A2ALL: Adult-to-Adult Living Donor Liver Transplant Cohort Study

Core Study Protocol

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Protocol Approval

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INSTRUCTIONS: The Principal Investigator must print, sign, and date below. The original signature page should be kept in the site's records. After signature, please scan the signature page and email or fax to the A2ALL DCC at the address listed below: Jenya Abramovich A2ALL DCC Jenya.Abramovich@ArborResearch.org Fax: 734-665-2103	
I confirm that I have read the above protocol in the latest version. I understand it, and I will work according to the principles of Good Clinical Practice (GCP) as described in the United States Code of Federal Regulations (CFR) – 21 CFR Parts 45, 50, 56, and 312, and the International Conference on Harmonization (ICH) document "Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance" dated April 1996. Further, I will conduct the study in keeping with local, legal, and regulatory requirements. As the Principal Investigator, I agree to conduct and to carry out the study by the criteria written in the protocol and understand that no changes can be made to this protocol without written permission of the A2ALL Steering Committee.	
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1 Introduction

Adult to adult living donor liver transplantation (LDLT) is a procedure used at major transplantation centers as an alternative to deceased donor liver transplantation (DDLT). The first iteration of the A2ALL study was performed because too few cases were performed at any one center and approaches to the recipient and donor were too diverse across centers to provide reliable and generalizable information on donor and recipient outcomes from individual centers. Therefore, the National Institutes of Health (NIH) organized a network of nine leading liver transplantation centers and a data coordinating center (DCC) to accrue and follow sufficient numbers of patients being considered for, and undergoing, LDLT to provide generalizable results from adequately powered studies. This network established the Adult to Adult Living Donor Liver Transplantation Cohort Study (A2ALL) that conducted retrospective, prospective and interventional studies of LDLT. In 2009, NIH issued a Request for Applications (RFA) in a competitive process to extend the A2ALL collaborative for another five years (A2ALL-2). Components to be implemented at all sites are a core data and biosample (blood and tissue) collection, intraoperative pressure and flow measurements on all donors and recipients, a liver biopsy at least three years post-transplant for subjects infected with the hepatitis C virus (HCV), and studies of Health-Related Quality of Life (HRQOL) on all donors.

2 Background/Significance

2.1 Overall historical perspective

The procedure of adult-to-adult LDLT is an extraordinary surgical therapy that involves the removal of up to 70% of the volumetric mass of an adult living donor liver and its implantation into an adult recipient. Adult-to-adult LDLT using the right lobe was first performed in Hong Kong in 1996, nearly a decade after LDLT was initiated in pediatric recipients[1,2]. A critical shortage of deceased donor livers, resulting in premature mortality among candidates in need of liver transplantation, remained the single most compelling force driving the need for adult-to-adult LDLT. The waiting list for liver transplantation grew at an alarming rate through the 1990s and early 2000s and has only recently started to stabilize [1]. In the United States, about 16,000 patients are currently on the liver transplant waiting list[1]. Death while awaiting a liver transplant claims more than 2,000 transplant candidates annually[1]. Adult-to-adult LDLT holds the promise of alleviating the donor organ shortage, thereby reducing waiting list deaths and offering improved longevity to patients with end-stage liver disease. Although less than 5% of all liver transplantations in the United States fall into the category of adult-to-adult LDLT, the global trend has been a rapid uptake and widespread adoption outside the United States and Western Europe, notably in Asia[3,4]. Since 1990, more than 7,000 LDLTs have been performed worldwide[5]. The global experience with LDLT is highly skewed towards Asia due to the non-availability of deceased donor programs[3,4,5]. One transplant center in Seoul, South Korea now accounts for nearly 20% of the cases done globally[1]. The total number of adult-to-adult LDLTs performed in the US declined modestly between 2002 and 2008, but the procedure remains widely practiced. Trends suggest improved recipient outcomes, decreases in donor complications, and concerted efforts to standardize donor selection criteria, as well as reporting and management of complications. There have been more than 2,000 cases of adult-to-adult LDLT performed in the United States[6], and the estimated donor mortality rate ranges from 0.24% to 0.4%[7]. Not only is there a trend toward lower rates and diminished severity of donor

complications, but adult-to-adult LDLT is increasingly performed with good results for new categories of patients and under extremely challenging scenarios, such as donation by Jehovah's Witnesses. The practice of adult-to-adult LDLT is likely to expand, as the pressure of the severe deceased donor organ shortage appears to be unremitting. Adult-to-adult LDLT remains the most viable alternative to mitigate the organ shortage, perhaps particularly enticing in patients with hepatocellular carcinoma (HCC) in whom expeditious liver transplantation is desired[6]. As will be described below, however, it is far from clear which candidates are best suited for LDLT. Lastly, adult-to-adult LDLT is being utilized in a small but growing number of patients with acute hepatic failure who must be transplanted within days of developing organ failure.

The objectives of the original A2ALL study were largely accomplished and have resulted in 31 peer-reviewed manuscripts and abstracts that serve as standards for the knowledge of LDLT in the United States. Accordingly, A2ALL has helped define the benefits and risks of LDLT for both donors and recipients. Among these advances are determination of the survival benefit of the recipient who chooses LDLT, recipient and donor morbidity, and resource utilization before and after LDLT. Informed decision-making competence of potential donors has been objectively measured. Disease-specific manuscripts on hepatitis C and HCC outcomes following LDLT as well as reports on the use of LDLT in fulminant liver failure have been published.

Despite A2ALL having achieved many of its original goals, several important questions warrant further research to determine the optimal role of adult-to-adult LDLT in end-stage liver disease treatment. There remain controversies regarding the process of donor consent and the impact of donor hepatic lobectomy on donor medical well-being, psychological health, and QOL. Surgical techniques still need refinement to lower the ongoing high risk of biliary complications in LDLT donors as well as recipients. Although data from the A2ALL study demonstrate a survival benefit of LDLT compared to continued pursuit of a DDLT, better quantification of survival benefit, particularly in selected patient subgroups, has yet to be accomplished. The continuation of A2ALL is critical to address many of these outstanding questions which must be answered to move the field forward. The researchers are in the process of developing research aims and protocols to answer those questions. However, it will take some time to develop these protocols. Since the funding period is limited, it is critical that the core cohort be enrolled and followed for basic key data elements that will form the foundation for the future planned studies.

2.2 Core Protocol data and biosample collection

During its first iteration, A2ALL sites stored about 60,000 serum aliquots and liver tissue samples from approximately 1500 subjects, and 1,121 DNA samples in the NIDDK repositories. The collection of patient and control biosamples and DNA samples from this and other studies for storage in the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) Repositories provides a resource with which researchers can rapidly validate clinical hypotheses and algorithms for clinical decision. The collections also advance the development of diagnostic and prognostic markers, and therapeutics. The repositories allow storage, maintenance, and quality control, and equitable, ethical distribution of biosamples and other resources important to the study of liver transplant. This allows sharing of resources, thus encouraging work by junior investigators, investigators with novel approaches, and others not included in current collaborations, without excluding those who are established in their fields. In addition, collection and storage of DNA samples may increase the sample size and the resulting power of a study to identify genetic

determinants of a disease. It has ensured that research participants are making a maximal contribution, and will decrease duplicative sampling efforts.

