss other conventional strategies as well as the recent innovations to expand the supply of cadaveric organs.

What is the impact threshold of donor registry promotion and how much does it cost to arrest the growth in organ shortage?

……Question 3

1.9. SUMMARY

The remarkable progress of transplant medicine in the latter half of the twentieth century that led to an unprecedented demand for donated organs has caught the transplant community off-guard. In response, the organ donation community has evolved into a highly specialized organ procurement network driven by the legislative developments over the past 35 years. Primarily governed by the CMS Conditions of Participation and Conditions of Coverage, the organ procurement network strives to attain effectiveness, efficiency and equity through the well-defined roles and responsibilities of donor hospitals, transplant centers and the organ procurement organizations. Two core activities of the OPOs, clinical services and public education, serve as the conceptual framework for studies 1 and 2. Study 1 examines the interaction between the OPO and donor hospitals- the organ donation process. Study 2 examines the OPOs public education efforts and their effect on the actual donor pool. Study 3 extends the analysis in study 2 to the level of the organ. Figure 3 presents the broad organization of the organ procurement and transplantation network as well as the aspects that form the focus of this dissertation.

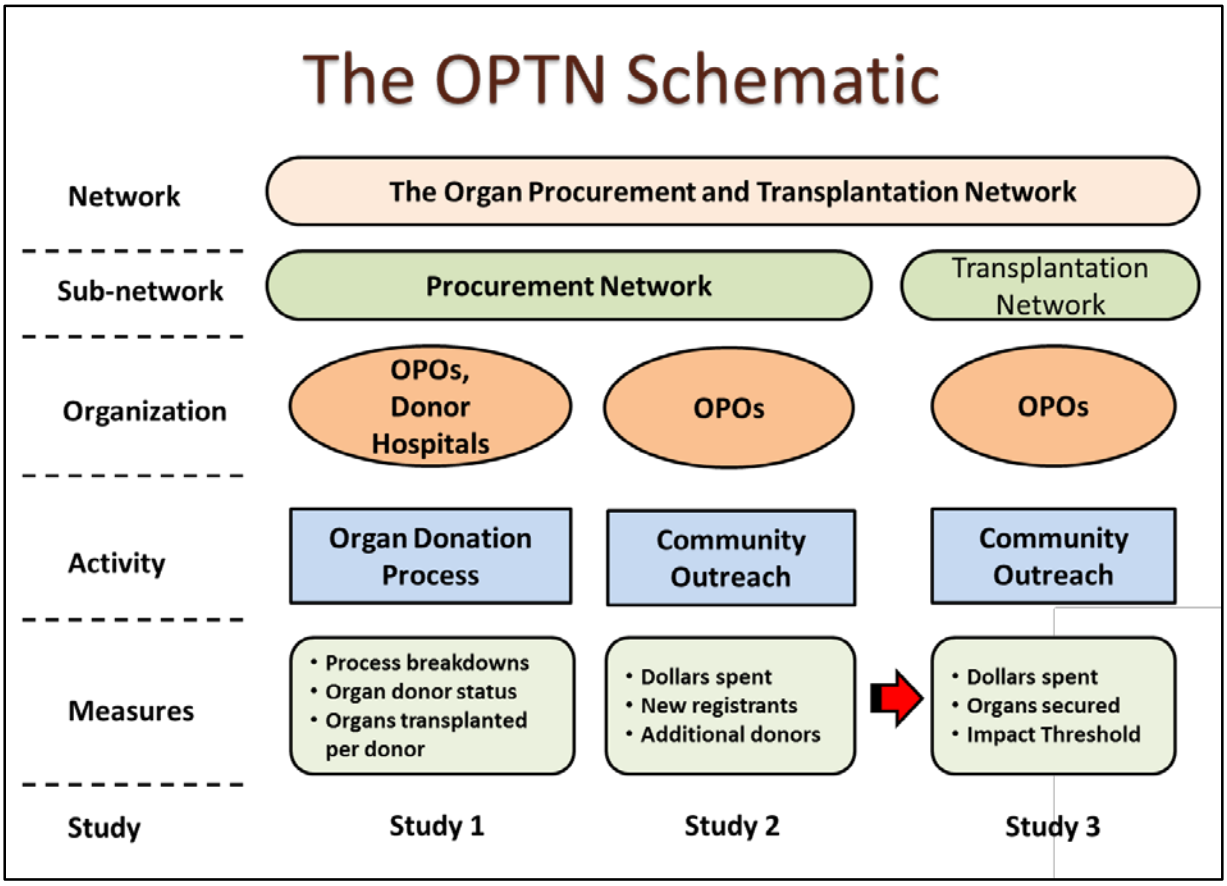


Figure 3: The OPTN Schematic

CHAPTER 2: THE EFFECT OF PROCESS BREAKDOWNS ON CADAVERIC ORGAN SUPPLY IS MEDIATED BY DONATION RATE AND NOT BY ORGAN YIELD PER DONOR.

2.1 INTRODUCTION

The success of organ transplants in treating end-stage organ failure has led to an unprecedented demand for transplantable organs that unfortunately remain in short supply. As a result, relatively few organs are transplanted compared to the number of people with end-stage disease. In 2012, more than 116,000 patients were on the waiting list for an organ transplant but only about 28,000 transplants were performed [123]. Consequently 6,508 patients died while waiting for a life-saving organ [123]. Increasing the availability of transplantable organs is therefore critical to improvements in health related quality-of-life and life-expectancy of people with end-stage organ failure. Thus, it is an urgent and an ongoing concern that opportunity for organ donation is preserved when caring for critically ill patients.

Estimates of organ donation potential indicate that there is a sizeable potential donor pool that the organ donation community is yet to completely realize. In the U.S. (1997-1999), there were estimated 40,610 brain-dead potential organ donors but only 17,127 actual donors [70]. Poor relationship between key organizations including organ procurement organizations (OPOs) and hospitals in their donation service area (DSA) is one of the several reasons for this tragic loss of donors [124]. In 2001, the Organ Donation Breakthrough Collaborative was established to, among other reasons, encourage collaboration between the OPOs and the donor and transplant hospitals [125]. By sharing experiences, collective

problem-solving exercises and celebrating success together, a community of OPOs and hospitals committed to quality improvement has emerged. Although considerable increase in the number of organs available for transplantation has been realized since the collaborative began [51-54, 81], acute shortage of organs continues to be a major challenge for the transplant community.

In recent years critical pathways for organ donation have been developed to preserve the opportunity for donation. Critical pathways, also called "clinical pathways" or "care maps", help standardize medical care, reduce variability and improve outcomes in high volume and high risk procedures [104]. In the context of organ donation, "high volume" means that the organ donation process must be initiated every time a patient nears death. "High risk" signifies the high likelihood of losing viable organs if the donation process is not optimally timed and sequenced. In the U.S., standardized protocols for organ donation have been jointly developed by the OPOs and their partnering hospitals. These protocols incorporate the best practices (Table 4) that are being continually identified and disseminated through the Donation and Transplantation Community of Practice and the National Learning Congress. OPOs invest considerable resources in training hospital staff in following the best practices, about their roles in the organ donation process, and on how to eliminate errors in patient care that may jeopardize the potential for donation. Although there is a committed and a quality-oriented culture, competing priorities in the hospital and the inherent complexity of critical care can sometimes lead to deviations from the best practices. OPOs identify these deviations as process breakdowns and spend considerable resources in identifying and addressing them. Process breakdown is a generic term applied to a set of failures in the donation process that can jeopardize the opportunity for donation. While several studies have identified a relationship between process breakdowns and conversion rate (the actual number of organ donors divided by the number of eligible deaths) [112, 126-129], it is unclear how process breakdowns affect the supply of viable organs.

Table 4: Best practices in donation process

- Prompt identification of imminent death patients.
- Timely notification to the OPO (within 1 hr. of identifying imminent death patient).
- Notifying the OPO about every death.
- Early and aggressive potential donor management, and
- Timely and designated family approach (optimal request for organ donation).

2.2. METHODS

A retrospective analysis of decedents was conducted using data from the Center for Organ Recovery and Education (CORE), an independent OPO that serves western Pennsylvania and most of West Virginia. All deaths from January 1st 2010 through December 31st 2012 were considered for the analysis. All data manipulation and analytic procedures were performed using MS Excel® 2010 (Microsoft Corporation) and Stata® SE 13.0 (StataCorp, College Station, Texas).

2.2.1. Inclusion and Exclusion Criteria

We included only those decedents that died an 'eligible death' in our analysis. CMS defines eligible death as brain-dead individuals up to age 70 who do not exhibit any of the exclusionary conditions listed in

CMS Conditions for Coverage for OPOs (42 CFR §486.302). Eligible decedents who become organ donors are called standard criteria donors (SCD). Donors after cardiac death (DCD) and expanded criteria donors (ECD) were excluded from the analysis. CMS does not define eligible deaths for DCD or ECD cases. Thus, while CORE tracks ECD and DCD cases, there is no objective definition or tracking possible for cases that might have proceeded to ECD or DCD but did not. Including DCD and ECD in the regression model may thus produce biased estimates of the effect of PBD on donation (See Appendix A-1).

2.2.2. Data Collection

We analyzed decedent records extracted from CORE's data system that contains information on all deaths that occur within its DSA. Real-time patient information that includes patient's demographics (age, race, and gender), eligibility for donation, designated donor status, final donor status, and whether there was a process breakdown is jointly entered into the system by the donor referral coordinator and the organ procurement coordinator. In addition, process breakdowns are often identified through retrospective medical record review and entered into the system by hospital development staff. Like hospitals, CORE uses a proprietary electronic medical record system to aid its procurement and referral coordinators in documenting patient-related information. Each variable was extracted as a separate Excel® spreadsheet and merged using referral ID that uniquely identifies each death.

2.2.3. Variables

For each decedent, information was retrieved for age, gender, race, hospital where death occurred, eligible death status, organ donor status, whether the decedent had joined the state donor registry, organs transplanted, and whether there was a process breakdown. In addition, we identified two hospitals that had

inhouse coordinator programs. Inhouse coordinators are assigned to a single hospital and perform the role of both organ procurement coordinators and professional services liaison. This model is often used at larger hospitals with high donation potential.

2.2.3.1. Outcome Variables

There are two outcome variables of interest in this analysis: 1) the likelihood of an eligible decedent becoming an organ donor. This variable can assume only two values- either “0” or “1"; and 2) the “number of organs transplanted per donor”. This variable assumes whole number values from “0” to “8” with “8” being the maximum number of organs that can be transplanted from one donor.

2.2.3.2. Predictor Variable

The predictor variable is whether there was a process breakdown in the care of an eligible decedent. Table 5 presents a list of process breakdowns that CORE’s personnel identify, document and resolve on a day-to-day basis. For missed referrals, untimely referrals and suboptimal request for donation, CORE assesses whether or not referral and request requirements specified in CMS Conditions of Participation for Hospitals (42 CFR §482.45) were met. De-escalation of care and early extubtion are documented if either happens before a request for donation is made to the family.

Table 5: Process breakdowns and determination criteria

Name	Description	Determination
Missed Referral	The OPO was never notified about the deceased.	Unaccounted patient deaths are found during medical/death record review by the hospital development staff.
Untimely Referral	The OPO was not notified about the imminent death within 1 hour of such determination, or if the patient has died, within one hour of death.	The donor referral coordinator who receives the call from the hospital verifies the time of imminent death determination, or if the patient has died, the time of patient's death. These times are then compared with the time when the hospital notifies the OPO.
Suboptimal Request for Donation	Either the timing of the request is poor or the person requesting donation is not a trained requestor. Poor timing of the request include discussing donation either before or soon after the family is informed about patient's death.	These process breakdowns are either self-reported by the hospital staff (for example, "Dr. Doug mentioned organ donation to the family") or by the family to the procurement coordinator ("We have been asked about donation and we don't want to do it").
De-escalation of Care	The referral is made timey but hemodynamic stability is not maintained and life-saving measures are discontinued. Only comfort measures are provided.	While assessing patient's medical record, the procurement coordinator finds that the patient is on "comfort only" measure.
Early Extubation	Initial referral is made on time but the patient is withdrawn from the ventilator before the family is offered the opportunity to donate.	Self-explanatory. The procurement coordinator records that the patient was removed from the ventilator and passed away before request for organ donation is made to the family.

2.2.4. Descriptive Analysis

We first computed the total number of eligible deaths that occurred in CORE's DSA. All analyses that followed were performed on eligible death subset of all deaths. We conducted univariate analysis on age, race, gender, organ donors, organs transplanted and process breakdowns.

2.2.5. Bivariate Analysis

For bivariate analyses, donors were compared with non-donors; and registered decedents were compared with non-registered decedents for age, race and gender. Significance of difference in age was tested using Wilcoxon Mann-Whitney rank-sum test (test of medians). Chi-squared test was used to test the significance of difference in race (proportion of Caucasians) and gender (proportion of females). Bivariate analysis using Chi-squared test was also performed on the probability of becoming a donor in a hospital with an inhouse coordinator compared to one without an inhouse coordinator. The unadjusted effect of process breakdown on the probability of becoming a donor was examined using Chi-squared test and organs transplanted per donor using Wilcoxon Mann-Whitney rank-sum test.

2.2.6. Regression Framework

The process being modelled is a two-stage process. In the first stage, an eligible decedent becomes an organ donor after the decedent's family authorizes donation. In cases where the family refuses donation, there is no possibility of recovering any organs from the decedent resulting in "structural zeroes" in the number of organs transplanted. In the second stage, organs from a donor are offered for transplantation. Depending on several factors including viability of the organs offered, the potential recipient's health etc.,

organs are either rejected or accepted for transplant. When the organ is rejected, “sampling zeroes” arise. When organs are accepted, the number of organs transplanted assumes discrete positive values. In other words, the number of organs transplanted is primarily a count distribution with a mix of structural and sampling zeroes.

Since our data had a large mass of zeroes, single stage regression was ruled out. Our first choice was a two-part hurdle model where, in the first part, we would model the likelihood that an eligible decedent becomes a donor using logistic regression. In the second part we would use Poisson or negative binomial regression to model the organs transplanted per donor. Two-part models are commonly used in modelling healthcare costs where majority of individuals, who do not utilize medical care in a given year, have zero healthcare costs. The zeroes observed in these data are purely structural and the two-part model evaluates the zero observations separate from non-zero observations. However, since the zeroes observed in our data are a mix of structural and sampling zeroes, a hurdle model would misclassify some of the donors who did not yield transplantable organs as non-donors. For our data, a zero-inflated model is more appropriate since it models only those zeroes separately that are in excess of what would be expected based on the remaining non-zero observations, that is, some sampling zeroes are expected. In essence, a zero-inflated model is a two-part model where the assumption that all zeroes are structural is relaxed. The other decision we made is to use Poisson regression in the zero-inflated model instead of negative binomial regression since in our data, the mean number of organs transplanted per donor is equal to its variance (data are not over-dispersed).

2.2.6.1. Model Selection

The choice of covariates to be included in the model was informed by theory, results of the bivariate analysis and *a priori* assumption; and confirmed using model fit statistics. For modelling excessive zeroes, the variable age, which is a known determinant of the likelihood of becoming an organ donor, was included [117, 119]. Other covariates included were whether or not a decedent had joined the state donor registry,

and being a Caucasian since these covariates were significantly different between donors and non-donors in the bivariate analysis. For modelling the organs transplanted per donor only age was included as a covariate based on *a priori* belief that older decedents will yield less viable organs.

Hospital-level differences were not controlled by inclusion as a covariate or using fixed-effects. There are two possible mechanisms through which hospital-level differences might affect organ donation rates. First, factors such as ownership, mission (profit vs. non-profit), level of trauma services, and having a transplant program are known to be associated with a wide range of indicators of organ procurement performance [130]. However these factors are unlikely to affect our estimates since their effect on donation rates is mediated through process breakdown. OPOs maintain inhouse coordinators in underperforming hospitals with large donation potential for the same reason, that is, to reduce process breakdowns so that donation rates can be improved. The other mechanism through which hospital-level differences might affect our analysis is if patients and their families are more likely to be similar to other patients and families in the same hospital. We treated this intra-hospital correlation as a nuisance and accounted for this clustering by computing clustered standard errors.

2.2.6.2. Model Fit and Sensitivity Analysis

We computed several statistics of model fit including Cragg and Uhler's Pseudo-R-squared, McFadden's Adjusted R-squared, AIC, BIC and model Deviance to check the appropriateness of the model selection. To assess the overall goodness-of-fit, we examined the sensitivity of our estimates under the zero-inflated Poisson model to alternative regression frameworks (zero-inflated negative binomial and two-part model). Although we did not examine individual organs transplanted separately due to a small sample size, we are certain that different organs are variably sensitive to process breakdowns. Using logistic regression and controlling for the same covariates as in the zero-inflated Poisson model, we computed the adjusted log

odds that a kidney, liver or heart is transplanted when there is a process breakdown. Lungs and pancreas transplants were excluded because these events are so rare to produce valid estimates.

2.3. RESULTS

2.3.1. Descriptive Statistics

Out of the 84,817 deaths reported to CORE between January 1st, 2010 and December 31st, 2012, there were only 424 eligible deaths of which 324 (76.4%) went on to become organ donors. As a result, 1,100 organs were transplanted in the three year period. The mean number of organs transplanted per eligible decedent was 2.6 with 115 out of 424 eligible decedents not yielding any transplantable organ (a mix of structural and sampling zeroes). Figure 1 presents the distribution of organs transplanted from eligible decedents. Among the 324 donors, 15 donors did not yield any transplantable organ (sampling zeroes). The mean number of organs transplanted per donor was 3.40 and the variance was 3.41 suggesting that Poisson regression (in the second part of the model) is appropriate. Figure 2 presents the distribution of organs transplanted from donors.

2.3.2. Eligible Deaths

There are 155 hospitals in CORE's DSA but only 41 hospitals had one or more eligible deaths. Furthermore, eligible deaths were highly concentrated; 82% of eligible deaths were concentrated in 10 hospitals and 58% in only 4 hospitals. CORE uses in-house coordinators program in the two hospitals with

the largest donation potential; these hospitals account for 35% of all eligible deaths in the DSA. Descriptive statistics on eligible deaths are presented in Table 6.

Table 6: Descriptive statistics on eligible deaths

Median age	37 years
Females	40%
Registered donors	32%
Race	
Caucasians	87%
African-Americans	11%
Process Breakdowns (N)	25
Suboptimal request	17
Untimely referral	5
De-escalation of care / Early extubation)	1
Unidentified	2

2.3.3. Bivariate Analysis

Comparison of donors with non-donors and registered decedents with non-registered decedents is presented in Tables 7 and 8.

Table 7: Difference between donors and non-donors

	Donors	**Non-donors**	**P value**
Median Age	35 years	47 years	0.000[1]
Females (%)	42%	33%	0.124[2]
Caucasians	89%	78%	0.004[2]

[1] Wilcoxon Mann-Whitney rank-sum test (test of medians)
[2] Chi-squared test

Table 8: Difference between registered and non-registered donors

	Registered Donors	Non-registered Donors	P value
Median Age	39 years	35 years	0.058[1]
Females	47%	37%	0.040[2]
Caucasians	95%	83%	0.001[2]

[1] Wilcoxon Mann-Whitney rank-sum test (test of medians)
[2] Chi-squared test

2.3.3.1. Inhouse Coordinator and Organ Donors

There was no difference in the likelihood of becoming an organ donor regardless of whether or not there was an inhouse coordinator in the hospital where the patient died. Seventy five percent of eligible decedents in hospitals with an inhouse coordinator became organ donors whereas this proportion was 77 percent in hospitals without an inhouse coordinator (Unadjusted OR: 0.89; 95% CI: 0.557, 1.414; $p>0.05$).

2.3.3.2. Process Breakdowns and Organ Donors

Overall, 76 percent of eligible decedents became organ donors. This proportion was slightly higher (79 percent) when there was no process breakdown but dropped to 36 percent when a process breakdown had occurred. There were 25 eligible decedents who had experienced a process breakdown in their care. Of these, only 9 decedents went on to become organ donors. Chi-squared test of conversion rate by process breakdown indicates a significant association between the two. An eligible decedent was 6.7 times more likely to become an organ donor if there was no process breakdown in the care of the patient (Unadjusted OR: 6.67; 95% CI: 2.85, 15.62; $p<0.001$).

2.3.3.3. Process Breakdowns and Organs Transplanted (from eligible decedents)

Overall, a mean of 2.59 organs were transplanted from an eligible decedent (includes eligible decedents who did not become organ donors), 52 percent of whom yielded at least 3 transplantable organs. In the presence of a process breakdown, the mean number of organs transplanted from an eligible decedent dropped to 1.16 with only a quarter of eligible decedents yielding 3 transplantable organs. When there was no process breakdown, 2.68 organs were transplanted per eligible decedent on average. Bivariate analysis using Wilcoxon Mann-Whitney rank-sum test indicates that an eligible decedent is expected to yield significantly greater number of organs when there is no process breakdown ($p<0.001$).

2.3.4. Zero-Inflated Poisson Regression

Holding other variables constant, the likelihood that an eligible decedent will become an organ donor is four times higher when there is no process breakdown (Adjusted OR: 4.01; 95% CI: 1.6838, 9.6414; $p<0.01$). However once a decedent becomes a donor, whether there was a process breakdown does not affect the number of transplantable organs yielded by the donor. Regression results are presented in Table 9.

In spite of effect-loss at the second stage in the organ donation process, process breakdowns exert strong detrimental effect on organs transplanted. For every process breakdown an eligible decedent yields around one less organ (dy/dx: -1.05; 95% CI: -2.0307, -0.0706; $p<0.05$). Age has a small but a strong effect on organs transplanted per eligible decedent. Joining the registry had a significant positive impact on the odds of becoming a donor. Decedent's race was not significant. and the marginal effects are presented in Table 10.

Table 9: Results from Zero-Inflated Poisson Regression

The likelihood of becoming an organ donor				
	Log Odds	**Clustered Std. Err.**	**P-value**	**95% C.I.**
Process Breakdown	-1.39	0.4452	0.002	-2.2663, -0.5211
Age	-0.04	0.0101	0.000	-0.0597, 0.0202
Joined the Registry	3.94	1.7474	0.024	-0.5172, 7.3667
Caucasian	0.51	0.357	0.129	-0.1489, 1.1732
Organs transplanted per donor				
	Log Counts	**Clustered Std. Err.**	**P-value**	**95% C.I.**
Process Breakdown	-0.16	0.1742	0.355	0.5027, 0.1802
Age	-0.01	0.0027	0.000	-0.1832, -0.0076
N =424				

Table 10: Incremental and Marginal Effects

	ExpOrgTx[1]	**Std. Err.**	**P-value**	**95% C.I.**
Process Breakdown	-1.05	0.5000	0.036	-2.0307, -0.0706
Age	-0.05	0.0085	0.000	-0.0684, -0.0351
Joined the Registry	1.79	0.7243	0.014	0.3675, 3.2067
Caucasian	0.23	0.1511	0.124	-0.0640, 0.5283

N = 424,
[1] Expected number of organs transplanted from each eligible decedent

2.3.4.1. Model Fit and Sensitivity Analyses

Fit statistics on various nested models are presented in Table 11. Fit statistics for the final model are either most favorable or very close. Results from sensitivity analyses using different regression frameworks are presented in Table 12. The coefficient estimates are almost identical for the predictor variable and other covariates (except joining the registry) under the zero-inflated Poisson, zero-inflated negative binomial and two-part model.

Table 11: Statistics for Model Fit

Excluded Variable(s)	Cragg & Uhler's Pseudo R^2	McFadden's Adj. R^2	AIC	BIC	Deviance
None (Saturated Model)	0.269	0.065	3.708	-948.87	<u>1548.69</u>
Age	0.156	0.032	3.840	-901.52	1608.15
Joined Registry	0.171	0.036	3.826	-903.06	1600.55
Female	<u>0.271</u>	0.067	3.698	-960.49	1550.15
Caucasian	0.266	0.065	3.709	-952.88	1550.74
IHC	0.269	0.067	3.704	-954.85	1548.76
**** Female & IHC**	0.270	<u>0.068</u>	<u>3.694</u>	-966.37	1550.32
Female, White & IHC[1]	0.270	<u>0.068</u>	<u>3.694</u>	<u>-970.38</u>	1552.36

* Underlined values represent most favorable model for each fit statistic.
** These variables were excluded from the final model.
[1] IHC is Inhouse Coordinator

Table 12: Sensitivity analysis- regression framework

	ZIP		ZINB		TPM	
Likelihood of becoming a Donor						
	Log Odds	**P-value**	**Log Odds**	**P-value**	**Log Odds**	**P-value**
PBD	-1.39	0.002	-1.39	0.002	-1.38	0.002
Age	-0.04	0.000	-0.04	0.000	-0.04	0.000
Joined Registry	3.94	0.024	3.94	0.024	2.40	0.000
Caucasian	0.51	0.129	0.51	0.129	0.51	0.151
Organs Transplanted per Donor						
	Log Count	**P-value**	**Log Count**	**P-value**	**Log Count**	**P-value**
PBD	-0.16	0.355	-0.16	0.355	-0.14	0.337
Age	-0.11	0.000	-0.11	0.000	-0.01	0.000

ZIP- Zero-Inflated Poisson Regression
ZINB- Zero-Inflated Negative Binomial Regression
TPM- Two-Part Model

Table 13 presents the log odds that a kidney, liver or heart is transplanted when there is a process breakdown. Liver is more sensitive to process breakdown than kidney and heart is more sensitive to process breakdown than liver. Kidney is most sensitive to increasing age while liver and heart are only slightly sensitive. All three organs are similarly sensitive to joining the registry. Being a Caucasian does not have a significant effect on the likelihood of kidney, liver or heart being transplanted.

Table 13: Sensitivity Analysis- Effect on Liver and Heart

	Kidney		Liver		Heart	
	Log Odds	**P-value**	**Log Odds**	**P-value**	**Log Odds**	**P-value**
PBD	-1.07	0.006	-1.67	0.000	-2.04	0.004
Age	-0.33	0.005	-0.04	0.000	-0.06	0.000
Joined Registry	0.99	0.000	0.93	0.000	0.91	0.000
Caucasian	0.79	0.001	0.12	0.648	0.07	0.748

Coefficients from logistic regression were computed to compare the sensitivity of kidneys, liver and heart to process breakdown. For kidneys, the dependent variable is at least one kidney.

2.4. DISCUSSION

Evidence from published evaluations of quality improvement initiatives undertaken by several OPOs suggests that there is an inverse association between process breakdowns and donation rate [112, 126-129]. Burris and Jacobs (1996) found that a mandatory twenty-minute training for staff in nursing, patient and family services, and pastoral care; and employing compliance monitoring tools resulted in an increase in the referral rate from 54 percent to 98 percent over a 10 month period. During the same time, donation rate for all decedents between 6 months old and 76 years old increased from 1.6 percent to 3.1 percent [126].

Sade et al. (2002) examined the effect of specialization within the procurement process on the consent rates in an OPO's DSA [127]. Between 1997 and 2001, after clinical services liaisons were recruited to educate the hospital staff about the donation process and review medical records for appropriateness of referrals, the number of referrals for all deaths increased by 49 percent. In addition, specialist family support counselors approached the family with the request for donation resulting in 90 percent increase in the

consent rate. During the same period, the donation rate per million population also increased by 83 percent [127].

Similar association between timely referrals and organ donation rates was suggested by Koh et al. (2007) in their assessment of the Massachusetts Organ Donation Initiative [112]. The program was a data-driven quality improvement program that involved coordination between the Massachusetts Department of Health, the regional OPO and the transplant centers [112]. They found that delayed referral and suboptimal request for donation accounted for most lost donation opportunities. The hospital liaisons implemented changes that increased referral rates from 83 percent to 94 percent. As a result the authorization rate increased from 60 percent to 67 percent, and conversion rate increased from 44 percent to 60 percent [112].

Franklin et al. (2009) found that systematic protocol driven changes to the organ donation process gradually improved organ donation rates across the OPOs DSA [128]. Changes relevant to best practices in organ donation included decoupling of the request process, family approached by clinical coordinator, and family support liaisons. Between 1993 and 2008, the conversion rate increased from 42 percent to 72 percent [128].

In one study however, researchers did not find an association between timely referral/appropriate family approach, and the conversion rate. Although implementing evidence-based best practices resulted in significant improvement in conversion rate (from 50 percent in 2004 to 80 percent in 2005), the referral rate, timely notification rate and the appropriate requester rate did not show significant improvement [129]. However, since that study only included 32 eligible decedents in the pre-implementation group and 30 eligible decedents in the post-implementation group, it probably lacked sufficient power to detect the small improvements.

Our study differs from the existing literature in two important ways. First, the existing literature is based on before-after comparison of donation rates at the level of the hospital or the DSA. We reexamined the relationship between process breakdowns and donation rates by using DSA-wide decedent level data to

adjust for other patient factors known to affect organ donation rates. Second, we also examined the effect of process breakdowns on organs transplanted per eligible decedent, which has not been previously studied.

Our analysis indicates that process breakdowns significantly reduce the likelihood of organ donation but have no effect on the number of organs transplanted. The loss of effect in the second stage is best explained by how different process breakdowns are distributed. While 25 eligible decedents had experienced a process breakdown, only 9 of those decedents went on to become organ donors. Eight of these nine organ donors had experienced either a delayed referral or a suboptimal request for donation. Since delayed referrals and suboptimal requests, in theory, do not affect organ health or function, their insignificance in the second stage of the regression model was somewhat expected. Nevertheless we wanted to investigate this relationship to determine if there were other mediating factors through which these process breakdowns could exert their influence. First, delayed referral of an imminent death can delay identification of a potential donor, brain death testing and donor management, all of which will adversely affect organ function. Second, suboptimal request for donation may either result in family's refusal to donate or more time spent on obtaining authorization resulting in a delay in organ retrieval. Even in optimally managed brain-dead donors, delay in retrieving organs can compromise organ quality. Although process breakdowns do not affect the number of organs transplanted once the family has authorized donation, the overall effect of process breakdowns is still significant owing to their strong effect on the likelihood of becoming a donor.

Age at death exerted significant influence on the likelihood of becoming a donor as well as organs transplanted per donor. Our results indicate that older decedents are less likely to become donors than younger decedents. Since all decedents in our dataset were, by definition, eligible to become donors, the effect of age on becoming a donor is probably mediated through family authorization. Families of younger patients tend to authorize donation more often than families of older patients [117, 119]. This effect can be explained in part by a higher proportion of traumatic accidental deaths in the younger patients compared to older patients who die more often from a medical cause. In CORE's DSA between 2010 through 2012, the

median age of donors who died from traumatic head injury was 28 years. In contrast, the median age of donors who died from a cerebrovascular accident or stroke was 59 years. Families of decedents who are brain dead from a medical cause (like stroke) have greater difficulty in understanding the concept of brain death and are more resistant to donation [119]. In addition, older decedents are likely in poorer health, also potentially leading to fewer organs transplanted per donor.

Our results indicate that race and gender do not predict the likelihood of organ donation. Previous evidence suggests that women are more willing to donate their organs and discuss their willingness to donate with their families [131]. Since, having knowledge of the deceased's wishes facilitates authorization for donation [115-117], we had expected female eligible decedents to have higher adjusted odds of organ donation. Contrary to previous studies [114, 119, 132], we did not find race to be a significant predictor either. While donors and non-donors in our data differed significantly by race (Caucasian), these differences disappeared when designated donor status was included in the regression model. Since Caucasians are more likely to have joined the state registry, the effect of being a Caucasian is mediated through the donor designation status, a significant covariate in the regression model ($p=0.052$).

Contrary to existing literature [110, 133-136], our analysis does not indicate any significant association between an inhouse coordinator (IHC) program and the likelihood of organ donation. This disagreement can be explained by the difference in the design of the previous studies and our study. While previous studies compared the conversion rate before and after the implementation of the IHC program, in CORE's DSA the IHC program predates our dataset and therefore ruled-out similar comparison. Our dataset only permitted comparison of donation rate between hospitals with and without IHC and there also, we did not find any differences. It is likely that the benefits from having an in-house coordinator have already been achieved in our DSA. IHC programs are typically implemented in large hospitals with high donation potential. The complexity of services these institutions provide puts undue burden on hospital resources resulting in competing priorities that negatively affect the donation process and lead to process breakdowns [134]. Having an inhouse coordinator improves adherence to best practices in the donation process [137]

and offsets the increased risk of process breakdowns in the larger hospitals. It stands to reason that OPOs would allocate resources to hospitals that are under-performing large donation potential. Accordingly, post-IHC process breakdown and donation rates in larger hospitals tend to match (and not exceed) the DSA-wide rates.

Model fit statistics suggest that our choice of covariates in the model is reasonable. In addition, sensitivity analyses with alternative regression frameworks suggest that our model is robust to alternative assumptions and therefore has a reasonably good fit. We did not use split-sample cross-validation to assess overall goodness-of-fit owing to a small sample size and rarity of process breakdowns. The effect of process breakdown on the likelihood that an organ is transplanted was separately modelled for kidney, liver and heart to informally asses the relative sensitivity of each type of organ. Results indicate that kidneys are least sensitive to process breakdowns followed by liver and then heart. The implication of this finding is that process breakdowns will differentially impact the viability of kidney, liver and heart with heart more likely to be lost due to the detrimental effect of process breakdown than liver or kidney.

The principal finding of this study is that process breakdowns have a strong adverse effect on the likelihood of organ donation but do not affect the organ yield once an eligible decedent becomes an organ donor. Nevertheless, process breakdowns exert a strong overall effect on organ availability. Our results suggest that for every process breakdown occurring in an eligible decedent, one less organ is available for transplant. Accordingly, we estimate that 25 organs were lost to process breakdowns over a three-year period. However it is worth noting that even if process breakdowns are completely eliminated, some organ donors will still be lost owing to other factors that make families averse to donation. These factors which are largely outside the control of the OPOs and the hospitals include patient and family demographics [115, 116], family's religious beliefs [115], fear of mutilation and high value placed on bodily integrity [115, 138], concern about use of organs and distrust of medical community [115], family not knowing decedent's wishes [115-117], poor understanding of brain death [113, 115], bereaved family's emotional state [115], and family disagreement regarding donation decision [118]. Understanding of brain death is especially

important because higher authorization rates cannot be achieved unless the relatives of the decedent understand that there is no hope of recovery [139]. However when decedents have their name on the registry, family's decision about donation became irrelevant owing to the legal guarantee afforded under the Uniform Anatomical Gift Act of 1987. It is therefore not surprising that 100% of eligible decedents who had joined the state donor registry became donors.

2.4.1 Limitations

This study was based on data from one OPO that serves western Pennsylvania and West Virginia. The results of our study may have limited generalizability outside this geographic region. In spite of efforts at dissemination and adoption of emerging state-of-the-art practices, there are wide variations in organ donor practices across different DSAs, including the way process breakdowns are defined and recorded.

In CORE's DSA, process breakdowns are documented and recorded by the procurement coordinators themselves. This poses two potential issues. First, there is a potential for measurement error if different staff interprets the categories differently or fail to record situations in order to protect themselves or to avoid conflict with the hospital staff. However, we believe that the likelihood of wide variation in classification of process breakdowns is low, due to the close teamwork among the PSL staff, use of a standardized electronic data system, and the fact that the data are auditable by CMS. The second issue is the potential risk of recall bias if the procurement coordinator's documentation of a process breakdown is correlated with whether or not an eligible death becomes a donor. To assess if this bias was affecting our analysis, we compared the eligible decedents with the non-eligible decedents for the fraction of process breakdowns. Three percent of all non-eligible deaths had a documented process breakdown while this fraction was slightly higher (4.1%) for eligible deaths ($p>0.05$) suggesting that there is a great degree of independence between documenting the process breakdown and the outcome of a particular case.

CHAPTER 3: PROMOTING DONOR REGISTRIES THROUGH PUBLIC EDUCATION- WHAT IS THE COST OF SECURING ORGAN DONORS?

3.1. BACKGROUND

United States faces an acute shortage of transplantable organs. The situation will worsen in the future as each year the number of people who become eligible for a transplant outpaces the number of organ donors. Organ donor registries, databases of individuals who have expressed an intention to donate their organs on death, are widely regarded as a remedy to this problem. Donor registries draw their authority from the Uniform Anatomical Gift Act [140]. According to this law, the document of anatomical gift is irrevocable other than by the individual himself. In addition, organ procurement organizations (OPOs) are legally obligated to honor the preferences of individuals who had joined the registry prior to death [140]. In such cases, the OPO does not need authorization for donation from the family. State donor registries are therefore crucial in reducing the shortage of organs. Individuals can join the donor registry by designating themselves on the driver's license or the state ID, registering online, or by signing a donor card. The most common method of joining the donor registry is at the Department of Motor Vehicles (DMV). While the driver's license/state ID may display an individual's designation status, the actual registration is stored online in a secure database. Each state maintains its own registry that can only be accessed by the OPO(s) that covers that state, and only for imminent death patients or decedents who have been referred to the OPO.