The purpose of this core protocol is to serve as a framework for gathering biosamples and accompanying clinical and demographic data from study subjects. These biosamples are a limited and precious commodity, and it is important to collect them as early as possible in the research process.

2.3 Long-term post-transplant outcomes

Adult to adult LDLT began in 1998, and prior to the A2ALL consortium, there had been no adequately powered long-term studies that compared outcomes between recipients of living donor and deceased donor grafts. We plan to continue follow-up on this original cohort of LDLT and DDLT recipients to glean more information on long-term outcomes. Transplant physicians need this information on outcomes to advise prospective recipients about the long-term health consequences associated with choosing to pursue a living donor vs. a deceased donor graft.

2.4 Donor HRQOL study

Optimizing donors' health-related quality of life is a foremost goal for living donor liver transplant programs and an overarching aim of the Adult to Adult Living Donor Liver Transplant Cohort Study 2009-2014 (A2ALL-2). Toward this goal, investigators in the initial A2ALL cohort study (2002-2009) repeatedly surveyed donor status in selected HRQOL domains during the first several years post-donation. These data, while valuable, are limited by poor response rates and the reductions in sample sizes and generalizability resulting from this problem. Moreover, the assessments performed to date do not fully evaluate the occurrence or severity of specific domains of donor psychosocial difficulties that anecdotal reports and single-center studies now suggest are important among living donors[8-18]. There is a critical need to augment the measures used to broadly assess HRQOL in A2ALL to date (e.g., SF-36) with assessments of specific domains that reflect important difficulties that liver donors appear to face not only in the early years but in the long-term after donation. Thus, there appear to be mental health problems, somatic complaints, family interpersonal difficulties, and financial distress that may emerge and even persist after donation. At the same time, any psychological benefits of donation in terms of personal satisfaction and growth also deserve ongoing consideration in order to provide a complete picture of the potential consequences of donation. All of these domains are relevant not only in new prospectively enrolled donors but also for long-term follow-up of previously enrolled donors; long-term living liver donor QOL outcomes have not been described in either A2ALL or other studies.

The proposed A2ALL-2 HRQOL Sub-Study will build upon the A2ALL HRQOL measures employed to date, informed by the A2ALL HRQOL Validation Study, which focuses on identifying the psychometrically strongest measures in the existing assessments to be carried forward into the work proposed herein. Of critical importance, the A2ALL-2 HRQOL Sub-Study will substantially augment these measures with specific assessment of psychiatric symptomatology; somatic symptoms including enduring fatigue and worries about health status; familial relationship strain; financial consequences of donation; and psychological benefits of donation. This carefully selected assessment battery will be deployed in order to study two cohorts of living donors: (a) a long-term donor follow-up cohort, i.e., donors previously enrolled in A2ALL from 2002 forward (all of whom will be > 2 years post-donation when recontacted), enriched by donors who are > 2 years post-

donation recruited from sites that have newly joined A2ALL, and (b) a new prospective cohort, i.e., individuals newly accepted for donation and enrolled in A2ALL-2, and then followed through the first two years post-donation. With each cohort, longitudinal, multi-wave assessments will be conducted in order to examine the prevalence and temporal patterns of change in the HRQOL outcome variables to be assessed, as well as risk factors for adverse HRQOL outcomes.

The strength of the long-term follow-up cohort for addressing these aims will lie in its ability to provide data regarding HRQOL difficulties that emerge and/or persist during the late-term years post-donation. Furthermore, it will be cost-efficient because its first wave of assessments will be partially funded through the A2ALL-2 "Cross-Sectional Long-Term Donor Follow-Up" Study (funded through ARRA). There are no previous studies of large cohorts with extended HRQOL follow-up; such data are at the heart of the mission of A2ALL-2.

The strength of the new prospective cohort will derive from the evaluation of important areas of HRQOL outcomes that have not previously been assessed in large cohorts of liver donors enrolled prospectively. These data will be critical for the future development of protocols designed to sustain HRQOL across the period from before through after recovery from the donation.

2.4.1 The problem

The protection of living donors' well-being and the prevention of any negative consequences of donation are among the highest priorities in transplantation, given that they undergo surgery from which they derive no direct medical benefit. Furthermore, we have an obligation to provide potential donors with information about the long-term implications of liver donation for their well-being. Well-being extends substantially beyond donor medical outcomes and also encompasses HRQOL outcomes. Moreover, there is increasing recognition that it is insufficient to consider these outcomes in only the immediate aftermath of liver donation; these donors require careful, long-term follow-up in order to identify any late-term sequelae associated with donation. Even in the short-term (e.g., first year) post-donation, there is growing concern about negative HRQOL sequelae of living liver donation.[14,15] Unfortunately, these concerns arise largely from anecdotal reports or retrospective analyses of medical records, rather than systematic assessment of a full range of HRQOL outcome domains. A2ALL-2 is well-positioned to provide critical prospective data to address these issues.

2.4.2 Evidence to date

Living liver donors almost uniformly express no regret at having donated, would donate again if that were possible, and report deep feelings of gratification at being able to help another person[8, 15-22] Moreover, generic, non-donation specific, HRQOL assessments of the type employed in A2ALL (e.g., SF-36) show that—at least in the early years post-donation—donors' well-being, on average, meets or exceeds that reported in the general population.[12,19,22-24] Nevertheless, a growing body of qualitative and small cohort studies suggest that significant proportions of liver donors experience major HRQOL difficulties after donation. For example, up to 78% of donors experience high psychological distress and/or meet diagnostic criteria for mood or anxiety disorders[10,11,14], up to 33% report that their health is poorer after donation and that they experience ongoing fatigue and/or pain[15,19,18], up to 50% worry about the lasting effects on their health[9,10,19], up to 20% report worsening and strained relationships with the recipient and/or other family members[25,26], and over 25% have financial hardships with prominent concerns about current and future insurance

status[19,22,27,28]. Surprisingly, time since donation (at least across the first several years—the focus of virtually all work to date), has not been found to be related to rates of these outcomes. Thus, these problems may persist during the first few years, but whether they persist, worsen or resolve thereafter is unknown. Most worrisome is the fact that the elevated rates of these specific problems are reported in the same literature—and sometimes within the same study—that also reports that generic HRQOL in liver donors meets or exceeds that of the general population. This suggests that generic measures are insensitive when used in living donors and, at best, should be used only as adjuncts to more sensitive, specific assessment of potential problems in donors[8,29,30].

Particularly alarming is the A2ALL report identifying serious psychiatric problems among donors, including two suicide attempts and one completed suicide[31]. The A2ALL study group noted that their data were very limited given their brief follow-up period (median = six months) and their reliance on medical records reviews rather than prospective assessments[31]. Therefore, it is likely that the rate of psychiatric disorders was greatly underestimated[32,33], suggesting the development of serious psychopathology potentially attributable to the donation experience may be more common, serious, and persistent than previously realized.

The issue of donor financial hardship is also becoming increasingly prominent. In addition to out-of-pocket costs that donors frequently report, significant long-term difficulties in obtaining or retaining health and life insurance can arise[34]. This has led to calls for ongoing monitoring of donors' experiences with insurability and other donation-related financial hardships during not only the initial months but subsequent years following donation[34-36].

In sum, a small literature encompassing anecdotal reports as well as single-site studies of small cohorts clearly points to the need for more focused attention on certain HRQOL outcomes in living liver donors, including psychological status, somatic complaints, familial interpersonal relationships, and financial concerns. At the same time, because donors also report deep satisfaction with having donated (and little to no regret), it is important not to neglect potential psychological benefits when assessing HRQOL in this population. Furthermore, existing work has focused almost exclusively on only the first few months or first year post-donation; long-term HRQOL has received virtually no attention. Finally, existing short-term studies, including work within A2ALL to date, have been limited by poor response rates, high levels of missing data and incomplete follow-up. The work that we propose, encompassing both a long-term donor follow-up cohort and the enrollment of a new prospective donor cohort, is designed to directly address each of these issues. This work will be cost-efficient because it will take advantage of and build directly upon two HRQOL-related studies that will be conducted with ARRA funding. Namely, the "Cross-sectional Long-term Follow-up Study" will provide partial funding and support to collect the first wave of data in the longitudinal long-term follow-up effort that we are now proposing, and the "Validation Study" will provide psychometric evaluation of existing HRQOL instruments employed in A2ALL in order to refine the selection of optimal measures in both study cohorts that we plan to enroll, as described below.

2.5 Intraoperative pressure and flow studies in LDLT recipients

2.5.1 General considerations

Since the beginning of A2ALL-1, there has been enormous worldwide technical progress in improving the operation. As LDLT moved from children to adults, it was observed early that the

size of the graft was related to function in the recipient and that inadequate graft volume led to poor recipient outcomes. Because of the asymmetry of the liver, the right lobe is the larger lobe and right hepatectomy became the procedure of choice in LDLT. Nearly all the transplants enrolled in A2ALL-1 were standard LDLT using the right lobe graft with graft sizes deemed "optimal" for the recipient. Although recipient results were good, removing more than half of the donor's liver remains an operation that is deemed risky for the donor. Consistently using the left lobe as a donor source is appealing as the resection removes only 40% of the donor's liver and thus decreases the chance of liver failure in the donor.

We propose that consistent use of a lesser donor operation will increase acceptability for both the public and the medical community and increase the numbers of LDLT. Because the decreased donor operation will result in a smaller graft for the recipient, it is necessary to develop and validate approaches that permit successful use of smaller donor livers and this is the principal goal of the surgical innovations study anticipated for A2ALL-2. In addition to increasing the use of left lobes, the reliable use of a very small graft will make it possible for smaller donors to donate to larger recipients leading to more LDLT.

The minimum graft size for LDLT has been a subject of study for nearly 15 years. Emond et al. first described the correlation between graft size and function in a series of children and adults receiving LDLT[37]. The pathophysiology of liver dysfunction when the graft is too small has been the subject of numerous publications in both preclinical and human transplant settings. A syndrome of graft injury, cholestasis and the delay of synthetic functional restoration as estimated by the normalization of prothrombin time (INR), has been the general pattern of small liver dysfunction, termed small for size syndrome (SFSS)[38]. Clavien et al. later added the presence of persistent ascites to the definition as the small graft becomes resistant to the passage of blood[39]. Early on, it was suspected that excess portal blood flowing through a limited graft was the cause of graft injury leading to poor function and failure. Animal models and subsequent clinical experience indicates that modulating portal blood flow improves the function and successful transplantation of small grafts. These descriptive studies have only begun to define the parameters that determine what measurements are relevant and what interventions are effective in ensuring the successful use of small grafts in LDLT. Therefore, in A2ALL-2 we seek to prospectively define the limits of graft size, the physiologic parameters associated with alterations of the graft, as well as to validate an algorithm of therapeutic interventions

2.5.2 Effects of pressure and flow on the results of liver transplantation

Surprisingly little is known about normal flow and pressure in the human liver. In partial hepatectomy, it is assumed that the entire portal blood is necessarily directed through the remnant liver. Since the normal liver is soft, it is reasonable to imagine that increased portal blood can flow through the liver up to some limit of compliance[40]. This seems to be an important limit of the amount of liver that can be safely resected. In rodents, 70% resection of the liver is readily tolerated, however an increase of the resection to 85% results in a high mortality[41]. This is better understood in terms of the remnant liver; after 70% resection the remnant is 30% of the liver while only 15% is left behind in 85% resection, a remnant only half as large[42]. Thus, beyond a certain limit of resection, portal flow decreases and pressure increases. The intact host may be able to auto-regulate by constriction of the hepatic artery and the mesenteric artery, decreasing the amount of total visceral blood flow[40,42]. Within the liver, excess portal blood must activate endothelium and local

inflammation, causing damage reflected in enzyme release. Local arterial vasospasm may occur leading to patchy necrosis in the parenchyma[41]. In LDLT and split liver transplantation, a syndrome of poor function associated with grafts smaller than 1% of body weight is characterized by cholestasis and ascites. It is believed that this complication is associated with excess portal flow through the graft and may be prevented/attenuated by interventions to modulate blood flow[43].

2.5.3 Effects of portal flow excess and clinical results of flow modulation in LDLT recipients

Early experience using left lobe grafts lead to markedly reduced recipient survival compared to right lobe grafts with left lobe recipient with 54% survival versus 85% for recipients of right lobe grafts[44,45], with an increased incidence of SFSS since the right lobe is typically 1.5-3 times larger than the left lobe. Patients with normal liver can undergo resection of up to 85% of the liver leaving only 15-20% of the standard liver volume. Recipients of liver transplant often have portal hypertension and can have portal flows 4-7x normal, and decreased arterial flow[46]. Efforts to minimize SFSS have focused on portal flow modulation accomplished by mechanical and/or pharmacologic interventions[39,46,47]. It is likely that severe perfusion injury associated with portal overflow is associated with pathologic endothelial activation in the portal system and the sinusoids. We previously observed severe flow damage in rodents when isolated perfused livers were exposed to excess flow rates (unpublished). In our experiments with machine preservation of human livers, we observed attenuated levels of ICAM-1, IL-8, and TNF-a with optimal preservation[48]. Surprisingly, there is no published data on endothelial phenomena in the small for size liver, though there is undoubtedly severe mechanical stress of the sinusoidal endothelium. A potential protective strategy to optimize flow was reported by Tokunaga et al[49]. Despite the lack of mechanistic work in this area, there is a growing body of empiric clinical and pre-clinical evidence that portal flow attenuation, at least transiently, is protective of the small liver remnant. *We propose that early portal flow attenuation is protective, though, over time, the hepatotrophic benefits of portal blood to the liver need to be restored.* In the clinical arena, there is conflicting data between the harm of portal flow and the consistent correlation showing an association between high portal flow and eventual regeneration[50]. Portal modulation may be accomplished by vasopressin for splanchnic vasoconstriction, somatostatin, splenic artery ligation, splenic artery embolization, splenectomy and portocaval shunts[46, 51, 52]. Splenic artery ligation in a small series has been shown to decrease portal flow by 33% in patients undergoing liver transplantation. Yamada et al found that hemi-portocaval shunting reduced portal flow by 33 and 50%[46]. Using this approach, they were able to transplant a series of extra-small grafts. Liver compliance has been equated to portal venous flow divided by portal venous pressure[41]. Thus optimal graft performance would be found with a high compliance graft with high portal flow and low portal pressure with a relationship of better performance of the liver tissue at higher flow until limits are exceeded and pressure begins to rise significantly. We seek to demonstrate that by altering portal flow, we can modulate compliance in the allograft and thus enable the use of smaller grafts.