Donor registries are a joint effort. While the registries are generally maintained by the states, typically by the DMV, OPOs invest considerable resources in promoting the registry in their designated

service areas (DSAs). The premise behind these investments is that more registrations will result in additional donors. However, it is difficult to precisely quantify by how much would additional registrations increase the supply of donors. First, the likelihood that a registered individual will die in a manner that makes him or her eligible for donation is very low. Estimates of eligible decedents range between 10,500 and 13,800 [70] compared with over 2.4 million deaths countrywide [122]. Second, for any individual who registers today, the donation event is expected to occur in distant future. Thus, the benefit of registering an individual must take into account the time before the actual payoff. It is therefore difficult to determine if the number of donor designations generated is worth the resources expended on promoting the donor registry.

To date, there are no studies that have examined the costs of promoting the registry and its effect on the supply of donors. The objective of this paper is to examine precisely that. Specifically, we attempt to answer three questions from the perspective of an OPO. First, what is the cost of promoting the donor registry? Second, how many individuals join the registry as a result of donor registry promotion and what is the "cost per registrant"? Third, what is the value of these registrants in terms of present-day organ donors and what is the "cost per donor"?

Previously, Mendeloff et al. have estimated the societal value of one donor by calculating the average number of quality-adjusted life years (QALYs) derived [141]. They estimated that one donor generates 13 QALYs of health benefit for the society. Assuming that the society is willing to spend up to $100,000 per QALY and based on estimated QALYs per donor, Mendeloff et al. concluded that the value of one donor would be $1,086,000 (after subtracting the costs associated with organ transplant) [141]. In 2006, using Mendeloff et al.'s estimate of $1,086,000 per donor, Howard & Byrne estimated that the value of one 18-year old registrant to the society is either $1900 under a first-person consent system or $840 if the family has the right to refuse donation [142]. Their estimate was based on an 18-years old individual's lifetime probability of becoming a donor. This probability was calculated based on the number of person-

years in that age group, age group-specific number of actual and potential donors, and age group-specific death rate.

Our study is in some ways similar to the works of Mendeloff et al. and Howard & Byrne except for certain differences. First, unlike Mendeloff et al. and Howard & Byrne who estimate donors' and registrants' monetary value to the society respectively, we estimate the actual "cost per registrant" and "cost per donor". Second, we employ a rather classical approach to this analysis. We first estimate the cost of promoting the donor registry and the number of registrations generated from promotion activities to estimate the cost per registrant. Next, we use Markov analysis to estimate the value of the registrants in terms of present-day organ donors to estimate the cost per donor.

3.2. METHODS

In this study we have primarily relied on data from the Center for Organ Recovery and Education (CORE). One of the 58 federally designated OPOs; CORE serves western Pennsylvania and most of West Virginia. We examined the costs and outcomes associated with CORE's registry promotion efforts from 2010 through 2012. While costs estimates were directly obtained from CORE's outreach budget, the number of registrants and donors that result from CORE's promotion efforts was estimated using decision analysis modelling. The probabilistic relationship between registrants and donors was modelled using Markov analysis. We do not have a comparison strategy in this analysis. Accordingly, we use published estimates of the monetary value of a registrant and a donor as benchmarks for comparison [141, 142].

The costs in our analysis are determined and fixed. For estimating registrants and donors, we first perform a base case analysis using central estimates of the model parameters. Furthermore for estimating donors, we develop two scenarios based on the manner in which authorization (more commonly referred to

as consent) for donation is given. These scenarios are discussed under assessment of donors. We also perform sensitivity analysis to test the robustness of our estimates of registrants and donors generated from CORE's registry promotion effort.

3.2.1. Base Case Analysis

3.2.1.1. Assessment of Costs of CORE's Donor Registry Promotion

We assume that the cost of operating the online database is zero since most state donor registries are appended to existing DMV information technology systems. We have therefore considered only the costs associated with CORE's outreach activities. Each year, CORE outlays a specific amount to invest in public education and promoting the donor registry. We obtained CORE's expenditure on community outreach from 2010 through 2012 [143] and aggregated it to calculate a three-year cost of promoting the donor registry. These expenditures include all monies that are spent on community outreach efforts including personnel wages, professional education expenses, travel expenses, cost of promotional materials, cost of media campaigns and departmental overheads. Although the costs are incurred over a three-year period, we consider these as one-time upfront costs since for any individual who joins the registry there are no recurring costs. For illustration, the planned and actual expenditure on community outreach in the year 2012 are detailed in Appendix E. Expenditure on community outreach in years 2010 and 2011 were provided to us by CORE in identical format.

3.2.1.2. Assessment of Registrations from CORE's Donor Registry Promotion

CORE, like all OPOs, uses a two-pronged approach for promoting the donor registry. On one hand, CORE uses broadcast media including radio, television, and billboards, as well as social media websites like Facebook® to educate the public about the importance of joining the donor registry (media approach); on the other, CORE reaches out to the community through in-person campaigns at a range of venues including faith-based events, youth festivals, sporting events, health fairs, and driver's license bureaus (in-person approach). The goal of the media approach is to expose large swaths of population to pro-donation messages while the in-person campaigns target smaller sections of the population but with greater intensity.

For the number of new donor registrations from CORE's promotion effort over the three year period (2010-2012), we used separate sources of data for registrations resulting from in-person outreach and those attributed to media campaigns. Registrations from in-person outreach were obtained directly from CORE. CORE regularly reaches out to the public at various community events. At these events CORE encourages individuals to join the registry by signing a donor card. CORE uses the donor card information to register people in Pennsylvania and West Virginia state donor registries via the internet and stores the donor card for future reference. CORE provided us a de-identified list of all individuals who joined the registry at all outreach events between 2010 and 2012 [144]. The list contained only registrants' date of birth and date of joining the registry. The total number of individuals on the list represents the total registrations generated through in-person outreach. At some of the outreach events, CORE's employees and volunteers use mobile devices to sign-up individuals directly into the state donor registry [145]. These online registrations are captured in a separate report provided by CORE [146]. Donor card registrations and online registrations at outreach events were added to obtain the total in-person registrations.

For registrations from media campaigns, we used quarterly reports that CORE receives from the Department of Motor Vehicles in Pennsylvania and West Virginia [147, 148]. These reports show, for each county and each quarter, total registrations regardless of whether the individual enrolled at the DMV or

online, and includes individuals that CORE enrolled through in-person outreach. Change in total number of registrations from December 31st, 2009 to December 31st, 2012 was calculated for each county that falls in CORE's DSA and aggregated. To calculate the registrations resulting from media campaigns, we assumed that a fraction of all registrations can be attributed to media campaigns (i.e., in the absence of such campaigns, the number of donor designations would be lower). In their meta-analytic review, Feeley & Moon have estimated that communities that are exposed to media campaigns promoting organ donation have 5% more registrations ($r=0.05$; 95% CI: 0.03, 0.07; $p<0.001$) [149]. That is, 5 out of 105 new registrations or 4.762% of new registrations result from exposure to media campaigns. For accuracy, we excluded the in-person registrants from the total DMV registrations prior to calculating registrants from media campaigns. Based on a summary of media purchasing by CORE [150], we assume that the entire population in CORE's DSA was exposed to pro-donation messages multiple times.

Registrations from in-person outreach and those from media campaigns were added to obtain the total number of registrants that resulted from CORE's promotion of the organ donor registry.

3.2.1.3. Assessment of Donors

For donors, we began with the above cohort of new registrants and simulated their death as a function of their age at the time of joining the registry. We used Markov analysis to calculate the expected value of this cohort in terms of present-day donors. The analysis was conducted using TreeAge® Pro 2014 (TreeAge Software, Inc., Williamstown, MA). In addition, estimates of some model parameters (discussed later) were obtained from the analysis of CORE's decedent records using Stata 13.0 (StataCorp, College Station, TX).

Markov Model

The Markov state diagram in Figure 4 presents the various states a registrant can enter. A registrant enters the Markov model at the time of joining the donor registry. From here each year, the registrant has a small risk of death that increases with the registrant's age in subsequent Markov cycles. One Markov cycle represents one year of life. The analysis was set to run until the entire cohort of registrants was absorbed into the two dead states (became or did not become an organ donor). In each cycle there is a small risk that the registrant will leave the donor registry and exit the model with zero payoff. The payoff is positive when a registrant becomes a donor and can only be realized when a registrant dies, i.e., there are no incremental pay-offs in this model but only a final payoff at the time of death.

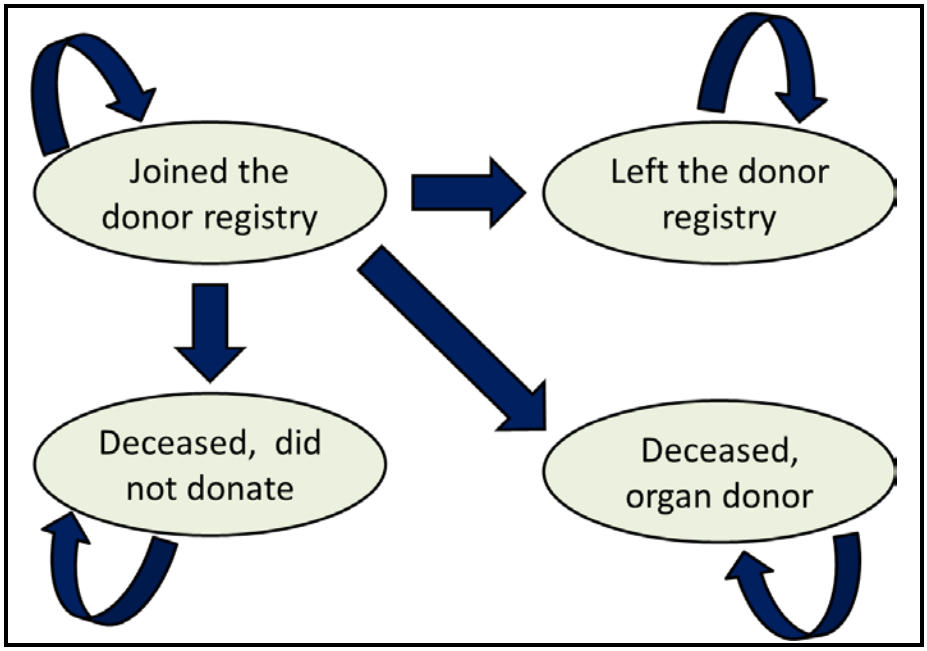
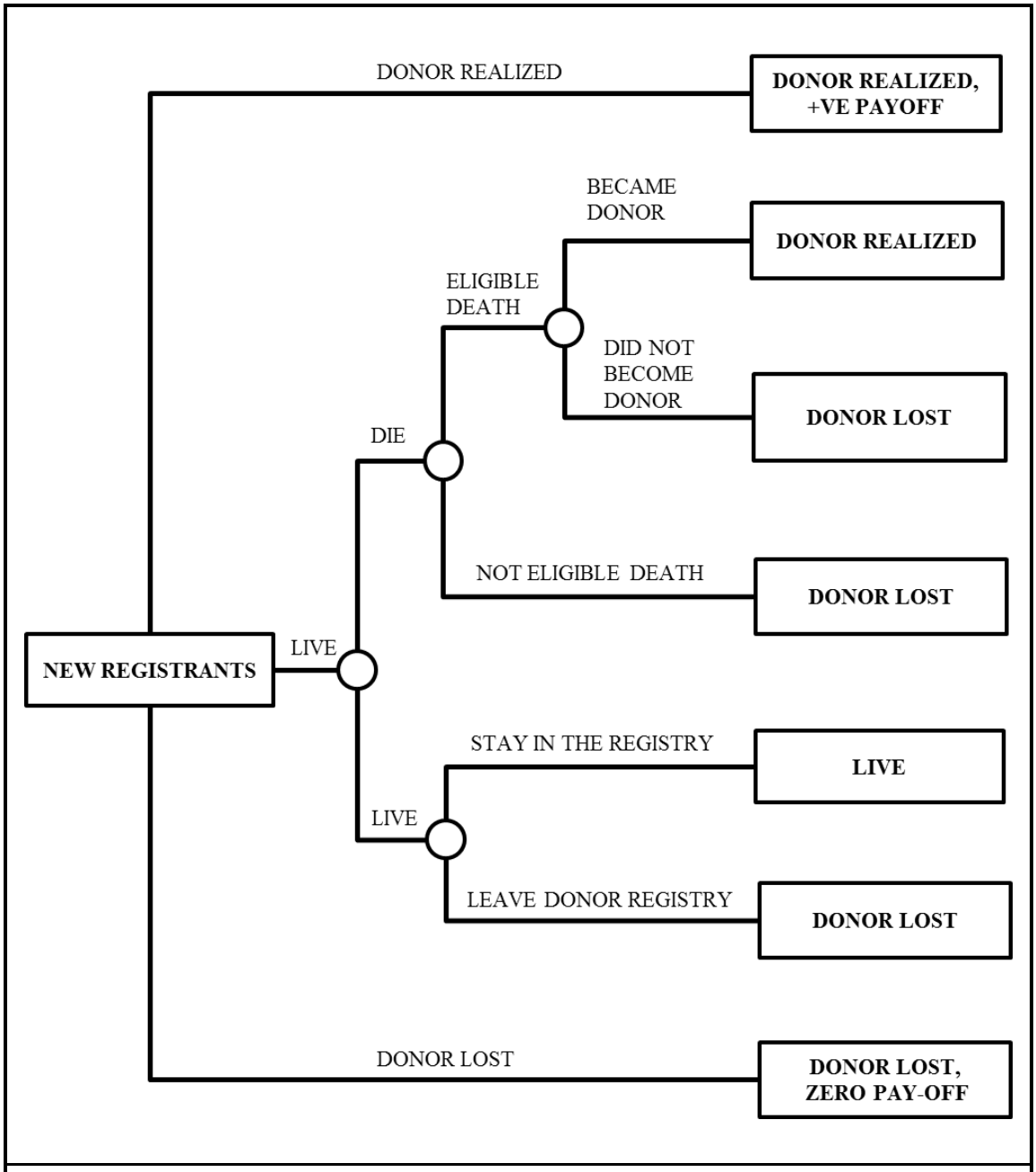


Figure 4: Markov state diagram for an individual who joined the donor registry

The Markov-cycle tree is presented in Figure 5. Upon death, the expected value of a registrant in terms of an organ donor depends on two factors: 1) the time-variant probability that the registrant dies in a

manner that renders him/her eligible to donate; and 2) the marginal probability that authorization for donation will be obtained for the eligible deceased registrant. The marginal probability accounts for the fact that eligible decedents who had not joined the registry (and who do not enter our model) can also become donors. Therefore the benefit of joining the registry is the difference in the probability of a registrant becoming a donor and the probability of a non-registrant becoming a donor.

The expected donor value of all registrants will accumulate until the entire cohort has been absorbed. Since registrants are expected to live certain number of years before they die, their expected donor value is at a point in future. Their present-day value is calculated by discounting the future value at a given social discount rate. We assume that 100% of eligible decedents are identified and referred to the OPO in a timely manner.



Separate Markov models were run for registrants from the media campaigns and those from in-person outreach because of differences in the age distribution of the two groups.
The probabilities of entering the various Markov states are discussed under “Model Parameters” and presented in Table 7.

Figure 5: Markov-cycle tree

Scenarios for Estimating Donors

By joining the registry individuals are guaranteed to become organ donors if they are deemed eligible to donate at the time of their death. This guarantee emanates from the Uniform Anatomical Gift Act of 1987 that mandates that donor cards and other expressions of intent to donate one's organs be recognized as a legally binding document [41]. In spirit of this law, if someone is eligible to donate and if he or she had her name in the registry then organ recovery can proceed without further authorization from the family. Under this first-person authorization model, the probability that a registered decedent who is eligible to donate will become an organ donor equals 1.0.

In reality however, OPOs generally abstain from such practice due to risk of negative publicity. Instead they use the donor registries as means to convey decedent's wishes to the family and convince them that donating their loved one's organs is what the decedent had desired. This is the family authorization model. Evidence suggests that family's knowledge about the decedent's wishes is an important determinant of the family's decision to donate [115-117] and therefore the probability of family authorizing donation is conditional on their knowledge about the decedent's designated donor status. This is corroborated by Siminoff & Lawrence who have found that 89.19% of families will authorize donation when they know that their relative had joined the donor registry compared to 47.55% when the family knows that the relative had not joined the registry [151].

We examined the donor value of registrants under the above two scenarios.

Model Parameters

Table 14 presents the model parameters used in the analysis. Feeley and Moon provide estimates of the effect of media campaigns [149]. The probability of family authorizing donation for an eligible deceased registrant is obtained from Siminoff and Lawrence [151]. For the probability of family authorizing

donation for non-registrants, we analyzed decedent records extracted from CORE's data system that contains information on all deaths that occur within its DSA. Real-time patient information that includes patient's demographics, eligibility for donation, decedent's registered donor status and final donor status is jointly entered into the system by the donor referral coordinator and the organ procurement coordinator [152]. Out of 424 brain-dead eligible decedents between 2010 and 2012, 136 decedents had their name on the donor registry and 100% of these decedents became organ donors. This is the probability of a registered eligible decedent becoming a donor under the first-person authorization model. Out of the remaining 288 non-registered eligible decedents where CORE had to request authorization from the family, only 65.28% became donors. This is the central estimate of family authorizing donation when they know that the patient had not joined the registry. Computation of marginal probability of an eligible deceased registrant becoming a donor under the first-person authorization and family authorization model is described in the footnotes of Table 7. The age-specific probability of death was obtained from the most recent U.S. Life Tables [153]. We assumed that there is a very small probability that an individual will leave the registry. This value was arbitrarily chosen since current literature does not inform our understanding of this phenomenon yet we are certain that this occurs, however infrequently.

We constructed tables of predicted probability distribution for two variables: registrants' age; and the age-dependent probability of dying an eligible death. The predicted probability that a registrant was of a particular age was computed using negative binomial regression. The dependent variable was the number of registrants and the predictor variable was age. This analysis was restricted to 18 years and older since only individuals of legal adult age can join the registry and become organ donors without parental consent. The post-regression predicted number of registrants by age was divided by the total number of 18 years and older registrants to obtain the predicted probability of a registrant being of particular age. For in-person outreach, we used CORE's de-identified list of all registrations that contained the registrant's date of birth and the date of joining the registry [144]. For media campaigns in West Virginia, we used West Virginia DMV Transaction Data for 2009-2011 [154]. These data were requested from the West Virginia DMV for

a previous study by one of the co-authors and contain every driver's license or state ID issuance and renewal transaction that took place in West Virginia between 2009 and 2011 (total 1.12 million transactions). For each transaction, the dataset contains among other variables, customer's date of birth, date of the transaction and whether or not the customer joined the organ donor registry. For registrants from media campaigns in Pennsylvania, we assumed that West Virginians do not significantly differ from Pennsylvanians in their age distribution. Indeed, according to the Demographic and Housing Estimates for 2013 [155], the distribution of the two populations by age-group is strikingly similar. A graphical comparison of the population distribution by age in the two states is provided in Appendix F.