2.6 Late evidence of fibrosis progression after LDLT or DDLT for HCV

HCV recurrence after liver transplantation is universal in patients who are viremic pre-operatively. Chronic hepatitis evolves to cirrhosis at a variable rate, but more rapidly than in non-transplant patients; ~20% of patients develop cirrhosis within 5 years of LT. Initial studies suggested that outcomes for recipients of LDLT with HCV were inferior to recipients of DDLT with HCV, with higher rates of graft loss, more frequent occurrence of severe cholestatic hepatitis, and higher rates

of cirrhosis[53-55]. However, subsequent studies, including results from the A2ALL-1 Study cohort, showed similar graft and patient survival once centers had mastered the technical aspects of the LDLT procedure[45,56-59]. In the A2ALL-1 cohort of 181 LDLT and 94 DDLT HCV-infected recipients, overall 3-year unadjusted graft survival was 68% for LDLT versus 80% for DDLT (p = 0.04), respectively. However, when analysis was restricted to LDLTs after the first 20 cases at each center, graft survival in recipients of LDLT and DDLT were not significantly different, 79% versus 80%, respectively (p=0.74)[56]. A significant limitation of the first A2ALL study is the fact that protocol liver biopsies were missing in approximately one third of recipients, and follow-up liver biopsies obtained more than 3 years post-transplant comprised only a small fraction of the liver biopsies available for analysis.

Initial studies of HCV disease progression reported higher rates of severe HCV recurrence in LDLT compared to DDLT recipients, observations which have not been confirmed in subsequent studies. However, studies to date are limited in the duration of follow-up, with most reporting disease progression up to only 2-3 years post-LT, and in relatively small patient populations. Thus, the outcome of HCV recurrence after LDLT vs. DDLT requires further study for longer periods of follow-up and in larger patient populations; patients enrolled in Retro and Cohort A2ALL-1 are ideally suited to answer this critical question.

Clinical factors influencing the rate of HCV disease progression and risk of graft loss have been well-described in DDLT, but not LDLT, recipients[60]. The factors most consistently linked with higher risk of recurrent cirrhosis in DDLT recipients include older donor age[61,62] , prolonged cold ischemia time, cytomegalovirus infection, acute cellular rejection requiring treatment, and post-transplant insulin-resistance or diabetes. The importance of donor factors is also very apparent, especially older donor age[61]. Using donors under the age of 40 years as a reference group, an increasing risk of graft loss is seen with HCV-infected transplant recipients with donors between the ages of 41-50 years [HR = 1.67; 95% CI (1.34-2.09)], donors between 51-60 years [HR = 1.86; 95% CI (1.48-2.34)] and donors > 60 years [HR = 2.21; 95% CI (1.73-2.81)][62]. Most LDLT recipients with HCV have younger donors, which would be predicted to improve outcomes; however, this possibility has only been evaluated in a single center with a relatively small study population[59]. An important aspect of this study proposal will therefore be to evaluate whether risk factors for aggressive HCV recurrence after DDLT also apply to LDLT recipients in long-term follow-up.

2.7 Pain Control in Living Donors Following Partial Hepatectomy: Measuring the Quality of Care

Physicians use anecdotal evidence or empiric reasoning to select postoperative pain care for live liver donors due to a lack of evidence guiding clinical decision-making. Consequently, the transplant community has no objective information about pain management in live liver donors to use for quality improvement. Recently, the American Pain Society (APS) developed a validated tool to measure the quality of pain management. The tool assesses multidimensional aspects of pain care. We propose a two part study: to survey centers to understand the previous experience with pain management and to use the APS tool to measure quality outcomes with pain care.

There is insufficient data to determine if one approach to pain treatment is better or safer than another in live liver donors. The choice of pain care is therefore empiric or based upon anecdotal evidence. Only two single center studies have reported pain management outcomes in live liver

donors[76,77]. Each used a different care plan and method to measure outcome. Consequently, little is known about the current approach to pain management in live liver donors. Further, the existing findings cannot be compared with other centers because there is no standardized means to measure outcome. Thus, there is no method to conduct quality improvement for postoperative live donor pain management.

The American Pain Society recently issued a Patient Outcome Questionnaire-revised (APS-POQ-R) that was validated to measure patient satisfaction[77]. The APS-POQ-R identified specific features of pain management that predict patient satisfaction[77]. These include: ongoing assessment, interdisciplinary collaborative care that includes patient input and treatment that is efficacious, cost conscious and culturally appropriate. These features are incorporated into the questions used to measure quality indicators. These characteristics are consistent with the concept of quality that encompasses the structure, process and outcome of pain management.

The revised tool for pain assessment is inclusive. It measures outcome as patient satisfaction. A low pain score (little reported pain) did not guarantee that patients were satisfied with their care[77]. Rather, patient satisfaction (outcome) was highly influenced by interactions with the care providers; the resources available at each site and the nature of the interactions.

The APS-POQ-R collects data about side effects, but does not collect information about more serious complications that could be related to pain management. For example, pneumonia may occur more frequently in patients who experience poor pain relief or have a high degree of sedation[78]. Additional information is needed to fully examine the relationship between pain management and outcome.

Postoperative pain management in live donors can be significantly improved if efficacy is measured in a consistent way. This can be done by using a single set of validated tools to measure the safety and quality of pain control in a multi-institutional study cohort. This should generate findings that can be generalized to other clinical settings. The data can be used to set quality-based goals for pain management in all live liver donors. The APS-POQ-R meets the stringent criteria needed to evaluate outcome and the A2ALL Consortium already has a uniform assessment tool to measure complications.

3 Specific Aims/Study Objectives/Hypotheses

The following table shows the categories of patients that are relevant for each of the Aims (1 through 6) below (R=recipients; D=donors).

		Era of Transplant or Donation		
		A2ALL-1 Cohort (or analog at new centers)	Gap	A2ALL-2
Continuing A2ALL -1 Centers	LDLT	**R: 1,2,5; D: 1,3**	**R: 1,2; D: 1**	**R: 1,2,4; D: 1,3,4,6**
	DDLT	**R: 1,2,5;**		
New A2ALL Centers	LDLT	**R: 1,2,5; D: 1,3**	**R: 1; D: 1**	**R: 1,4; D: 1,3,4,6**
	DDLT	**R: 5;**		

3.1 Primary Aim 1: To collect data and biosamples prior to, during, and after LDLT among all donors and recipients for use by other A2ALL protocols and future studies.

3.1.1 Objectives

- To facilitate and inform studies of samples and data collected, thus enhancing the value of this and future investigations.
- To continue contributing to the NIDDK genetics, biosample and data repositories so that current and future questions regarding liver disease, living donation and liver transplantation can be investigated by A2ALL and external researchers as new technologies and resources become available.
- To ensure that samples are stored under uniform conditions, and to simplify access by other scientists to samples. Similarly, study datasets will be maintained to facilitate new analyses after the study closes.

3.2 Primary Aim 2: To characterize the differences between LDLT and DDLT in terms of recipient post-transplant outcomes including patient and graft survival, surgical morbidity, and resource utilization.

3.2.1 Objectives

- To continue to discern the long-term risks and benefits associated with choosing a living donor vs. deceased donor liver transplant with respect to the following metrics:
  - Patient and graft survival analysis starting from the time of transplantation
  - Comparison of the incidence of defined medical and surgical complications after transplant between LDLT and DDLT
  - Comparison of resource utilization (hospitalization) between LDLT and DDLT.