Age-dependent predicted probability that a decedent died an eligible death was computed using logistic regression. The dependent variable was whether a decedent died an eligible death and the independent variable was the age of the decedent. The dataset used was CORE's decedent records [152]. The predicted probability distributions of registrant's age and age-dependent probability of dying an eligible death are graphically presented in Appendix G.

3.2.2. Sensitivity Analyses

Monte Carlo probabilistic sensitivity analyses were performed using TreeAge® Pro 2014 (TreeAge Software, Inc., Williamstown, MA). Since we use CORE's actual expenditure of promoting the donor registry, the upfront costs in this analysis are 'certain' and therefore cannot be subject to sensitivity analyses. We use sensitivity analysis to determine the expected range of registrants and donors that result from CORE's promotional activities.

For the expected range of registrants resulting from CORE's promotion activities, registrations resulting from in-person outreach, like costs, are fixed and therefore are not amiable to sensitivity analysis.

For registrations resulting from media campaigns, we used Feeley and Moon's 95% confidence bounds of the effect of media campaigns [149].

For the expected range of donors, we performed Monte Carlo probabilistic sensitivity analyses on the probabilities of family authorization and first-person authorization, Markov transition probabilities, the effect of media campaigns and the social discount rate. For all sensitivity analyses, the plausible range of values that each model parameter can assume is presented in Table 7. Unless otherwise specified, the plausible range of values depicts the 95% confidence intervals that we computed around the central estimates. For the probability that a registrant might leave the registry, the lower and upper bounds were arbitrarily chosen. Feely and Moon provided the 95% confidence intervals for the effect of media campaigns [149]. The range of probability that the family will authorize donation when it is known that the decedent had not joined the registry is described in footnote 2 in Table 7. Registrants' age distribution and the probability of dying an eligible death are predicted probability distribution tables similar to U.S. Life Table. Sensitivity of the model to key parameters is presented through tornado diagrams.

Table 14: Model Parameters

Item	Baseline	Plausible Range	Ref.
Probabilities			
Family Authorization Model[1]			
If the family knows the patient is a registrant, family will authorize donation.	0.8919	0.7981 – 0.9522	[151]
Even if the family knows the patient is not a registrant, family will authorize donation.	0.6528	0.5517 – 0.7529[2]	
First-person Authorization Model[3]			
A registrant who dies an eligible death will become a donor.	1.0	N/A	[41, 152]
Individual leaves the donor registry.	0.001	0.0005 – 0.0015	Assmp.
A registrant will die at a given age.	U.S. Life Tables		[153]
An individual dies an eligible death	Eligible death probability table		[152]
Age at the time of joining the registry			
Registrants through mass media campaigns	Table of predicted probability that a registrant is of a particular age.		
Registrants through in-person outreach	Table of predicted probability that a registrant is of a particular age.		
Effect of mass media campaigns	0.05	0.03 – 0.07	[149]
Total Registrants	91,705	N/A	
Social discount rate	0.03	0.01 – 0.05	

[1] For the family authorization model, the marginal probability is calculated by subtracting the probability that the family will authorize donation even if the family knows the patient is not a registrant (0.6528) from the probability that the family will authorize donation if the family knows the patient was a registrant (0.8919).
[2] The lower and upper limit of the range was determined from CORE's conversion rate for non-registered eligible decedents for 2010, 2011 & 2012. The lower limit is the probability that the family authorizes donation for a non-registered eligible decedent in 2010. The upper limit is from the year 2012.
[3] For first-person authorization, the marginal probability is calculated by subtracting the probability that the family will authorize donation even if the family knows the patient is not a registrant (0.6528) from the probability that an eligible registrant will become a donor under the first-person authorization model (1.0).

3.3. RESULTS

3.3.1. Costs

All cost estimates with the exception of cost per registrant are rounded off to the nearest thousand. Over the three-year period CORE spent $3,049,000 on promoting the donor registry.

3.3.2. Registrants & Cost per Registrant (Base Case)

An estimated 6,708 individuals joined the registry during the study period. Of these, 2,458 individuals joined the registry at an in-person outreach event either by signing the donor card or online through mobile devices and 4,250 registered at the DMV or online as a result of exposure to media campaigns. Steps in computation of the central estimates are presented in Table 15. The mean age of registrants through the media campaigns was 40.4 years and of registrants from in-person outreach was 41.3 years. The cost of registering any individual is $455 which is less than Howard and Byrne's estimate of the monetary value of a 65 year old registrant ($478), the least valuable registrant.

Table 15: Total registrations from public education

	Total new registrants in CORE's DSA (from Appendix H)			91,705
Step 1	New registrants from in-person outreach			2,458
Step 2	Net registrants after excluding registrants from in-person outreach	91,705 – 2,458	=	89,247
Step 3	Registrations attributable to media campaigns @4.762% [149]	89,247 * 0.04762	=	4,250
Step 4	Total registrations from public education	4,256 + 2,458	=	6,708

3.3.3. Donors and Cost per Donor (Base Case)

First-Person Authorization

Under the first-person authorization model, the 6,708 individuals who joined the registry as a result of CORE's promotion activities will result in 8.2 donors after 23 years of joining the registry. After discounting at 3 percent for the fact that the benefits accrued in future have a lesser present-day value, these equal 4.2 present-day donors. That is, 1,597 registrants will result in 1 present-day donor. If all registrants were 18 years old, they would result in 5 present-day donors. The cost per donor for a 41-year old registrant is $726,000 compared to Mendeloff et al.'s estimate of the donor's monetary value to the society of $1,086,000.

Family Authorization

Under the family-authorization model, the 6,708 registrants will result in 5.4 donors after 23 years of joining the registry, which is equal to 2.8 present-day donors after discounting at 3%. That is, 2,396 registrants will result in 1.0 preset-day donor. If all registrants were 18 years old, they would result in 3.2 present-day donors. For our average registrant, who is 41 years old, the cost per present-day donor is $1,089,000 which is very close to Mendeloff et al.'s estimate of the donor's monetary value to the society of $1,086,000.

3.3.4. Sensitivity Analyses

Monte Carlo probabilistic sensitivity analysis indicates that 95% of estimates of additional registrants are bounded within 5,429 and 7,956 registrants. Accordingly, the cost varies from $383 to $562 per registrant. For the number of donors, the results from one-way sensitivity analysis are presented as tornado diagrams in Figure 6 (first-person authorization) and Figure 7 (family authorization).

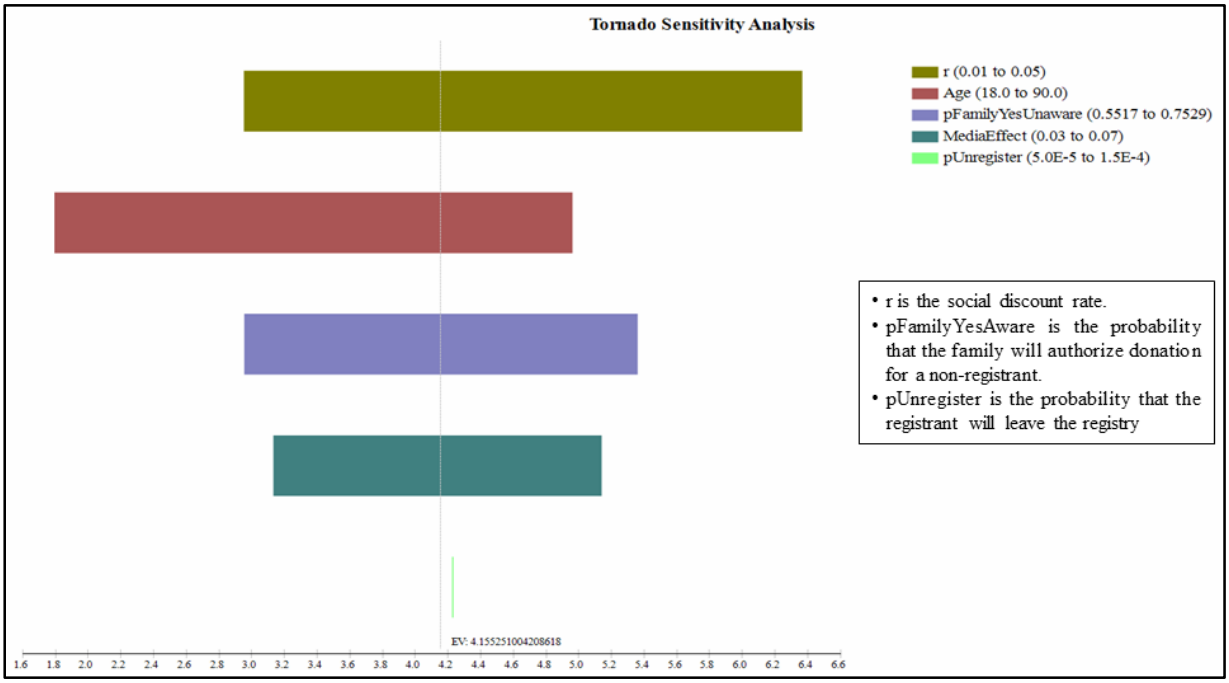


Figure 6: One-way sensitivity analysis of key model parameters (first-person authorization)

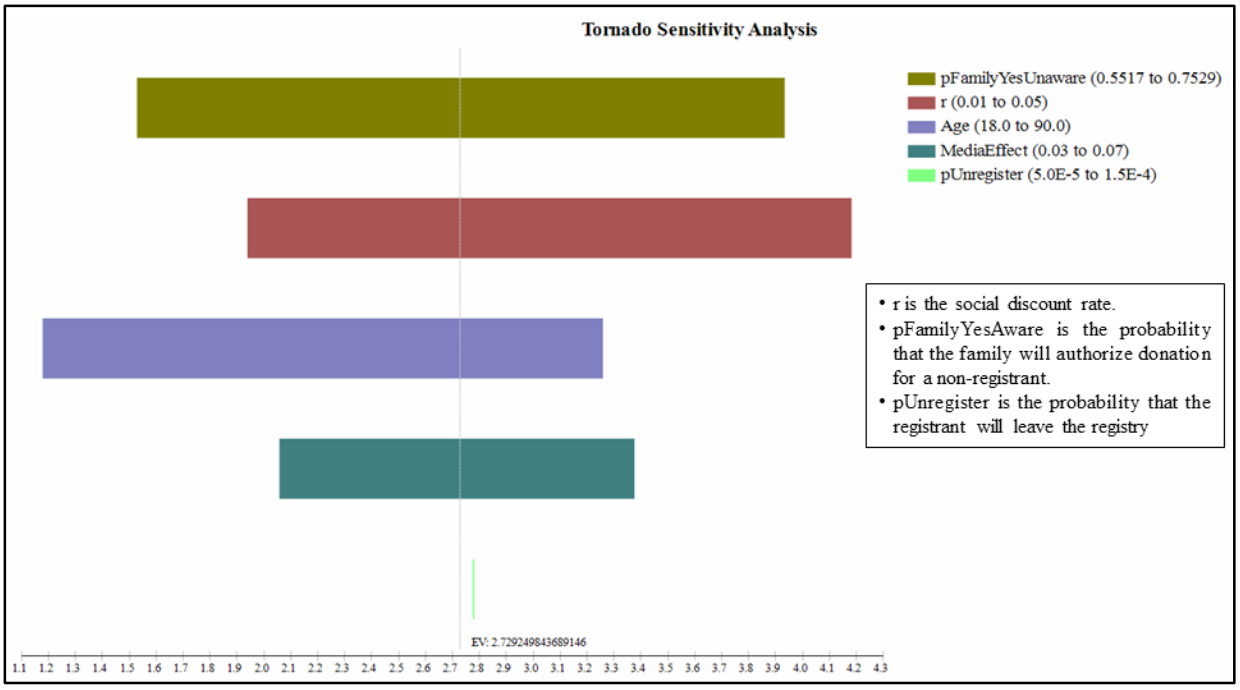


Figure 7: One-way sensitivity analysis of key model parameters (family authorization)

Probabilistic sensitivity analysis of the number of additional donors indicates a 95% confidence interval of 2.5 to 6.6 donors under the first-person authorization model with cost per donor ranging between $462,000 and $1,220,000. Under the family authorization model, the 95% confidence interval spans from 1.3 to 4.8 donors and the cost per donor falls between $635,000 and $2,345,000. Figure 8 presents the probability distribution of expected donors under the two authorization models.

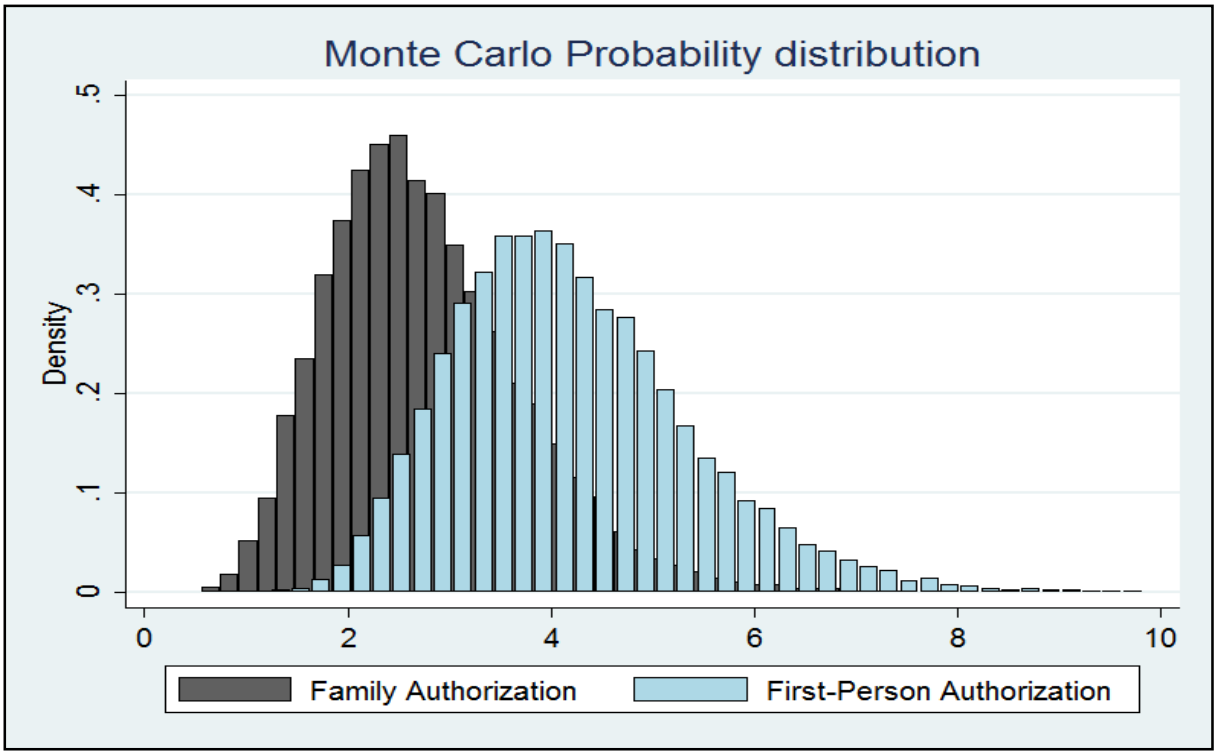


Figure 8: Additional donors under the first-person and family authorization models

3.4. DISCUSSION

In spite of concerted efforts of the organ donation community to promote state donor registries, less than half of all Americans have signed up as organ donors even though over 90% endorse organ donation as a positive altruistic choice [156]. In 2012, there were only 108 million individuals on state donor registries nationwide, that is only 45 percent of all individuals 18 years and older [77]. While Pennsylvania is slightly better than the national average (46 percent), only 35 percent of individuals 18 years and older are registered donors in West Virginia [77]. In the last decade, OPOs nationwide have invested considerable resources in promoting the registry with the belief that additional registrations will have a positive impact

on donor supply. However as we have discussed earlier, determining the relationship between registrants and donors can be tricky.

Previously, Beasley et al. have proposed a simple analytical model to estimate the number of new registrations required to generate one additional donor [157]. They estimated that 83,300 new registrants will produce one incremental donor in the same year under a 100% efficient system where each potential donor is identified and referred, and a request for donation is made to the family [157]. In contrast, using the same assumptions (100% efficient system, family can refuse donation), we estimated that 2,396 registrants are needed to generate one present-day donor (6708 donors result in 2.8 present-day donors). Our examination of this enormous difference reveals following critical differences between the two models. First, Beasley et al. have used crude probability of death that takes into account the very low probability of death in children after infancy (p=0.008). In contrast, we have used age-adjusted death rate on a registrant population that was 18 years or older (crude p=0.0096) suggesting that individuals in our model die sooner (less effect of social discounting). Second, the probability of a decedent being an eligible donor in Beasley et al.'s analysis is 0.0075 while the same probability in our analysis after adjusting for age distribution of the registrants is 0.05. This difference is probably the biggest contributor to the discrepancy between Beasley et al.'s model and our model. The high probability of a decedent being an eligible donor in our model is largely due to two reasons. First, we have included all eligible deaths regardless of whether they are brain-dead or not while Beasely et al. included only the brain-dead donors. In CORE's decedent records, the probability that a decedent is a brain-dead eligible decedent is 0.005 while the probability that a decedent is any type of eligible death is 1.7 times higher (p=0.0085). If we had considered only brain-dead donors, we would underestimate the number of donors that will result from the registrants. Second, young registrants (between 18 and 30 years) are overrepresented in our cohort of registrants when compared with the national estimates. In our simulated cohort, 36% of registrants are between the age of 18 years and 30 years. Within this age group, the probability of a decedent being an eligible donor is 0.07, more than 9 times higher than the overall probability of 0.0075 in Beasley et al.'s model.

3.4.1. Donor Registry Promotion- Outcome and its Cost

Compared to Howard and Byrne's estimate of $840 for the value of one 18 year old registrant under the family-authorization model [142], we estimated the cost of registering one individual of any age at $455. This is lower than Howard & Byrne's estimated monetary value of a 65+ registrant at $478. This means that even if all registrants were 65 years old, CORE's public education strategy would cost less than the society is willing to pay for an additional registrant. We also estimated that under the first-person authorization model, CORE's promotion efforts would generate 4.2 present-day donors at a cost of $726,000 per donor. This estimate of cost per donor is 33% less than the monetary value of one donor that Mendelof et al. had estimated ($1,086,000). However under the family authorization model, the cost of generating one donor increased to $1,089,000 surpassing Mendeloff et al.'s estimate by a narrow margin of $3,000. However if all the registrants were 18 years old, our estimates of cost per donor under the family authorization model would remain under the Mendeloff et al.'s estimate.

Following points should be considered before interpreting the above comparisons. First, the family authorization model is much less relevant to our analysis than the first-person authorization model. The fact that CORE converted every deceased registrant who was eligible for donation into an organ donor during the study period suggests CORE's preference for first-person authorization model when an eligible decedent is a registered donor. While we do not have access to CORE's decedent records predating our study period to corroborate this observation, Beard et al. have noted CORE's atypical behavior as an exception in the OPO community as far back as 2006 [158]. Second, although our analysis suggests that CORE's registry promotion offers good return on investment, our cost per donor reflects the cost of "securing" one donor which only guarantees that an eligible decedent will become an organ donor. However for this to happen, a series of procedures must take place. These include identification and referral of imminent-death patients, brain death testing, optimum donor management and request for donation. Every process incurs additional costs that are borne by the clinical services department of CORE and have not

been considered in our analysis. In addition, several of CORE's personnel are involved in educating critical care staff at over 100 hospitals in their service area. The efficiency of these hospitals in the procurement process is, in part, a function of professional education. The true cost of "procuring" one donor should include these costs as well. We do not have information on the cost of these processes but if we could include these in our analysis, our estimates of the first-person authorization model would shift in the direction of Mendeloff et al.'s estimate. Nevertheless, it is unlikely that the costs would escalate so much that they will surpass the monetary value society places on one donor. Overall, since the return on registry promotion in terms of monetary value of a donor is greater than the investment, promoting donor registries appears to be a good bargain for the society.

A more fundamental observation is that CORE's donor registry promotion has a positive impact on the supply of organ donors. This observation is in direct conflict with Beard et al.'s argument that the resources spent on organ donation education do not increase the supply of cadaveric donors, at least not anymore [159]. Using ordinary least squares regression, Beard et al. have estimated the effect of public education expenditure on donors per 1000 hospital deaths at the DSA level. After controlling for population size, race, education, income, region of the U.S., and professional education expenses in their analysis, these authors did not find public education expenditures to be significantly associated with donation rate per 1000 deaths.

The first reason these authors posit is that public education programs have been in existence for several years so their effect would progressively decrease according to the law of diminishing returns. However this would not hold true if public education also encourages the community members to join the donor registry, for two reasons. First, each year there is a steady stream of 16-year olds who are eligible to join the registry and there is no evidence that baseline registration rate will be sustained if exposure to pro-donation messages is stopped. Second, assuming that the baseline registration rate is sustained, the law of diminishing returns applies only if the public education strategy remains unchanged. Present public outreach activities are more focused and target ethnic and racial minorities and older adults, who are more

resistant to the idea of organ donation as well as young adults who are underrepresented on the donor registries.

The second reason Beard et al. give is that public education programs target the entire population while only a fraction of the population will ever have to make a decision about donation [159]. Verble and Worth also make this point in arguing that spending should be increased on professional education rather than public education because the former offers a more targeted approach while the latter is broader and therefore less effective [160]. But this is true for any type of effort that uses mass media. For instance, prescription drug manufactures often target a wide population base with advertising although only a small fraction of the population is expected to ever make a decision on brand. The fact that manufacturers continue to spend heavily on such advertisements strongly suggests that it has the desired effect. By analogy, even a small effect of public education on the number of organ donor designations can have an important impact on the number of actual donors. In fact if public education encourages people to join the donor registry that, in theory, guarantees organ donation when eligible; then public education's protective effect against family refusal offers a clear advantage over professional education.

3.4.2. Study Assumptions

Assumptions concerning the model parameters have been discussed before. In addition, we made two assumptions that guided our model development. The first assumption we made is that the media campaign reached the entire service area's population. Based on the summary of CORE's media purchases, CORE's pro-donation messages were relayed over 3 television stations and 20 radio stations [96]. In addition, outdoor messaging was placed in 212 locations and online campaigns were launched on Google® and Facebook® [96]. The pro-donation messages were relayed 3,087 times through the radio stations alone. Further, the public education program reached more than 5.5 million people, the entire population of CORE's service area. Before we used these estimates, we tested if this extent of reach was even possible.

As a reality check, we assumed that CORE could comprehensively reach only 20% of the counties. We further assumed that to maximize the effect of their media campaign, CORE would target counties with the greatest potential, those with the largest populations. Our calculations indicate that 79 percent of new drivers and state ID holders came from only 20 percent of the counties in CORE's service area (16 out of 81 counties). We inferred that a well thought-out campaign strategy could reach the entire service area population.

The second assumption we made is that the system of identification and referral of potential donors is 100% efficient. We believe this is a reasonable assumption for several reasons. First, OPO personnel who are responsible for public education regularly conduct retrospective review of medical records for eligible deaths. If eligible decedents are identified, they are noted and remedial measures are employed. As a result, some of the unidentified pool is captured and reflects in the lower conversion rate of eligible deaths to organ donors. Second, the loss of eligible decedents is a function of hospital-centered processes (and professional education) rather than public education. Adjusting for this loss in the analysis would penalize the effectiveness of public education programs. Third, this assumption introduces minimal bias in our estimates. This is because since we have used incremental probability of an eligible registrant becoming a donor, any loss of donors during the identification and referral process would be scaled down to the magnitude of incremental probability. This is illustrated with the following hypothetical situation. Suppose the probability of family authorizing donation is 1.0 for registrants and 0.75 for non-registrants, and the probability of an eligible donor not being identified / referred is 0.2. If we used the absolute probability of becoming a donor then the true effect of education programs would be 20 percentage points less than our estimates (1.0 x 0.2 = 0.2). However, if we used the incremental probability (1.0 - 0.75 = 0.25) to measure the effect, the true effect would be only 5 percentage points less than our estimates (0.25 x 0.2 = 0.05).

3.4.3. Do Additional Registrants Equal Additional Donors?

Howard and Byrne note that people who are likely to become organ donors are unlikely to register [142]. Consequently, current registrants are under-represented in the potential and actual donor pools. To test if our analysis is affected by this phenomenon, we compared the proportion of eligible deceased registrants in CORE's decedent records (2010 thru 2012) with the registration rate in CORE's service area. From 2010 through 2012 in CORE's service area, 35 percent of the eligible decedents were registered donors compared to 44 percent of drivers/state ID holders (2012) suggesting that under-representation of registrants is in fact affecting our analysis. But when we restrict our analysis to individuals 18 years and older and living in CORE's DSA, we find that 38 percent of eligible decedents are registered donors compared to 40 percent of those alive. These findings suggest that the registrants in CORE's service area are only slightly under-represented in the eligible death and donor pools. The interpretation is that currently non-registered individuals in CORE's DSA do not differ from those on the state registries in their probability of dying an eligible death. For this reason, the society will value a "marginal" registrant (someone who is not currently registered) at the same level as current registrants.

3.4.4. Sensitivity Analyses

We tested the sensitivity of our model to only those parameters that did not vary with the individual's age of joining the registry. The age-dependent probability of death and the age-dependent predicted probability of dying an eligible death were excluded for this reason. Another parameter that we excluded from the sensitivity analysis was the probability that an eligible deceased registrant will become a donor under first-person authorization since this parameter, by definition, cannot assume any value other than 1. The first-person authorization model was most sensitive to the social discount rate followed by age. With the mean age of 40.7 years, an average registrant is expected to live for 40 more years, which explains

the model's sensitivity to changing values of the social discount rate. Under the family authorization model, the probability that the family will authorize donation for a non-registrant has the greatest influence followed by social discount rate and age of the registrant. Since we have used marginal probabilities in our analysis, the value of a registrant under this model depends on the difference in the probability of the family authorizing donation for a registrant (0.8919) and that of a non-registrant (0.6528). Compared to the first-person authorization model where the marginal probability is 0.3472 (1.0 - 0.6528), the marginal probability under the family authorization model is 0.2391 (0.8919 – 0.6528). This means that for an identical increase in the probability of family authorizing donation for a non-registrant, there is greater percentage reduction in the marginal probability under the family authorization model which explains the model's sensitivity.

Monte Carlo probabilistic sensitivity analysis indicates that younger registrants are more valuable than older registrants in terms of future organ donors. At any age assuming a constant authorization rate, the trade-off between the risk of death and the probability of dying an eligible death determines the overall probability of becoming a donor. While the risk of death increases with age, the probability of dying an eligible death decreases. Since the probability of dying an eligible death diminishes faster than the risk of death increases, younger registrants are valued more than the older registrants in the model. In Figure 10, we have presented the density distribution of expected number of donors. The expected values of donors under the first-person and family authorization model considerably overlap owing to our distributional specifications and a small magnitude of difference in the mean expected number of donors under the two models of authorization. Given the extent of overlap, the two simulated samples will not be significantly different in statistical terms. One explanation for this insignificance is that there is actually no difference between the two models and that it doesn't matter whether an OPO goes ahead with donation in an eligible deceased registrant or defers the decision to the family. Alternatively, the distributions used for the sensitivity analyses should be more tightly specified.

3.4.5. Average Costs and Effects vs. Incremental Costs and Effects

According to Drummond et al. [161], studies that do not have a comparison strategy (including this study) classify as a "cost-outcomes description" which is a partial economic evaluation. We want to point out that although we did not have a comparison strategy, this analysis is a special case of cost-effectiveness analysis since the costs and effects in our analysis represent incremental rather than average costs and effects. Using registrants in our analysis to illustrate this point, the number of individuals who signed the donor registry as a result of CORE's promotion efforts was estimated from two sources. For the in-person outreach, CORE provided us a list of 2,458 individuals who either signed the donor card or registered online at the event. Had CORE not reached out to these individuals, it is unlikely that they would have joined the donor registry. These 2,458 individuals therefore represent the incremental benefit generated by CORE's promotion strategy. For the media campaigns, we had used Feeley and Moon's effect of media campaigns on registrations [149]. They found that communities exposed to media campaigns have 5% more registrations than those not exposed to media campaigns [149]. That is, media campaigns have a 5% incremental effect. Together, the in-person outreach and media campaigns generated 6,708 registrants in incremental benefit. For estimating the cost of registry promotion, we had assumed that the cost of operating the online database is zero since most state donor registries are appended to existing DMV information technology systems. Howard and Byrne also note that while the costs of operating the registry are unknown, the cost of enrolling registrants requires minimal "administrative machinery" [142]. Accordingly, we did not include "no promotion" as a comparison strategy in our analysis since the cost per registrant and cost per donor of this strategy would always be zero. Had we included the "no promotion" strategy in the analysis, the incremental cost-effectiveness ratio (ICER) would be calculated as:

$$ICER = \frac{Cost_{Promotion} - Cost_{No\ Promotion}}{Benefit_{Promotion} - Benefit_{No\ Promotion}}$$

Since the cost of not promoting the registry would be zero, the incremental cost of promotion would be what CORE had spent on promoting the registry. The incremental benefit would be the number of individuals who joined the registry as a result of CORE's promotion efforts. If we substitute these values in the above mathematical formula, the ICER would equal to $455 per registrant, and by extension, $726,000 per donor (under first-person authorization) which is the same as our estimates without the comparison strategy.

3.4.6. Limitations

We have examined the cost of securing future donors from the perspective of the OPO but costs are incurred by other stakeholders too. Organizations like Donate Life America are nationally active in registry promotion. In addition, we are aware of at least two HRSA-funded projects to promote donor registry that were active in CORE's service area during the study period. The results of these studies have not been published yet so we cannot say to what extent these projects increased the donor registration rate. Additionally, CORE relies heavily on its volunteers to promote donor registry. We were able to obtain these costs but did not include these in our analysis to keep the perspective of our analysis clearly defined. However, we examined the average number of volunteers that went to each event and the average number of hours they spent at each event (including two hours of travel time). Based on the minimum wages in PA and WV [162], we estimated that $34,000 worth of unpaid volunteer work was involved in community outreach. This is just 1% of CORE's total spending on public education.

The majority of parameters we used in our model are largely specific to CORE's service area. An advantage of such specificity is that our estimates accurately represent the costs and effects of CORE's public education program. A disadvantage is that our results lack generalizability to other OPO service areas or to national estimates. In fact, it is questionable if estimates from this type of analysis can ever be generalized to other OPOs given the variation in the baseline registration and donation rates, population

demographics and OPO management structures. Moreover, unlike one drug that may vary by dose, education programs can come in innumerable shapes and sizes. If the subject of the analysis is not comparable, it becomes extremely difficult to produce generalizable estimates. However, in lieu of generalizability, this paper serves as an analytical framework for other OPOs to examine the return on their investments in donor registry promotion.

CHAPTER 4: IMPACT OF DONOR REGISTRY PROMOTION ON ORGAN SHORTAGE AND ITS ASSOCIATED COSTS

4.1. BACKGROUND

Current efforts to address the shortage of cadaveric organs have primarily relied on four approaches. These include transplanting organs from marginal donors, hospital development, improving the organ donation process, and promoting the donor registry [163-165]. Organs from marginal donors (non-standard criteria donors) have shown promise but their transplant is associated with poorer health outcomes [165]. Although their use is on the rise, the effect on the waiting list has been minimal since these organs are currently less readily accepted. OPOs have used hospital development to educate the critical care staff about their role in the donation process. The goal is to improve coordination on donor cases and minimize process failures. Its impact on organ shortage is limited by the high rate of nursing staff turnover in hospitals. In addition, hospital development is costly due to the need for repeated exposure of nursing staff to donation education. Improvements in the organ donation process brought about through the organ donation breakthrough collaborative [51-54, 81] and required request and referral legislation (42 CFR §482) have markedly increased the conversion of potential donors to actual donors. In recent years however, the conversion rate has plateaued at less than 100% primarily because of factors affecting family authorization that are outside the control of the OPOs and the hospitals [113, 115-118, 138, 139].

Donor registry promotion is one frontier that has attracted much attention for its untapped potential. It is hypothesized that if more individuals participate in the registry, the problem of family refusal can be solved (provided first-person authorization is honored). OPOs and organizations like Donate Life America invest considerable resources in the promotion of donor registries. In recent years, HRSA has funded a large portfolio of research on innovative approaches to adding donors to the state registries. The premise behind

these efforts is that more donor designations will result in more organ donors. Recent DLA annual report suggests that this is actually happening. Nationwide participation in the donor registry has witnessed a steady rise with total participation in the donor registries crossing the 100 Million mark in 2011 [77]. According to the 2012 Donor Designation Report Card, the fraction of donors who had joined the registry before their death is also displaying an upward trend (28% in 2009, 33% in 2010, and 36% in 2011) [77].

Our principal finding in chapter 3 that donor registry promotion results in additional donors also substantiates the presumption that additional registrants result in additional donors. In addition, our results suggest that donor registry promotion is cost-effective when compared to previously published estimates of a donor's monetary value to the society [141]. In this paper we extend this analysis to the level of the organ. The extent to which registry promotion can impact the organ shortage, and its financial impact on the society have not been previously quantified. These relationships warrant examination for several reasons. For one, the transplant waiting list is a composite list of individuals who are waiting for one or more organs and the demand for some organs is more than others. Second, donors do not yield all organs equally. Some organs such as kidney are more frequently recovered than other organs. The interaction between these two factors has important implications on the extent to which shortage of specific organs is addressed as well as the costs incurred.

In this paper, we examine two key issues: 1) what is the maximum potential effect on organ shortage that we can achieve through registry promotion (we refer to this as the "impact threshold"); and 2) what is the cost of reaching the impact threshold (budget impact)? The impact threshold of registry promotion is benchmarked against the goal of arresting the growth of the transplant waiting list. At present, the prospects of supplying enough organs to clear the waiting list are gloomy. A more reasonable goal for the society would be to arrest the growth of the transplant waiting list. The implication of this exercise can be illustrated as follows: If greater investment in registry promotion can yield enough organs to arrest the growth in waiting list, then parallel advancements in transplant medicine that aim to increase organ supply (for instance, further expansion of the donor pool or increasing the use of marginal organs) can potentially

shrink the waiting list. Our intent in this paper is to initiate a discussion on whether donor registry promotion has the potential to address the organ shortage in a meaningful manner and if the associated costs are affordable.

4.2. ANALYTIC FRAMEWORK

The impact threshold of donor registry promotion and the associated cost were examined from the perspective of an OPO. We used data from a typical OPO located in the mid-Atlantic region of the United States. The Center for Organ Recovery and Education (CORE) is one of the 58 federally designated OPOs; it serves western Pennsylvania and most of West Virginia. For this analysis, we focused on the four major solid organs including kidney, liver, lung and heart. We excluded pancreas from our analysis since it is typically transplanted either simultaneously with or following a kidney transplant. Small intestines were also excluded since they too are typically part of multi-visceral transplants. In addition, we assume that all organs are intended to be single organ transplants.

4.2.1. Impact threshold of registry promotion on organ shortage

If there are no budget constraints and assuming that there is a constant rate of positive marginal return on investment in the donor registry, any number of organs desired can be secured by spending more on registry promotion. This is depicted by line segment AE in Figure 10. Under this assumption, the number of additional donors secured by investing greater resources in registry promotion has no ceiling.

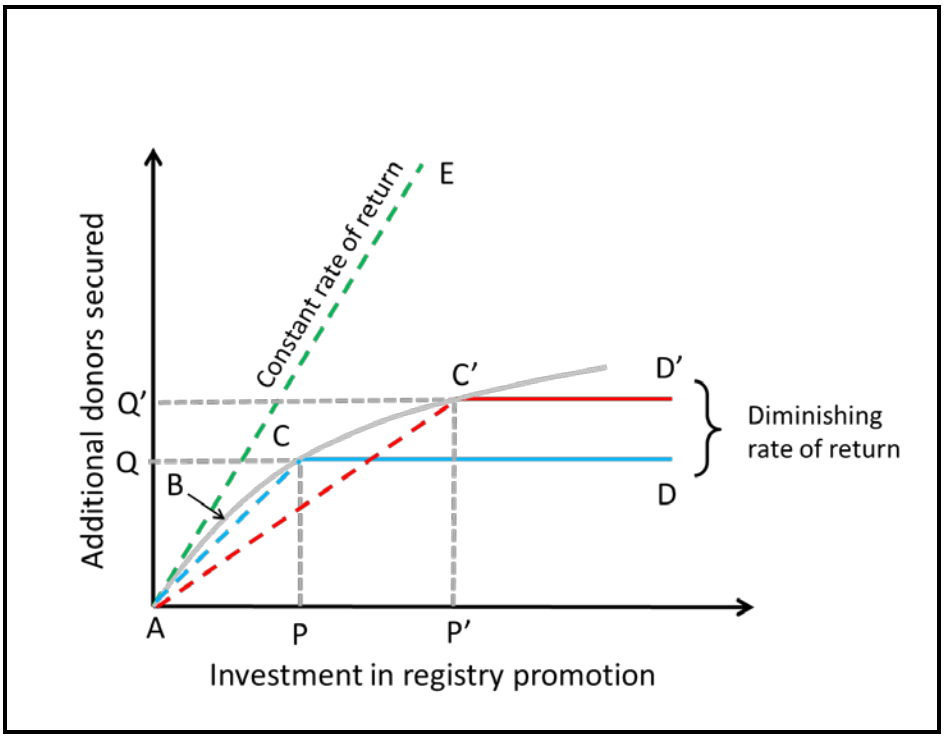


Figure 9: Marginal return on investments in registry promotion

In reality however, the number of incremental donors will progressively decrease as more money is invested in registry promotion (arc ABC) according to the law of diminishing marginal return. Let us assume that point Q represents the impact threshold. That is, Q represents the maximum number of donors that can be secured through registry promotion. At point Q, the identified potential donor pool is completely realized (conversion rate equals 100%) and no additional donors can be secured by investing more resources in donor registry promotion since the marginal return on investment in registry promotion beyond this point will equal zero. Therefore the true marginal return on investment in donor registry promotion assumes the line ABCD. For simplification, we assume that marginal return on donor registry is represented by a constant return on investment up to the point Q (line AC) beyond which the marginal return equals zero (line ACD). The point P represents the marginal cost of securing the Q^{th} donor and the rectangle QAPC represents the total cost of reaching the threshold impact.