3.3 Primary Aim 3: To determine the prevalence, course, and predictors of poor HRQOL outcomes associated with living liver donation.

Measures used to broadly assess HRQOL in A2ALL to date (e.g., SF-36) will be augmented with assessments of specific domains that reflect important difficulties that liver donors appear to face not only in the early years, but long after donation.

A cohort will be assembled consisting of (a) all A2ALL donors previously enrolled in A2ALL from 2002 onward, all of whom will be >2 years post-donation at re-enrollment, enriched by the addition of (b) all living liver donors >2 years post-donation recruited from the new A2ALL-2 sites (Pittsburgh, Toronto, Lahey). This enriched cohort will receive a "baseline" assessment at time of (re)contact, and they will be surveyed annually for the next 3 years in order to achieve the following objectives:

3.3.1 Objectives – Long-term donor follow-up cohort

- To determine the prevalence and course of change in poor HRQOL outcomes in five domains during the extended years after donation:

- Clinically significant psychiatric symptomatology related to depression and anxiety
- Enduring fatigue, other somatic symptoms, and lasting health concerns
- Negative changes in relationships with the transplant recipient and/or other family members
- Financial strains related to health-related expenses and to changes in employment, and health-, Disability- or life-insurance benefits.
- Reductions in global/overall HRQOL

- To determine the prevalence and course of change across time in positive psychological outcomes of donation, including satisfaction with donation and personal growth related to the experience.
- Among donors followed since donation, to examine whether pre-donation characteristics (e.g., demographics, motivations and ambivalence about donating) and medical factors (e.g., perioperative complications) predict poor HRQOL at baseline and predict persistently impaired HRQOL across the study period.

3.3.1.1 Hypotheses:

In the long-term years post-donation:

- the prevalence of poor HRQOL outcomes at initial follow-up contact will be higher than the rates of these problems in normative (population-based) samples,
- based on studies in kidney donors, we hypothesize that ~30% of liver donors will experience clinically significant (above-threshold) HRQOL impairment at initial follow-up contact.
- Concerning course and predictors of HRQOL:
  - on average across the follow-up assessments, we expect that donors who have clinically significant HRQOL impairment at baseline will be likely to continue to show such impairments over time
  - we also expect the differences between "screen positive" and "screen negative" donors will grow smaller with time, i.e., the rates of some problems, e.g., financial strains, will not only persist in the "screen positive" donors but will show a steady increase in the long-term years in the "screen negative" donors
- risk factors such as higher ambivalence about donating and perioperative complications will increase the likelihood of showing poor HRQOL at study entry and of showing persistently impaired HRQOL across the study period.

3.3.2 Objectives – Prospective donor cohort

A cohort will be assembled consisting of all individuals approved as liver donors at A2ALL-2 sites. These subjects will be enrolled and assessed pre-donation, and at 3-, 6-, 12-, and 24-months post-donation. The following objectives will be addressed:

- To examine the post-donation prevalence, and trajectory of change from pre-donation through two years post-donation, of poor HRQOL outcomes in five domains:
  - Clinically significant psychiatric symptomology related to depression and anxiety
  - Enduring fatigue, other somatic symptoms, and lasting health concerns
  - Negative changes in relationships with the transplant recipient and/or other family members

- Financial strains related to health-related expenses and to changes in employment and health-, Disability- or life-insurance benefits
- Reductions in global/overall HRQOL.

- To determine the prevalence rates and trajectory of change in post-donation positive psychological outcomes reflecting personal satisfaction and growth related to the experience.
- To examine whether pre-donation characteristics (e.g., demographics, motivations and ambivalence about donating) and medical factors (e.g., perioperative complications) predict which donors are at risk for poor outcomes in the domains listed above.

3.3.2.1 Hypotheses:

- The prevalence of poor HRQOL will increase from pre- to post-donation,
- the prevalence of poor HRQOL outcomes post-donation will be sustained through the first year post-donation, show some improvement during the second year, but not return to pre-donation levels,
- the majority of donors will report satisfaction and growth related to the donation experience,
- risk factors such as higher ambivalence about donating and perioperative complications will increase the likelihood of poor HRQOL outcomes and decrease their likelihood of sustained satisfaction and personal growth.

3.4 Primary Aim 4: To study the effects of pressure and flow on the outcomes of LDLT.

3.4.1 Objectives

The main objectives of this aim are to:

- Establish the normal hepatic blood flow and portal compliance in the human liver
- Determine the relationship between hepatic flow and pressure, and graft size and function and clinical outcomes in living donor liver transplantation
- Establish the benefit, if any, of portal flow modulation interventions on hepatic compliance, and functional and clinical outcomes.

3.4.1.1 Hypotheses:

- It is generally thought that the limits of portal compliance are exceeded when graft size is less than 40% of normal (<.8% of liver/recipient body weight ratio (BWR). We hypothesize that grafts smaller than this limit will demonstrate altered hemodynamics, limited compliance, and impaired function.
- We hypothesize that restoration of pressure and flow in the "normal" range will permit grafts below 0.8% BWR to function normally with good results.

3.5 Primary Aim 5: To compare the long-term histological outcomes in recipients of LDLT and DDLT with recurrent HCV infection.

3.5.1 Objectives

To determine whether recurrent hepatitis C in LDLT recipients is associated with less severe histological fibrosis (particularly, slower rate of progression to cirrhosis) compared to DDLT recipients.

3.5.1.1 Hypothesis:

Living donor liver transplant (LDLT) recipients will demonstrate slower rate of progression to cirrhosis than deceased donor liver transplant (DDLT) recipients as determined by histology. Given that little difference has been seen in the initial 3 years post-transplant, we anticipate that any difference will be expressed more than three years post-transplant.

3.6 Primary Aim 6: To understand the history of pain management and to measure quality of care in pain control in living donors following partial hepatectomy.

3.6.1 Objectives

- To understand each institution's previous experience with pain management in living donors utilizing a retrospective survey (see Appendix E) of appropriate medical staff to:
  - Determine all methods and personnel at each center used to manage postoperative pain in live liver donors since the start of their program
  - Identify how pain was assessed during the postoperative period (current and previous assessment methods)
  - Identify methods care providers used to assess the outcome (quality) of pain management.
- To measure the quality of postoperative pain management in live liver donor and identify areas for improvement. After implementing a single method (patient survey instrument) for reporting quality indicators at all nine A2ALL centers (see Appendix F), the investigators will:
  - Assess overall patient satisfaction with pain management
  - Assess satisfaction with aspects of pain management thought to affect overall patient satisfaction
  - Identify quality indicators that differ in overall donor satisfaction

3.6.2 Hypothesis

Using these methods, we reason that individual centers may perform equally well using different approaches to pain management and suggest that variations in the quality of a patient's experience will be influenced by the structure and process of care.

4 Investigational Plan

4.1 Primary Aim 1: To collect data and biosamples prior to, during, and after LDLT among all donors and recipients for use by other A2ALL protocols and future studies.

4.1.1 Study methods

In order to maximize the study population, there are several cohorts of subjects who will enter the protocol, based on:

- Their previous enrollment in the original A2ALL Cohort Study.