To estimate the number of additional donors that are secured before reaching point Q, we conducted a retrospective analysis of CORE's decedent records for the year 2010 through 2012. During this period, 324 (standard criteria donors) out of the 424 brain-dead eligible decedents became organ donors and 100 eligible decedents were lost to family refusal. If infinite resources were invested into donor registry promotion, then all eligible decedents would be registered decedents and the 100 decedents that were lost to family refusal would become organ donors under the Uniform Anatomical Gift Act. When these 100 donors are realized, the identified donor pool would be exhausted and no more donors would result. That is, unlimited donor registry promotion would result, at maximum, in 30.9% more donors (100/324). From 2010 through 2012, CORE's DSA has produced, on an average, 206 donors annually (includes standard criteria, expanded criteria and non-brain dead donors). If CORE had an unlimited budget, the benefits from CORE's expansion of registry promotion would be limited to 64 additional donors (30.9% of 206)[27].

The average yield of each type of organ from a donor from CORE's DSA is listed in Table 1. According to Table 1, the 64 additional donors would have yielded 73 kidneys, 45 livers, 18 lungs and 15 hearts. This is the maximum number of each type of organ that would be secured even if CORE invested in registry promotion beyond rectangle QAPC. This is the impact threshold of donor registry promotion in CORE's DSA with the current identified potential donor pool.

[27] For CMS reporting purposes, non-standard criteria donors are considered eligible deaths only if they become donors, therefore the observed conversion rate for non-standard criteria potential donors is always 100%. However we assume that the unobserved conversion rate of non-standard criteria potential donors will be similar to the observed conversion rate of standard criteria potential donors. Therefore improvement in conversion rate will result in additional standard criteria as well as non-standard criteria donors.

Table 16: Total organs transplanted and organs transplanted per donor

	From 618 Donors	OrgTxDon*
Kidneys	702	1.14
Liver	433	0.70
Lung	175	0.28
Heart	144	0.23
All organs	1454	2.35

* OrgTxDon is organs transplanted per donor calculated by dividing the total number of organs by the number of donors.
There were 618 deceased donors in CORE's service area (2010 – 2012).

If improvements in identification and referral of potential donors expand the identified potential donor pool, then the impact threshold will rise. In Figure 10, the new impact threshold is represented by Q' and the new marginal return on investment is defined by line ABC'D'. Sheehy et al. estimated that in 1999, there were 13,317 potential brain-dead donors among 2.4 million deaths in the United States [70, 90]. Assuming that this rate has not changed significantly over time and is representative of CORE's DSA, CORE should identify, on an average, 155 deaths as eligible brain-dead donors out of the 28,000 deaths reported annually. In reality, CORE identified 141 brain-dead eligible deaths annually during 2010 through 2012. At the current conversion rate of 76.4%, 11 out of the 14 now identifiable eligible deaths would become organ donors but the remaining 3 donors could potentially be secured through investment in registry promotion. Under Sheehy et al.'s estimates, the impact threshold of registry promotion would be reached at 67 donors who would yield 76 kidneys, 47 livers, 19 lungs and 15 hearts.

4.2.2. Impact threshold compared to the benchmark of arresting waiting list growth

As of May 30th, 2014, there were 2,738 patients waiting for an organ transplant in CORE's DSA. Of these 2,055 patients need a kidney transplant, 523 patients need a liver, 78 patients are waiting for a heart and 82 patients require a lung transplant [1]. Since these are active waiting list registrations, the only

factor preventing these individuals from getting off the waiting list is the availability of a suitable organ. Each year more patients are added to the waiting list. While many individuals are removed from the waiting list for various reasons, many more are added each year.

Using waiting list data from Organ Procurement and Transplant Network [1], we calculated a three-year average (2010-2012) of waiting list additions and removals in CORE's DSA. For the number of people added to the waiting list, we aggregated new registrations on the waiting list from 2010 through 2012 and divided it by 3 to obtain the average annual additions to the waiting list. For removal from waiting list, we defined removals as only those individuals who were removed because they received a transplant in the United States or their condition improved that made them ineligible for a transplant. Individuals who died while waiting for a transplant or received a transplant in another country, and those who became too sick for a transplant were not considered as removals. Removal for these reasons from the waiting list is not an indicator of organ supply. Table 19 presents the average additions and removals as well as the net growth in the waiting list by organs in CORE's DSA. The impact threshold of donor registry promotion with the current donor pool is presented in the last row.

Table 17: Average additions, removals, and growth in the waiting list by organ

	Total	Kidney	Liver	Heart	Lung
Waiting List Additions	1269	664	350	93	162
Waiting List Removals	900	428	248	85	139
Net Growth	369	236	102	8	23
Impact Threshold (Current potential donor pool)	151	73	45	15	17

Except for heart, the net growth in the demand for organs exceeds the impact threshold of registry promotion. Since it is not possible to secure more organs than the impact threshold, the cost of arresting the growth in the waiting list is irrelevant and the costs are capped at the threshold impact.

4.3. DISCUSSION

Donor registry promotion is widely regarded as the remedy for the growing waiting list problem. The goal of this paper was to examine the maximum possible impact that registry promotion can have on organ shortage and the cost of reaching that impact threshold. Our results suggest that donor registry promotion can increase the supply of organs but the net growth in demand far outstrips the potential supply (except in the case of hearts). In addition, reaching the impact threshold alone is prohibitively expensive. According to our estimates, CORE would need to invest around $46 million to reach the impact threshold that is 46 times their current budget of community outreach, and represents an unrealistic level of spending.

This analysis (in conjunction with chapter 3) demonstrates that large-scale implementation of even the cost-effective programs can have significant impact on societal budget. Previously Mendeloff et al. estimated that up to $1 million could be spent on procuring one additional donor (based on the value of one QALY at $100,000) [141]. In Chapter 3, we found that the cost of securing this additional donor was $726,000. Even if the cost of organ recovery (approximately $100,000 at $25,000 for each organ) were added [141], it is unlikely that the total cost of procuring the additional donor would exceed $1 million. To put the cost of securing one donor in the perspective of medical treatments that society routinely pays for, we conducted an ancillary analysis to estimate the cost of registry promotion in terms quality-adjust life years (Appendix K). We estimated that the cost of securing one quality-adjusted life year is $66,500. In comparison, recent estimates of cost-effectiveness of renal dialysis, a traditional benchmark for comparing cost-effectiveness, indicates an average cost of $129,000 per QALY [166]. We therefore concluded that CORE's donor registry promotion is cost-effective. But if registry promotion efforts are to be to be expanded to maximize their impact, the aggregate cost becomes prohibitive.

Nevertheless investing in registry promotion offers some advantages. In CORE's DSA, joining the state registry guarantees organ donation if a decedent is eligible. In comparison, educating the critical care staff or improving the organ donation process only improves the probability of donation but do not

guarantee it. In other words, some eligible decedents who are not on the donor registry will always be lost due to family refusal regardless of how efficient the organ donation process is or how effectively CORE educates the critical care staff. One implication of this assessment is that based on the costs and outcomes of critical care staff education and the organ donation process, CORE might be able to allocate its resources more efficiently. However, this area needs further research.

Policy reforms to increase donation rates have primarily focused on two proposals, the presumed consent model and the free-market approach.

4.3.1. Presumed Consent

Under the presumed consent model, all individuals are considered to have authorized donation unless they take affirmative action to opt-out. Although the final say on donation rests with the potential donor's family, Abadie and Gay (2006) have demonstrated that countries with presumed consent have 25-30% higher donation rates than informed consent countries. Their conclusion was based on analysis of donation rates and other potential factors affecting organ donation in 22 countries over 10 years. They however note that if the population's strong preference for donation results in passage of presumed consent legislation, then the causal effect is likely to be overestimated.

4.3.2. Paying Donors

Many economists have criticized the dependence of the current procurement system on altruistic donation. They argue that the current shortage of organs is a result of setting the price of cadaveric organs at zero. Economists, in general, argue that a market for cadaveric organs where the price is allowed to rise to market-clearing levels is the answer to the organ shortage [167-174]. Beard et al. (2008), in their

particularly severe critique of the current procurement policy, claim that all major efforts and legislations including increased expenditure on public education, donor cards, required request and referral legislation, the breakthrough collaborative, and reimbursing (but not rewarding) donors for the costs they incur are a part of “illusionary responsiveness” [174]. That is, these efforts are not intended to address the organ shortage but are designed to create the illusion that a serious effort is being made. Indeed, in their opinion, and truly so, parties like the dialysis clinics, organ procurement organizations, investigators who receive funding for xenograft research, and even transplant centers have significant financial interests in maintaining status quo [174]. The imbalance of economic and political power between the procurement and transplantation industry, and the 134,000 people with end-stage organ failure ensures that the status quo is maintained [174]. These authors conclude that only a free market approach can satisfactorily address the problem of organ shortage.

Howard, in his review of procurement policy reform proposals, identifies two modes of compensation for organ donation [175]. The first is to financially reward individuals who join the donor registry. Cohen [170] and Hansmann [171] describe this as “futures market” where the individuals receive a payment for agreeing to donate their organs should they die an eligible death in the future. However, the involvement of the family in decision making complicates this idea. In the absence of a payment for registration, the donor family will correctly interpret that the patient registered because of the intent to donate [176]. With payment, the “signal becomes distorted,” and family may not trust the authenticity of the donor designation decision [176]. In theory, therefore, payments for joining the registry may actually reduce family authorization rates [175] unless the first-person authorization model is strictly adhered to. The second form of compensation is to offer financial incentives to families of eligible decedents. Critics argue that the apparent sale and purchase of organs will offend those donor families who want to donate for altruistic reasons and will result in their crowding-out [175]. However a financial reward that acknowledges superior performance and the value of the contribution made can reinforce the intrinsic

altruistic motivation for donation [177]. Furthermore, an in-kind payment (example funeral benefit) may lead to less crowding-out than a cash payment [175].

It is highly unlikely, however, that either presumed consent or a free-market approach will solve organ shortage. The fundamental reason for this observation is that there are simply not enough people dying in a manner that makes them suitable to become an organ donor. Thus, other approaches are required to address the organ shortage.

4.3.3. Living Donation

A free market has the potential, in theory, to increase the number of living kidney and partial liver donors. Although historically, living donors have been an important source of kidneys, their number has not increased much in the last decade. In fact it has averaged around 6,000 over the last 12 years (6,045 in 2001 compared with 5,732 in 2013). Becker and Elias (2006), strong proponents of free markets in living donation, have estimated that the market price of a kidney from a living donor is around $15,000 [178]. Since living donors are an important source of kidneys (34% of kidneys in 2013 were sourced from living donors), allowing the price of organs to rise to a market clearing level has the potential to increase the supply, assuming the donors respond to financial incentives.

Critiques of a free-market approach in living donation point out two issues with this idea. The first issue is that living donors are may experience adverse health consequences. There is currently a lack of clinical research on the long-term consequence of donation. Anecdotal reports of mortality associated with living liver donation have had a chilling effect [179, 180]. In surveys of living donors in India and Iran, a considerable proportion of respondents reported adverse health effects (48% and 60% respectively) [181, 182]. Becker and Elias note that the healthcare in low-income developing countries is hardly comparable to the standards in developed countries where living kidney donors have reported excellent health in the

long-term [183]. This is no substitute, however, for high quality longitudinal research. The second issue is that a free-market approach in living donation entails risk of economic exploitation. That is, the current economic divide in society will segregate the benefactors (donors) from the beneficiaries (recipients, health professionals etc.). Indeed, markets are prone to trade away equity for efficiency. Any step towards a free-market approach would require extensive regulation to protect against economic exploitation. For example, incentivizing members of minority communities to become living donors can be potentially very risky if they themselves develop end stage disease. Given the high burden of disease in these communities, this type of policy may actually compound the problem.

4.3.4. Increase In-Hospital Deaths

In 2011, New York City conducted a six-month pilot project on using the Rapid Organ Recovery Ambulance to preserve the "newly dead" [184]. Many potential donors in the United States are lost because they die outside the hospital. The objective of the rapid organ recovery ambulance project was to readily identify potential donors who had joined the state registry, quickly transport them to a hospital and salvage transplantable kidneys. During the six months, nine deaths were considered but did not qualify mostly because the decedent had not joined the donor registry [184]. The research team is considering repeating the pilot study for lungs since lungs have a longer time window for recovery.

4.3.5. Improve Organ Yield

In 2013, NIH-funded research on ways to perfuse and ventilate lungs outside the body included a proof-of-concept pilot project to test if potentially transplantable lungs could be recovered and transported from non-hospital cardiac deaths by the EMS crew [185]. Unlike other organs, lungs do not depend on perfusion for cellular respiration as long as they are ventilated [186]. The objective of the study is to

examine if lungs that are recovered at the site of death and transported to the hospital maintain acceptable organ function.

4.3.6. Increase Non-Standard Criteria Donors

The most recent legislative effort to expand the potential donor pool has come in the form of the HIV Organ Policy Equity (HOPE) Act that was signed into law on November 21st, 2013. This Act legalizes research in organ transplants between HIV-positive individuals with the goal to strengthen the supply of organs in the future [187]. However, given the small fraction of HIV positive donors and recipients, the HOPE act appears to be more symbolic than pragmatic.

4.3.7. Conclusion

In conclusion, we have considered several ways in which the number of organs available for transplant could be increased by improving the efficiency of the procurement system. However, these approaches are unlikely to make a significant impact on the overall waiting list, either in terms of the overall registrations or the annual additions. A fundamental question remains, therefore, over the underlying source of the waiting list growth. Although the transplant waiting list has continued to grow since its inception, its growth, in and of itself, cannot be attributed to inefficiencies in the procurement system. Growth in the waiting list is also due to the expanding application of organ transplantation to new conditions. In addition, OPTN allocation policies that are intended to balance equity and net health benefits can affect the size of the waiting list. For instance since 2004, most of the increase in waitlisted ESRD patients has been due to the addition of 'inactive' patients [188]. These are the patients who meet the clinical criteria of having an end-stage disease, but are not ready for an immediate transplant (e.g., due to an active infection or an incomplete evaluation). This was in part because of the change in the OPTN policy, that in 2003, permitted waitlisted ESRD patients to accumulate waiting time points. In addition, improvements in medical care

such as better renal dialysis and the advent of bridging therapies (e.g. left ventricular assist device and implantable cardiac defibrillators) have helped waitlisted candidates live longer [189, 190]. Over several years, patients who would have been removed from the waiting list due to death or worsening of their health have contributed to the growth in the waiting list. The organ shortage we see is thus the result of more and more patients becoming, and remaining eligible for a transplant, a factor that is outside the control procurement system. Finally, a perverse incentive exists: if more organs become available for transplant, then physicians might be encouraged to add more patients to the waiting list, thus perpetuating the problem.

Increasing the supply of organs for transplantation continues to be a valuable goal for the health care system. Every organ transplanted represents a patient who does not die from end stage disease. However, the increasing demand is anticipated to far outstrip the supply gains from potential donor pool expansion or improving the organ acceptance rate. Prevention of and early intervention in the underlying pathogenesis of organ failure remain the first line of defense.

CHAPTER 5: CONCLUSION

The remarkable progress of transplant medicine in the latter half of the twentieth century that led to an unprecedented demand for donated organs has caught the transplant community off-guard. In response, the organ donation community has evolved into a highly specialized organ procurement network driven by the legislative developments over the past 35 years. Primarily governed by the CMS Conditions of Participation and Conditions of Coverage, the organ procurement network strives to attain effectiveness, efficiency and equity through the well-defined roles and responsibilities of donor hospitals, transplant centers and the organ procurement organizations (OPOs).

OPOs have many functions. These include training hospital staff in the donation process, educating the public and raising awareness about organ donation, and supporting donor families. Their defining role however is in the organ donation process where they function as a bridge between the donor hospitals and transplant centers. In chapter 2, we examined the impact of breakdown in the organ donation process on the availability of donors and organs. The principal finding was that process breakdowns have a strong adverse effect on the likelihood of organ donation but do not affect the organ yield once an eligible decedent becomes an organ donor. Nevertheless, process breakdowns exert a strong overall effect on organ availability. We found that for every process breakdown that occurred in an eligible decedent, one less organ was available for transplant. Consequently, 25 organs were lost to process breakdowns over the three-year study period. Although reducing process breakdowns can potentially increase the availability of transplantable organs, some organ donors would still be lost owing to other factors that make families averse to the idea of organ donation.

Organ donor registries are widely regarded as a remedy to the problem of family refusal. When decedents have their name on the registry, family's decision about donation is irrelevant owing to the legal guarantee afforded under the Uniform Anatomical Gift Act of 1987. OPOs invest considerable resources in donor registry promotion by reaching out to their communities through in-person outreach and mass media campaigns. The premise behind adding donors to state registries is that more donor registrations will result in more organ donors. In reality, it is difficult to determine if the number of registrations generated is worth the money spent on promoting donor registries. In Chapter 3, we analyzed the cost of enrolling individuals into the donor registry (cost per registrant) and by extension to analyze the cost of securing organ donors for future (cost per donor). Compared to Howard and Byrne's estimate of $840 for the value of one 18 year old registrant under the family-authorization model [142], we estimated the cost of registering one individual of any age at $455. We also estimated that under the first-person authorization model, CORE's promotion efforts would generate 4.2 present day donors at a cost of $726,000 per donor. This estimate of cost per donor is 33% less than the monetary value of one donor that Mendeloff et al. had estimated ($1,086,000) [141].