- Whether their clinical care occurred/is occurring at one of the new consortium centers. When the project was renewed, three of the original A2ALL clinical centers' funding was not renewed, and three new centers were added to the consortium (University of Toronto, Lahey Clinic and University of Pittsburgh Medical Center).
- When the transplant/donation occurred. In order to have a contiguous sample, those subjects from the original sites and new sites whose transplant/donation occurred during the period of time that began with the end of enrollment into the original Cohort study (Aug. 31, 2009) and ends with opening of enrollment in the current core protocol (February, 2011); this is referred to as the "Gap Era".

Subjects who enroll after their donation/transplant will join the protocol schedule of events at the next scheduled visit time point in the study, with interim data collected by chart review. Those who have already reached study endpoints (death or graft failure) will have follow-up data collected through the endpoint under waiver of consent.

Enrollment for LDLT recipients and donors who were not in the A2ALL-1 Cohort Study or from the gap era will occur prior to living donation.

Biosamples will be collected from donor and recipient subjects preoperatively, intraoperatively, and at selected times postoperatively (see Appendices A and B).

Clinical and demographic data will be collected from the subjects preoperatively, intraoperatively, and at selected times postoperatively (see Section 4.1.3) in order to carry out planned studies researching topics in immunosuppression minimization, regeneration, HCC, HCV treatment and recurrence, and analysis of intraoperative and perioperative factors that affect graft and patient survival. The DCC plans to periodically update outcomes and mortality information (graft failure, liver failure, mortality) in the study population by linking to the Scientific Registry of Transplant Recipients (SRTR).

The NIDDK Central Repositories are two separate contract-funded components that work together to store data and samples from significant NIDDK-funded studies. One component is the Biosample Repository, which will gather, store and distribute biological and genetic samples from studies. The second component is a Database Repository that will gather, store and distribute the incremental or finished datasets from studies.

The collection of subject biosamples and DNA samples from this and other studies for storage in the Biosample and Data Repositories has the potential to become a resource with which researchers can rapidly validate clinical hypotheses and algorithms for clinical decision-making. The collections will also advance the development of diagnostic and prognostic markers, and therapeutics. To date, no such collection has been available to the investigators interested in studying liver disease and transplant issues. The repositories will allow storage, maintenance, and quality control, and equitable, ethical distribution of biosamples and other resources important to the study of liver transplant. This will allow sharing of resources, thus encouraging work by junior investigators, investigators with novel approaches, and others not included in current collaborations, without excluding those who are established in their fields. In addition, the genetics samples may increase the sample size and the resulting power of a study to identify genetic determinants of a disease. It will ensure that research participants will be making a maximal contribution, and will decrease duplicative sampling efforts. During its first iteration, A2ALL sites stored more than 60,000 serum

aliquots and liver tissue samples from approximately 1500 subjects in addition to 1,121 genetics samples in the NIDDK repositories. A2ALL is committed to sharing the resources collected in this study with current and future researchers via the use of the NIDDK repositories.

4.1.2 Participant selection

All potential subjects will be presented with information and approached for consent to have their biosamples, genetic material and deidentified data stored in the NIDDK repositories for future study.

4.1.2.1 Inclusion criteria

- Recipients
  - Age 18 or older at the time of consent
  - Has had a living donor identified and accepted and LDLT is planned
  - Informed consent obtained
  - Is listed for single organ (liver) transplantation

- Donors
  - Age 18 or older at the time of consent
  - Has undergone donor evaluation process and was accepted and donation surgery is planned
  - Informed consent obtained

4.1.2.2 Exclusion criteria

  - Prospective donors and recipients should not have undergone transplant/donation surgery prior to consent.

4.1.3 Data elements

- **Recipients**
  - Liver function tests (LFTs) – baseline, postoperative Days 1, 2, 3, 7, and 14 (record on any additional days in the first two weeks if done for clinical reasons), Month 1, Month 3, Month 12 and annually thereafter
  - Complete blood count (CBC) – baseline, postoperative Days 1, 2, 3, 7, and 14 (record on any additional days in the first two weeks if done for clinical reasons), Month 1, Month 3, Month 12 and annually thereafter
  - BUN baseline, postoperative Days 1, 2, 3, 7, and 14 (record on any additional days in the first two weeks if done for clinical reasons), and at Month 1
  - Serum Creatinine - baseline, postoperative Days 1, 2, 3, 7, and 14 (record on any additional days in the first two weeks if done for clinical reasons), Month 1, Month 3, Month 12 and annually thereafter
  - Sodium - baseline, postoperative Days 1, 2, 3, 7, and 14 (record on any additional days in the first two weeks if done for clinical reasons), and at Month 1
  - Coagulation (PT/INR) – baseline, postoperative Days 1, 2, 3, 7, and 14 (record on any additional days in the first two weeks if done for clinical reasons), Month 1, Month 3, Month 12 and annually thereafter
  - Imaging studies of the liver and spleen at Baseline and 3 months post-transplant
    Demographics

- Cause of liver disease
- Intraoperative data (warm and cold ischemia time, estimated blood loss, length of operation, etc.).
- Medical history
- Post-operative morbidity
- Clinical information (indication and pathology report) for all "for cause" liver biopsies (rejection episode confirmation, elevated LFTs, suspected HCV recurrence, etc.).
- For subjects with hepatocellular carcinoma (HCC), clinical information regarding tumor characteristics will be collected.
- Hospitalizations, survival status and cause of death in those who died
- Whole blood – collected for genetic analysis/DNA studies for extraction by the study's contracted DNA Core Lab (Fisher BioServices), and storage in the NIDDK Biorepository (one-time collection)
- Serum – collected pre-operatively, and postoperatively at Week 1, Week 2, Month 1, Month 3, Month 12, and annually thereafter, for storage in the NIDDK repository
- Plasma and peripheral blood cells – collected pre-operatively, and post-operatively at Month 1, Month 3, Month 12, and Month 24 postoperatively, for storage in the NIDDK repository
- Whole blood for extraction of RNA – collected pre-operatively, and post-operatively at Month 1, Month 3, Month 12, and Month 24 postoperatively, for storage in the NIDDK repository
- Liver tissue collected intraoperatively while graft is on the back table, and 1 hour after arterial and portal venous reperfusion prior to closure for storage in the NIDDK repository and for genomic analysis of regeneration

- **Donors**
  - LFTs - baseline, postoperatively at Week 1, Month 1, Month 3, Month 12 and annually thereafter
  - CBC - baseline, postoperatively at Week 1, Month 1, Month 3, Month 12 and annually thereafter
  - BUN and serum creatinine - baseline, postoperatively at Week 1and Month 1
  - Coagulation (PT/INR) - baseline, postoperatively at Week 1, Month 1, Month 3, Month 12 and annually thereafter
  - Demographics
  - Relationship to recipient
  - Intraoperative data (lobe donated, estimated blood loss, donated lobe weight, length of operation, etc.).
  - Liver tissue collected intraoperatively just prior to resection, closest to the line of resection and at one hour post-resection, or prior to closure, for storage in the NIDDK repository and for genomic analysis of regeneration
  - Medical history
  - Post-operative morbidity
  - Imaging studies of the liver and spleen pre-operatively and at 3 months post-donation
  - Hospitalizations

- Whole blood – collected for genetic analysis/DNA studies for extraction by the study's contracted DNA Core Lab (Fisher Bioservices), and storage in the NIDDK Biorepository (one-time collection)
- Serum – collected preoperatively and postoperatively at Week 1, Month 1, Month 3, Month 12 for storage in the NIDDK repository
- Plasma and peripheral blood cells – collected preoperatively, and at Month 1, Month 3, and Month 12 postoperatively, for storage in the NIDDK repository
- Whole blood for extraction of RNA – collected preoperatively and postoperatively Month 1, Month 3, and Month 12 for storage in the NIDDK repository.