In chapter 4, we extended the analysis of chapter 3 to the level of the organ. The goal of this study was to analyze the cost and potential impact of donor registry promotion in relation to organ shortage. Later these issues were analyzed in the context of arresting the growth of the transplant waiting list. Although donor registry promotion can increase the supply of organs, the potential increases in organ supply fall short of the net increase in waiting list. The threshold impact of registry promotion is reached at 64 donors that yield 73 kidneys, 45 livers, 18 lungs and 15 hearts. The cost of reaching the threshold impact is $46 million; this amount is 46 times CORE's present community outreach budget. This study demonstrates that although registry promotion is cost-effective, its large-scale implementation will have significant impact on societal budget.

The scope of this research was to examine the effectiveness and the efficiency of the organ procurement system as it operates under the current legislative framework. Although eliminating errors in

the organ donation process and promoting the donor registry will improve organ availability, these efforts alone cannot solve the growing waiting list problem. The fundamental reason why various approaches to increase the cadaveric organ supply have enjoyed limited success in reducing organ shortage is that there are simply not enough people dying in a manner that makes them suitable to become an organ donor. Since patients with end-stage renal disease represent almost 80 percent of all waiting list candidates, living kidney donation offers a promising avenue because of the potentially limitless pool of donors.

Increasing the supply of organs for transplantation continues to be a valuable goal for the health care system. Every organ transplanted represents a patient who does not die from end-stage disease. However, the increasing demand is anticipated to far outstrip the supply gains from potential donor pool expansion or improving the organ acceptance rate. Prevention of and early intervention in the underlying pathogenesis of organ failure remain the first line of defense.

APPENDIX A: CMS EXCLUSIONARY CONDITIONS

Exclusionary conditions are described in *CMS Conditions for Coverage for Organ Procurement Organizations; Final Rule* (71 Federal Register 30928).

Active Infections

Bacterial

- Tuberculosis.
- Gangrenous bowel or perforated bowel and/or intra-abdominal sepsis.

Viral

- HIV infection by serologic or molecular detection.
- Rabies.
- Reactive Hepatitis B Surface Antigen.
- Retroviral infections including HTLV
- I/II.
- Viral Encephalitis or Meningitis.
- Active Herpes simplex, varicella zoster, or cytomegalovirus viremia or pneumonia.
- Acute Epstein Barr Virus (mononucleosis).
- West Nile Virus infection.
- Severe acute respiratory syndrome (SARS).

Fungal

- Active infection with Cryptococcus, Aspergillus, Histoplasma, Coccidioides.
- Active candidemia or invasive yeast infection.

Parasites

- Active infection with Trypanosoma cruzi (Chagas'), Leishmania, Strongyloides, or Malaria (Plasmodium sp.).

Prion

- Creutzfeldt-Jacob Disease.

General Exclusions

- Aplastic Anemia.
- Agranulocytosis.
- Extreme Immaturity (<500 grams or gestational age of <32 weeks).
- Current malignant neoplasms except non-melanoma skin cancers such as basal cell and squamous cell cancer and primary CNS tumors without evident metastatic disease.
- Previous malignant neoplasms with current evident metastatic disease.
- A history of melanoma.
- Hematologic malignancies: Leukemia, Hodgkin's Disease, Lymphoma, Multiple Myeloma.
- Multi-system organ failure (MSOF) due to overwhelming sepsis or MSOF without sepsis defined as 3 or more systems in simultaneous failure for a period of 24 hours or more without response to treatment or resuscitation.
- Active Fungal, Parasitic, viral, or Bacterial Meningitis or encephalitis.

APPENDIX B: GLASGOW COMA SCALE

Eye Opening Response	
Spontaneous--open with blinking at baseline	4 points
To verbal stimuli, command, speech	3 points
To pain only (not applied to face)	2 points
No response	1 point
Verbal Response	
Oriented	5 points
Confused conversation, but able to answer questions	4 points
Inappropriate words	3 points
Incomprehensible speech	2 points
No response	1 point
Motor Response	
Obeys commands for movement	6 points
Purposeful movement to painful stimulus	5 points
Withdraws in response to pain	4 points
Flexion in response to pain (decorticate posturing)	3 points
Extension response in response to pain (decerebrate posturing)	2 points
No response	1 point

Coma: No eye opening, no ability to follow commands, no word verbalizations (GCS Score: 3-8)

Source:

- Teasdale G, Jennett B. Assessment of coma and impaired consciousness. Lancet 1974; 81-84. [191].
- Teasdale G, Jennett B. Assessment and prognosis of coma after head injury. Acta Neurochir 1976; 34:45-55. [192].

APPENDIX C: EFFECTIVE REGISTRY CRITERIA

1. No follow-up step required for DMV or online enrollment.

2. Active UAGA legislation that obligates OPOs to honor the registered decedent's wishes.

3. 24/7 access to the online database for the OPOs to query donor designations.

4. Department of Motor Vehicles enrolls donors via all available channels to maximize designation.

5. Dedicated website that allows individuals to enroll at any time.

6. Donor cards available for those individuals who do not have a driver's license or state ID, or access to internet.

7. Department of Motor Vehicles donor records are searchable within one week of enrollment.

APPENDIX D: CLINICAL CRITERIA FOR NEUROLOGIC DETERMINATION OF DEATH

1. PREREQUISITES

- Presence of Central Nervous System (CNS) catastrophe that is compatible with brain death.
- Absence of complications that may confound assessment of brain death including hypotension and metabolic derangements.
- Absence of drug intoxication or poisoning, absence of sedation and neuromuscular blockage.
- Core temperature $\geq$ 32ºC (90ºF).

2. CARDINAL SIGNS OF BRAIN DEATH

- **Coma:** Coma is defined as having no cerebrally mediated motor response to noxious stimuli. A patient in coma will show no response to nail-bed pressure in any extremity, or to supraorbital or temporomandibular joint pressure.
- **Absence of brainstem reflexes**
    - **Pupils:** Both pupils show no response to bright light. Size of the pupils may vary from 4 mm to 9 mm. They may be round, oval or irregular. Preexisting pupillary abnormalities must be ruled out.
    - **Ocular Movement**: Occulocephalic reflex is absent giving the impression of doll's eyes[28] . Occulovestibular reflex is also absent[29].
- **Facial sensation and facial motor response**
    - No corneal reflex to touch with a cotton swab or gauze.

[28] Must assure that the spinal cord is intact prior to performing this examination.

[29] Occulovestibular reflex is the deviation of the eyes to irrigation in each ear with 30-50 ml of ice water. Observe for 1 minute after irrigation and wait at least 5 minutes before testing on the opposite side

- **Pharyngeal and tracheal reflexes**
    - No response to stimulation of posterior pharynx with tongue blade
    - No cough response to bronchial suctioning
- **Apnea**
    - Apnea is defined as the absence of respiratory movement and exchange of gases.
    - Following conditions must be met prior to performing the apnea test.
        - Core temperature ≥ 36.5°C or 97.7°F
        - Arterial $PCO_2 \geq 40$ mm Hg
        - Arterial $PO_2 \geq 100$ mm Hg
    - **Testing procedure**: PO_2 and PCO_2 are measured before the test to ensure that requirements have been met. The patient is pre-oxygenated for 10 minutes with 100 percent oxygen via the ventilator. Apnea testing is done with pre-oxygenation[30] to eliminate respiratory nitrogen stores, accelerate oxygen transportation, and decreases the risk of hypoxic complications during apnea testing. The ventilator is removed and the patient receives 100 percent oxygen passively. The patient is monitored for any signs of chest movement. Arterial blood gases are measured every two minutes until one of the following occurs: 1) PCO_2 is greater than or equal to 60 mm of Hg; 2) PCO_2 is 20 mm Hg greater than pre-test level; or 3) patient becomes unstable. At the end of the apnea testing the patient is placed back on the ventilator at the previous settings.

[30] Department of Surgical Education, Orlando Regional Medical Center.

3. CONFIRMATORY TESTING

Sometimes the patient is unstable before apnea testing or may become unstable during the test compelling the physician-on-call to abort the test. In such cases, alternative tests may be performed to determine brain death although some hospitals may require both apnea testing and confirmatory testing before pronouncing a patient dead by neurological criteria. Tests that may be used for alternative testing include Cerebral Flow Scan, Transcranial Doppler Ultrasonography, Electroencephalography, and Cerebral Scintigraphy [193]. Electroencephalography was once the gold standard for determining brain death. However, EEG frequently gives false positive results and is therefore less accurate. The general trend across the country today is to use the cerebral flow scan.

Cerebral Flow Scan: This test provides unequivocal evidence of brain death. The test involves intravenous injection of radioactive isotope and taking static images at several time intervals including immediately after isotope injection, and between 30 and 60 minutes. To confirm that the isotope was injected into the blood stream, additional liver images may be taken to demonstrate uptake. If the images do not reveal blood perfusion in the brain, the patient is brain dead. Many hospitals however do not perform cerebral flow scans. A limitation of this test is that it may be false positive for patients who have undergone craniotomy or in children as they have a well perfused scalp.

APPENDIX E: DONOR MANAGEMENT PROTOCOL USED IN CORE'S DSA.

The critical care endpoints that CORE strives to achieve through the donor management order set include:

- Mean arterial pressure between 60 and 100 mm Hg
- Central venous pressure between 4 and 10 mm Hg
- Ejection fraction greater than 50%
- Arterial blood gas pH between 7.3 and 7.45
- PAO2:FIO2 >300 on PEEP = 5 cm H20
- Serum Sodium level between 135 and 160 mEq/L
- Blood glucose level less than 150 mg/dL
- Hemoglobin level greater than 10mg/dL
- Urine output between 1 and 3mL/kg/hr. for preceding 4 hrs.

In CORE's designated service area, a potential organ donor is managed by the recovery team using the following protocol.

Blood Pressure

To maintain adequate organ perfusion and minimize ischemic injury to organs, systolic blood pressure is maintained above 100 mm of Hg. Alternatively, mean arterial pressure is maintained between 60 and 65 mm of Hg. Fluids including crystalloids, colloids and blood products are infused to maintain adequate blood volume. Pressor drugs including Dopamine, Neosynephrine (Phenylephrine), Levophed

(Norepinephrine), Epinephrine, Dobutamine and Vasopressin are administered to induce vasoconstriction and maintain blood pressure.

Hormone Replacement Therapy

The brain dead organ donor undergoes a number of metabolic changes. Triiodothyronine (T3) & Thyroxine (T4) is limited resulting in decreased glucose metabolism. Anaerobic metabolism occurs leading to metabolic acidosis, decreased muscle contractility, and decreased cardiac output. This is also responsible for myocardial irritability, and responsiveness to inotropic drugs, leading to further vasodilation, and variations in heart rate and rhythm. Administration of T3 and T4 (converted to T3) reverses this process [194, 195]. Aerobic metabolism is once again established. T3 also replenishes myocardial energy stores, decreases serum lactate, and reduces inotropic support. This improves and stabilizes myocardial function. After 30 - 90 minutes, the donor will mostly likely become tachycardic, temperature and blood pressure will rise. Titration of other pressors can then begin. CORE has developed its own hormone replacement regime for donor management in its designated service area.

Fluid & Electrolyte Balance

All electrolytes (Na, K, Ca, Mg, PO_4) are maintained at optimal level. Maintenance fluids are adjusted to balance for excess or depleted sodium and potassium. Central Venous Pressure is maintained between 6 to 8 mm of Hg. Urine output is maintained above 100 ml/hr.

Diabetes Insipidus

Diabetes Insipidus occurs because Antidiuretic Hormone (vasopressin) is no longer being produces and secreted into the circulation. As a result, kidneys excrete excessive amount of urine. and is characterized by urine output that is greater than 7 ml/kg/hr or 300 ml/hr with specific gravity of urine less than 1.005 and rising sodium levels. Diabetes Insipidus can be managed by Desmopressin infusion and replacing all urine in excess of 250 ml/hr with 0.2 NaCl.

Oxygenation

CORE uses following guidelines to ensure that the donor is adequately oxygenated:

- $Pa(O_2)$[31] > 100 mm Hg
- Aspiration Precautions: over-inflate cuff, kerlex
- Titrate $Fi(O_2)$[32] to maintain $Sa(O_2)$[33] > 98%
- Tidal Volume between 10 to 12 ml/kg
- Maintain PEEP[34] at 5-8 cm H2O
- Rate adjusted to maintain normal pH (7.35-7.45)
- Suction airway as indicated.

If the patient meets the criteria for lung donation, these additional requirements are followed:

- Recruit lungs to maximize functionality
- Ventilator settings: Tidal Volume 12ml/kg ideal body wt, rate 10, PEEP at 5 cm H_2O, $Fi(O_2)$ 1.0 (0_2 Challenge)

[31] Partial pressure of oxygen in arterial blood.
[32] Fraction of inspired oxygen maintained in a mechanically ventilated patient.
[33] Arterial oxygen saturation as measured by pulse oxymetry. Measures tissue perfusion of oxygen.
[34] Positive End Expiratory Pressure. Positive pressure ventilation keeps the alveoli patent.

- Mucomyst & Albuterol q3 hrs
- Solumedrol 15 mg/kg IV
- Chest physiotherapy
- $P(O_2) > 300$ & PAP < 30 = Donor
- $P(O_2) < 300$ & PAP > 30 = further evaluation with bronch

Temperature Regulation

Warming and cooling blankets are used to maintain body temperature above 32ºC.

Insulin and Hyperglycemia

In a brain dead donor, the body is no longer able to control insulin regulation. Blood sugar is closely monitored (every 2 hrs. or every hour if necessary). Insulin drip may be used after consulting with the OPC.

APPENDIX F: JUSTIFICATION FOR EXCLUDING NON-STANDARD CRITERIA DONORS.

To be reimbursed through the Medicare and Medicaid programs, organ procurement organizations must meet the requirements established in the Centers for Medicare and Medicaid Services (CMS) Conditions for Coverage for OPOs (42 CFR §486.318). One of the Conditions for Coverage is that OPOs must have a donation rate that is not significantly lower than the national average for all OPOs. The donation rate, also called the conversion rate, is defined as the fraction of eligible deaths that become organ donors. CMS defines an eligible death as a patient 70 years old or younger, who is legally declared brain dead, and who does not exhibit any of the exclusionary conditions listed in CMS Conditions for Coverage for OPOs (42 CFR §486.302). Donation rate allows CMS to assess how well an OPO has performed when compared to other OPOs. An organ donor who meets the eligible death criteria is called a standard criteria donor (42 CFR §486). The way eligible death and standard criteria donor (SCD) are defined under 42 CMS §486, eligible deaths can only result in standard criteria donors and standard criteria donors are always a subset of eligible deaths.

Individuals who do not die an eligible death can also become organ donors. These donors are classified as either donors after cardiac death or expanded criteria donors. Donors after cardiac death are declared dead using the circulatory determination of death criteria set forth in the Uniform Determination of Death Act. Expanded criteria donors are brain dead donors that do not fit the standard criteria donor profile. The Venn diagram in Figure 13 represents the relationship between all decedents, brain-dead decedents, eligible decedents, and the three types of donors. Relative sizes of the different pools are correctly depicted but are not to scale.

CMS does not define eligible deaths for donors after cardiac death and expanded criteria donors. For the lack of an objective definition, these eligible deaths are neither observed in the real world nor in

our data. Eligible deaths observed in our data can only result in standard criteria donors. As a result, donors after cardiac death and expanded criteria donors lack a superset of eligible deaths. Since only standard criteria donors have an eligible death superset, we will restrict our analysis to estimating the effect of process breakdowns on the availability of organs from standard criteria donors. Including donors after cardiac death and expanded criteria donors in the regression model will produce biased estimates of the effect.

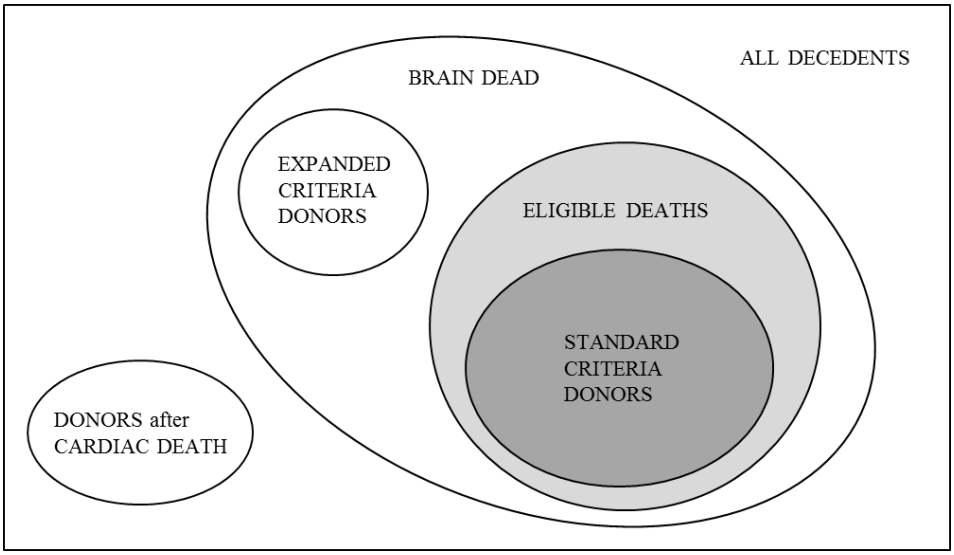


Figure 10: Donors as a subset of eligible deaths and all decedents

APPENDIX G: CORE'S COMMUNITY OUTREACH BUDGET

2012 – Budget

- Salaries

  Budget - $326,753 Actual - $326,753

- Professional Education Expenses – this is for my staff to take seminars that would improve job performance

  Budget - $8,000 Actual - $7,504

- Parking Expenses – parking while traveling to events and presentations

  Budget - $825 Actual - $901

- Printing Expenses – brochures, annual report, flyers, etc.

  Budget - $30,530 Actual - $2,943

- Dues and subscriptions – local chambers of commerce and national organizations

  Budget - $5,850 Actual - $530

- Registration fees/Meeting Expense – Conferences and meetings relevant to community outreach

  Budget - $8,000 Actual – $3,160

- Travel expenses – This includes tolls, mileage, hotel and meals for travel related to community outreach

  Budget - $101,480 Actual - $87,613

- Outside Consulting Expense – This is for any consulting we may need related to community outreach

  Budget - $3,600 Actual - $520

- Telephone Expense – This is for a partial cell phone reimbursement for calls relating to CORE

  Budget - $1,800 Actual - $270

- Volunteer Expenses – This includes the annual volunteer dinner and gifts for volunteers

  Budget - $39,800 Actual - $28,315

- Advertising Expense – Media to promote donation including print, TV, radio, billboards

  Budget - $1,000,000 Actual - $860,000

- Public Education Expense – This includes activities for multicultural and faith based outreach, DMV events and materials, high school and college events

  Budget - $131,090 Actual - $54,083

- Promotional Expense – This is for all of the promotional materials purchased like bracelets, pins, mugs, etc.

  Budget - $53,510 Actual - $23,795

- Public Relations Expenses – This would include our newsletter, chamber of commerce fees, and partnership programs

  Budget - $53,500 Actual - $1,907

Totals Budget - $1,764,738 Actual - $1,398,294

APPENDIX H: PREDICTED PROBABILITIES

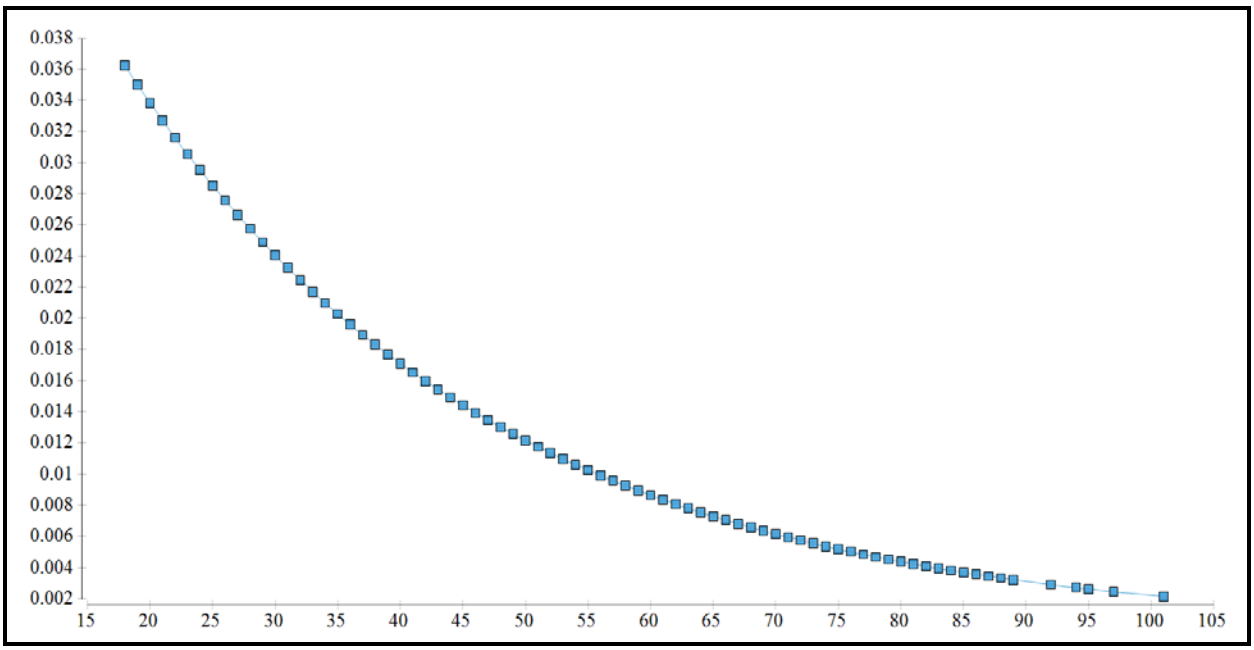


Figure 11: Predicted probability distribution of age of registrants from in-person outreach.

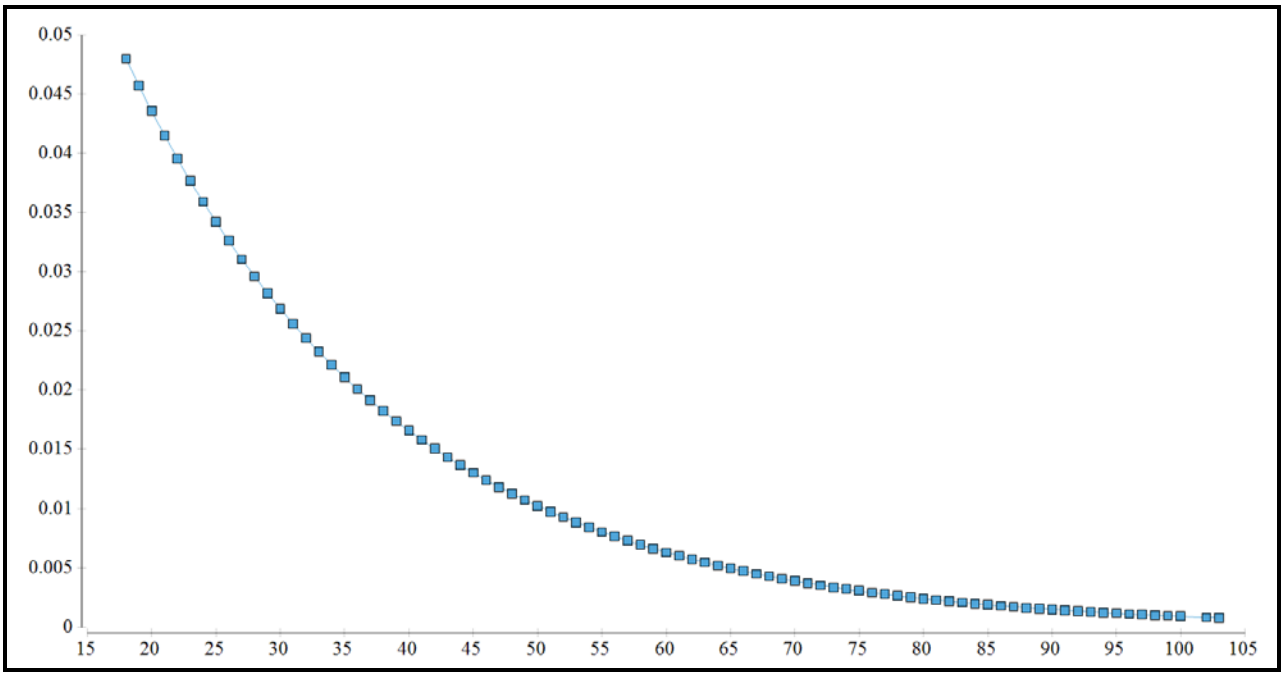


Figure 12: Predicted probability distribution of age of registrants from media campaign.

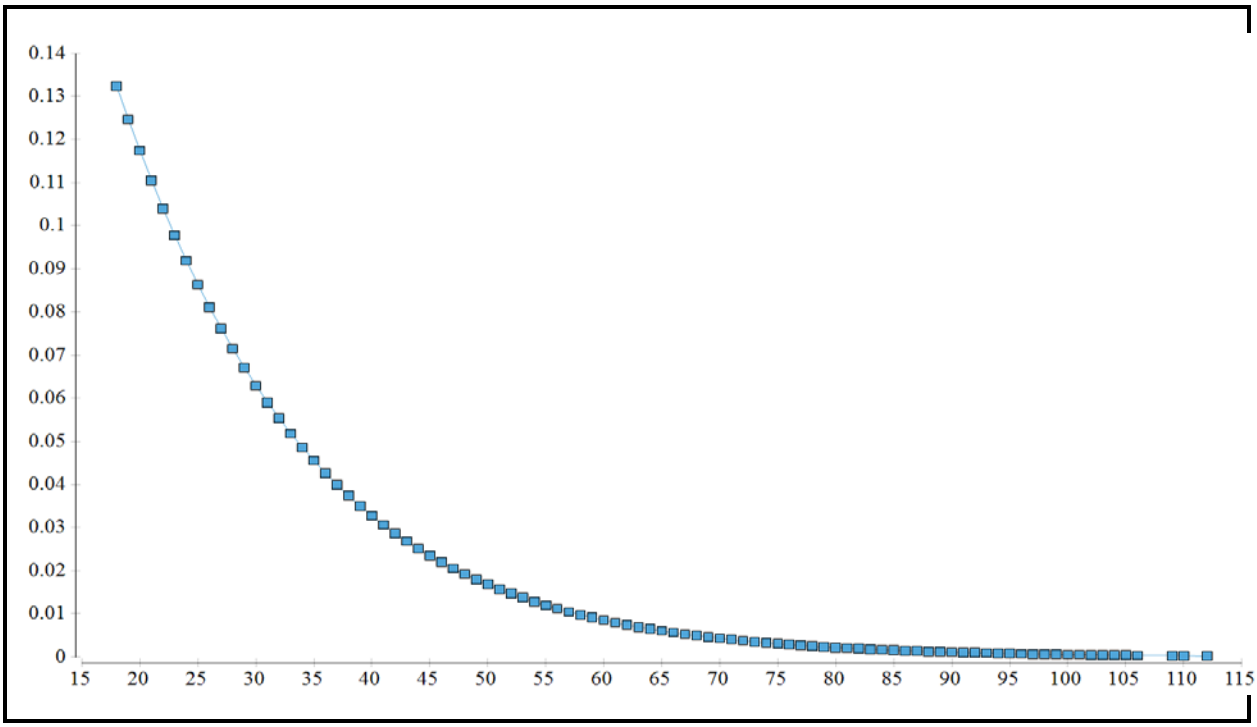
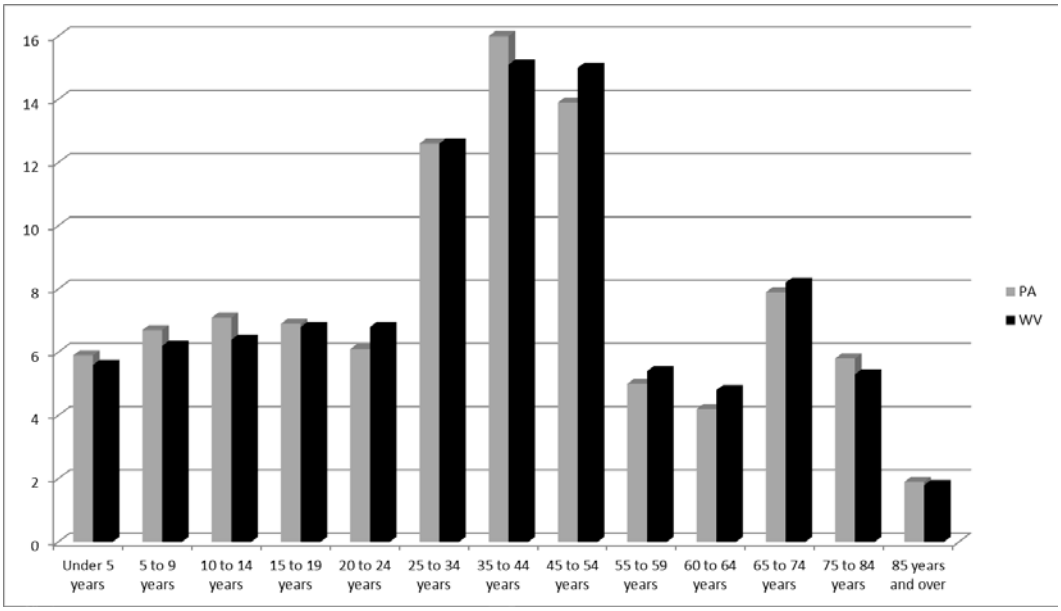


Figure 13: Predicted probability distribution of eligible death by decedent's age.

APPENDIX I: POPULATION COMPARISON OF WV AND PA.



Source: United States Census Bureau [155]

Figure 14: Comparison of age distribution of WV and PA populations.

APPENDIX J: REGISTRATIONS IN CORE'S DSA.

Table 18: Registrants in Pennsylvania Counties (CORE's DSA)

COUNTY	Year 2009	Year 2012
ALLEGHENY	422,757	451,732
ARMSTRONG	24,047	24,386
BEAVER	56,275	59,307
BEDFORD	15,544	16,328
BLAIR	46,221	47,498
BRADFORD	23,618	24,288
BUTLER	71,248	74,917
CAMBRIA	49,335	49,839
CAMERON	2,034	2,116
CLARION	11,596	11,767
CLEARFIELD	28,103	28,809
CRAWFORD	31,465	31,601
ELK	12,804	12,984
ERIE	103,602	105,763
FAYETTE	39,053	40,943
FOREST	2,026	2,020
FRANKLIN	49,474	52,831
FULTON	4,389	4,541
GREENE	10,072	10,444
HUNTINGDON	14,974	15,330
INDIANA	25,635	26,177
JEFFERSON	15,511	15,713
LAWRENCE	30,470	31,411
MCKEAN	15,935	15,949
MERCER	37,337	38,868
POTTER	6,073	6,111
SOMERSET	25,888	26,303
VENANGO	19,112	19,201
WARREN	16,601	16,835
WASHINGTON	70,305	74,473
WESTMORELAND	120,330	125,247
	1,401,834	1,463,732

Table 19: Increase in registrants with and without adjusting for increased drivers (PA)

Year	Registrants	New Registrants
2009	1,401,834	
2012	1,463,732	61,898

Table 20: Increase in registrants with and without adjusting for increased drivers (WV)

Year		Registrants	New Registrants
2010Q1		475806	
Counties Outside CORE's DSA	Berkley	-33732	
	Cabell	-27435	
	Jefferson	-19168	
	Morgan	-4825	
	Wayne	-5675	
	Wood	-26369	
	CORE 2010Q1	358602	
Est. CORE 2009Q4*		354910	
2010Q4		491298	
Counties Outside CORE's DSA	Berkley	-35157	
	Cabell	-28453	
	Jefferson	-19947	
	Morgan	-4942	
	Wayne	-5747	
	Wood	-27262	
	CORE 2010	369790	
2012Q4		513088	
Counties Outside CORE's DSA	Berkley	-37996	
	Cabell	-30002	
	Jefferson	-20988	
	Morgan	-5253	
	Wayne	-5782	
	Wood	-28350	
	CORE 2012	384717	9111

***** We estimated 2009Q4 using data from 2010Q1. First, we calculated the number of new drivers added in the three quarters between 2010Q1 and 2010Q4. Then we up-adjusted the number of new drivers by 33% to account for drivers that would have been added in the one missing quarter. We subtracted this adjusted number from 2010Q4 to obtain the estimate of drivers in 2009Q4. This was repeated for the number of registrants.

Table 21: New registrants in all of CORE's DSA

	New Registrants
Pennsylvania	61,898
West Virginia	29,807
CORE's DSA	91,705

APPENDIX K: QALYS GENERATED FROM A DONOR IN CORE'S DSA

Number of quality-adjusted life years generated by transplanting organs from a donor in CORE's DSA is a function of the average QALYs benefit from transplanting each kidney, liver, heart and lung and the average yield of these organs from one donor. To compute the QALYs benefit from transplanting each type of organ, we rely almost entirely on published estimates of QALYs, and where applicable, make necessary adjustments to reflect the net health benefits that would be generated by transplanting organs recovered from CORE's donors.

Kidney, Heart and Liver Transplants

For kidney, heart and liver we rely on the estimates provided by Mendeloff et al. [141]. These authors have used data from multiple sources to estimate the quality-adjusted life years generated from transplanting kidney, heart and liver. For survival rates after kidney transplants, they relied on the work of Wolf et al. [196] who have calculated the average survival of 20 years for cadaveric kidney recipients. For heart and liver, survival rate up to 10 years was obtained from SRTR Annual Report, 2002 [87]. From years 11 through 18, the survival rate was based on Hertz et al. [197] for heart transplants and Jain et al. [198] for liver transplants. Beyond 18 years, they made two assumptions: 1) the survival rate continues to fall at an absolute rate of 3.5%; and 2) the survival rate falls by 15% every year.

Life expectancy of those waiting for a transplant were obtained from Wolfe et al. [196] for kidney, from 2002 SRTR Annual Report [87] for heart, and from the Institute of Medicine study for liver [199]. For kidney transplant, health-related utility values were obtained from Russell et al. [200] and Hornberger et al. [201]. For heart and liver transplants, health-related utility states were obtained from Pinson et al. [202]. Mendeloff et al.'s central estimates of quality-adjusted life years gained are 4.40 from renal transplants, 5.62 from heart transplants and 5.71 from liver transplants.

Lung Transplants

Groen et al. have estimated the quality-adjusted life years gained from lung transplantation in relation to the end-stage pulmonary disease [203]. They conclude that there is a small difference in the utility gains from lung transplantation depending on the type of end-stage pulmonary disease. We adjusted Goren et al.'s estimates for the mix of different end-stage pulmonary diseases in recipients of lungs from CORE's deceased donors. A simplifying assumption we make is that all lungs that are recovered from CORE's deceased donors are transplanted within its service area. Our analysis suggests that a lung recipient gains 2.32 QALYs if the lung comes from CORE's donor. These computations are presented in Table 22.

Table 22: QALY estimates adjusted for the case-mix of ESPD in CORE's DSA

	Lung recipients by type of ESPD (2010-2012)* N = 175		**QALYs by type of ESPD [203] (2)**	**QALYs generated (2010-2012) (3) = (1)*(2)**
	Proportion	**# (1)**		
Pulmonary Hypertension	0.06	10	2.53	26.17
Cystic Fibrosis	0.13	23	2.31	53.91
COPD	0.34	60	2.56	153.41
Pulmonary Fibrosis	0.43	75	2.04	152.66
Other	0.04	7	2.99	19.61
All causes		**175**		**405.76**
Net QALYs gained per lung transplant from CORE's donor = 405.76 / 175 = 2.32				

* ESPD is end-stage pulmonary disease.
* The proportion of lung recipients by type of ESPD (2010 – 2012) was obtained from OPO-Specific Reports on Scientific Registry of Transplant Recipients **[204-206]**. The actual number of transplant recipients by ESPD was calculated by multiplying the proportions by total number of livers transplanted from CORE's donors. For example to calculate the number of lung recipients

After estimating QALYs from each type of organ transplant, we weighted these estimates by the yield of the respective organ from CORE's donor to estimate the value of CORE's donor in quality-adjusted life years. These are presented in Table 23.

Table 23: Weighting QALYs by the organ-specific yield in CORE's DSA

	OrgQALY	***OrgTxDon***	***Wt.OrgQALY***
Kidney	4.40	1.14	5.016
Liver	5.71	0.70	3.997
Heart	5.62	0.23	1.2926
Lung	2.19	0.28	0.6496

Using the weighted quality-adjusted life years from each organ transplant and the cost of securing one additional donor, the cost of securing one additional quality-adjusted life year can be calculated using the following mathematical formula:

$$QALY\$ = \frac{Don\$}{\sum_{k=a}^{d} Wt.OrgQALY_k}$$

Substituting values from Table 23 in Equation 4, the value of one quality-adjusted life year (using central estimates of quality-adjusted life years) is:

$$QALY\$ = \frac{\$726{,}000}{5.02 + 4.0 + 1.29 + 0.61} = \$66{,}491$$

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