4.2 Primary Aim 2: To characterize the differences between LDLT and DDLT in terms of recipient post-transplant outcomes including patient and graft survival, surgical morbidity, and resource utilization.

4.2.1 Study methods

In the A2ALL-1 Cohort Study, recipient candidates who were eligible to receive a living donor graft, but received a deceased donor graft (DDLT) were followed in the study. In order to characterize differences between DDLT and LDLT post-transplant outcomes, DDLT recipients who participated in the A2ALL Cohort Study will be approached for consent into the A2ALL-2 Core Protocol for continued data and specimen collection.

A2ALL-1 Cohort Study LDLT and DDLT recipients will join the protocol at whatever post-transplant time point they have reached, with interim follow-up data collected by chart review. Those who have already reached study endpoints (death or graft failure) will have follow-up data collected through the endpoint by waiver of consent.

All A2ALL centers will consent and enroll willing eligible LDLT recipients from the "Gap Period" who have not yet met study endpoints, with retrospective data obtained by electronic medical records or chart review; for those who have met study endpoints, data will be collected under waiver of consent. Prospective post-transplant data and biosamples will be collected from this population as is described in Primary Aim 1 for LDLT recipients.

4.2.2 Participant Selection

All potential subjects will be presented with information and approached for consent to have their biosamples, genetic material and deidentified data stored in the NIDDK repositories for future study. Please see Appendix D to view a table detailing subject eligibility by site type, graft type and study era.

4.2.2.1 Inclusion Criteria

- Age 18 or older at the time of consent
- Had a living donor identified and receipt of an LDLT was or is planned, and
- Received an LDLT graft, or donated in the Gap Period (all sites)
- Received a DDLT graft (continuing sites only)
- Participated in the A2ALL-1 Cohort Study (continuing sites only)
- Informed consent obtained

4.2.2.2 Exclusion criteria

- Prospective subjects should not have undergone transplant/donation surgery prior to consent.

4.2.3 Data elements

See Section 4.1.3.

4.3 Primary Aim 3: To determine the prevalence, course, and predictors of poor HRQOL outcomes associated with living liver donation.

4.3.1 Study methods – Long-term donor follow-up cohort

Sample: The sample will consist of all donors undergoing surgery in 2002 or later who were enrolled during the first A2ALL study period, and who are >2 years post-donation at time of recontact. This sample will be enriched through enrollment of donors >2 years post-donation who underwent surgery during the same time period, from new A2ALL sites. American Recovery and Re-investment Act (ARRA) funding from the A2ALL-1 "Cross-sectional Long-term Follow-up Study" will be utilized to re-consent and re-enroll existing A2ALL donors and conduct the first follow-up reassessment with them; thus the additional costs of enrollment will be limited to recruiting and consenting donors from new A2ALL sites.

All donors will receive a baseline assessment and will be reassessed annually for the next 3 years using the same assessment battery.
We expect a sample size of 600 at the baseline assessment (see Section 4.3.4, Sample size and power calculations, below).

Procedures: The procedures to be utilized have been deployed successfully in other multi-site longitudinal survey research with living donor and other patient populations. They are designed to maximize recruitment and retention and thereby avoid many of the difficulties experienced in the HRQOL studies during the initial A2ALL funding period (see also Section 6, Study Management). All donors consented during the first A2ALL study period will require re-consenting, and donors recruited from new A2ALL sites will need to provide informed consent (see Human Subjects section below). They will be approached for re-consent (or for first-time consent at new sites) either during the first year of A2ALL-2 funding (near the anniversary date of their donation) or as soon as they are > 2 years post-donation. The requirement that they be > 2 years post-donation for enrollment in the long-term cohort was selected for three reasons. First, the vast majority of existing HRQOL studies of living donors focus on the first 1-2 years post-donation; there is a dearth of evidence on longer-term HRQOL outcomes. Second, even the most recently enrolled donors in the original A2ALL cohort will advance beyond 2 years post-donation during the period of A2ALL-2 and thus be eligible for enrollment. Third, these new data from > 2 years post-donation, considered in concert with the evaluation of identical outcome areas up to 2 years post-donation in the new prospective cohort study described in Section 4.3.2, below, will provide seamless coverage of understudied outcomes (e.g., psychiatric symptomatology) from pre-donation through many years post-donation.

The decision to use 2002 as the earliest year in which donors could have donated and be eligible for the long-term follow-up stems from several considerations. First, there is a diminishing return for the investment of attempting to relocate and contact individuals as time since donation increases.

Second, the pool of available donors becomes markedly smaller in years earlier than 2002 at the A2ALL sites. Third, we reasoned that individuals who donated earlier than 2002 did so during a period in which many centers were developing their expertise in living donor surgery and thus there could be marked "era" effects if we included individuals enrolled during the very early years of centers' practice of living liver donor surgery.

Once the long-term donors are enrolled, they will be re-assessed annually for 3 years. The rationale for repeated assessments of donors rests on the need to chart the course of changes in these donors' HRQOL outcomes during a time period for which virtually no empirical information is currently available.

The study will utilize telephone-based survey methods to collect data at each assessment time point. A centralized approach to data collection will be utilized in order to maximize response rates and retention in the study (see Section 6, Study Management, below). Thus, donors will be informed during the re-consenting process (or initial consenting for donors from new A2ALL sites) that their contact information will be forwarded to the survey research center responsible for data collection, and survey center personnel will then contact each donor to complete the telephone surveys. The re-consenting (or initial consenting at new sites) will be performed by a member of the A2ALL team located at each site. After the completion of each of a total of 4 surveys (the initial follow-up, and 3 annual surveys thereafter), each donor will be paid $20 for each completed survey. It is essential to provide such payments in order to maximize recruitment and retention and demonstrate appreciation for donors' efforts. Used alone, the promise of payment incentives consistently boosts response rates by 20%-30%.[69,70]

4.3.2 Participant selection

4.3.2.1 Inclusion criteria:

- All donors previously enrolled in A2ALL will be eligible if they are now >2 years post-donation and donated in 2002 or later.
- All donors from new A2ALL sites who meet these criteria will also be eligible. They will be enrolled utilizing the procedures specified above.

4.3.2.2 Exclusion criteria

- Inability to comprehend spoken English

After informed consent is obtained by staff at individual centers, all assessments will be conducted by telephone; no visits will be required. As noted above, donors will complete a maximum of four assessments.

4.3.3 Data elements

Table 1 lists the measures to be included in the first of the three annual telephone assessments. (Subsequent assessments are identical to the first assessment except that one item about recovery and two demographic items are omitted, and the time frame for some of the items is modified to cover the period since prior assessment.) Our selection of measures was guided by the following principles: for domains not previously assessed in A2ALL (e.g., mental health, somatic issues such

as fatigue), new measures were selected that met two criteria: (a) they have known psychometric properties and have been used extensively in donor and/or other relevant populations and (b) they are brief. For domains previously assessed in A2ALL (e.g., positive psychological outcomes of donation), we will retain and/or augment existing measures rather than replace them with new measures. We have proposed the measures most likely to be retained; results of the A2ALL "Validation Study" (funded through ARRA) will provide additional guidance on which of the candidate measures to be retained also show the strongest psychometric properties.

778 **4.3.3.1 Table 1: HRQOL measures for long-term donor follow-up cohort, Time 1**

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Domain	Specific Items in Survey	Total No. of Items
Demographic items	34, 42, 43, 57 – 60	7
Mental health • PRIME-MD Brief Patient Health Questionnaire (depression, anxiety, alcohol)[63]	39a-i, 40a-g, 41, 41a-e	11 to 22**
Somatic complaints • FACIT-Fatigue[64] • Brief Pain Inventory Short Form: numeric rating + activity impairment subscale[65] • Post-Donation Symptom Checklist[20,25] • Post-Donation concerns about health (Simmons Worries about Donation items, Simmons Donation Stressfulness items; general QOL physical items)	 29a-m 28, 28a-g 27a-s 1, 9-15, 51, 52, 54, 61	 13 1 to 8** 19 12
Interpersonal relationships • Relationship with Recipient items (Simmons and general QOL items) • Simmons Family Support items • Simmons Worry about Recipient item • Toronto Recipient Behavior item • Simmons Preoccupation items • Simmons Grief items	 30, 32, 32e-j 33, 35 32d 32k 7, 31 32a-c	 2-14** 1-2** 1** 1** 2 4**
Financial concerns • Financial Burden of Donation items[28,66]	 44-48, 49a-d, 50	 10
Positive psychological outcomes • Simmons Better Person scale items • Simmons Satisfaction with donating items • Campbell Global Life Satisfaction item • Regret item from general QOL items • Posttraumatic Growth Inventory[67]	 2-6, 36a-c, 55, 56 8a-g 38 53 37a-j	 10 7 1 1 10
Generic HRQOL • SF-36v2	 16, 17, 18a-j, 19a-d, 20a-c, 21-23, 24a-i, 25, 26a-d	 36
Total No. of items/duration of assessment		146 to 176/** 25 to 40 min***

*most of the measures and items are copyrighted and are reproduced with permission
**depending on whether respondent skips out of sections
***estimate based on pilot testing

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We anticipate a total sample size of 300 donors from the existing A2ALL cohort, enriched with 300 additional donors from the new A2ALL sites (Total N = 600). This sample size estimate is based on the sampling frame requirements described above, an assumption that we will be unable to locate 10% of donors despite using state-of-the-art internet-based search strategies for donors lost to follow up at centers, and an assumption that 20% to 30% of donors recontacted will refuse to provide consent for a long-term follow-up study. Furthermore, across 3 years of follow-up, we anticipate (based on our past experience in following transplant-related samples using the type of survey strategies described earlier), that attrition will range between 10% to 15%.

With a sample of 600 donors at the initial assessment, our power to detect whether the rate of poor HRQOL in the donors differs from a population/normative rate (at alpha < .05, two-tailed) exceeds .995, even for very small differences of less than 2% between the observed and normative rates (Specific Aim 2, Objectives a.1. and a.2.). For hypotheses focused on specific effects or relationships, our power exceeds .80 at alpha = .05, two tailed, for moderate-sized[68] effects even if as much as 50% of the sample is lost to attrition (a percentage much higher than expected, as noted above). We note that we will not restrict our analyses to consideration of outcomes at only individual time points but will utilize a mixed effects approach (which is appropriate both for interval and discrete outcomes). Power will be even greater under a mixed effect approach because such models allow for the inclusion of cases with incomplete data, and thus our effective sample size will be the total cohort enrolled. Therefore, even if we apply corrections for multiple comparisons (given the fact that we will examine multiple domains of HRQOL), our power will continue to exceed .80 for examining relationships such as risk factor-outcome associations.

4.3.4 Sample size and power calculations

Not applicable for this cohort.

4.3.5 Statistical analysis

A critical component of the analyses is to provide descriptive information about the long-term follow-up cohort at each follow-up time point post donation (Specific Aims a.1. and a.2.). Standard approaches to examine distributions of responses to survey measures will be examined (e.g., descriptive statistics, box plots, histograms). An important goal is the examination of prevalence of poor HRQOL outcomes in each identified domain at the initial assessment. We will examine the percentage of the cohort at study entry that report clinically significant difficulties within a given domain (e.g., in the mental health domain, the percentage who meet diagnostic criteria for major depression, generalized anxiety disorder, or alcohol abuse). These rates, as well as mean scores on continuous measures, can be compared to norms for the measures in order to determine whether the cohort is experiencing more or fewer difficulties than community-based or other patient samples.

Other key analytic goals focus on course and predictors of poor HRQOL. We have two hypotheses about course, as well as hypotheses about predictors (see Specific Aims, list of hypotheses). Mixed effects models will be used to examine the hypotheses. These models will allow us to examine temporal patterns of responses in each outcome domain. We will evaluate assumptions regarding missing data patterns and mechanisms and engage in sensitivity analyses to test the stability of our models. To examine risk factors for poor outcomes in the identified domains at (or by) a particular time point post-donation, we will initially utilize regression-based strategies (linear, logistic, or Cox proportional hazard, depending on the outcome measure of interest).

We will engage in additional exploratory analyses in order to determine whether, in the donors followed longitudinally, we can identify distinct temporal patterns of change (or lack thereof) over time. There are several latent structure techniques that can be used for this purpose (e.g., cluster analysis as well as trajectory modeling and growth curve analysis). These techniques can be used to identify subgroups of individuals according to how persistently they show HRQOL impairment in a given area. Thus, we might expect to observe (a) a group who show persistent impairments (impairments observed at a majority of assessment time points), (b) a group for whom the proportion with impairment increases, (c) a group with consistently low rates of impairment and (d) a group whose rate of impairment fluctuates over time with no consistent pattern. If we identified such groups, we could then examine whether they differ as a function of other variables (e.g., pre or early post-donation characteristics). The ability to predict group membership is important because clinical education and early intervention efforts to potentially avoid or limit HRQOL impairments could be more precisely targeted.

4.3.6 Study methods – Prospective donor cohort

Sample: All English-speaking individuals approved for living donation at A2ALL sites during the enrollment period of A2ALL-2 will be recruited.

Study design: prospective single-arm repeated measures (assessments pre-donation, and 3 months, 6 months, 1 year, and 2 years post-donation).

Procedures: The procedures to be utilized resemble those described above for the long-term follow-up cohort and are designed to maximize recruitment and retention across the 2-year observation period. The decision to follow the sample for 2 years was made for two reasons. First, the first several years post-donation are described as an important period of adaptation following living donation, yet little is known about the HRQOL difficulties that may emerge in liver donors during this period in the domains to be examined. Second, the follow-up in the long-term cohort will begin at >2 years and we noted above that, across the two cohorts described in the present protocol (i.e., the long-term and new prospective samples), we will collect previously understudied outcomes data across a full range of years from pre-donation through late-term post-donation.

All prospective donors at A2ALL-2 sites will be consented by a member of the A2ALL team located at those sites for general participation in A2ALL. The consent form will specify that, for the HRQOL Substudy, their contact information will be provided to the survey research center that will be calling them to conduct the telephone surveys. The study will utilize telephone-based survey methods to collect data at a total of 5 assessment time points across 2 years post-donation, with the surveys administered by survey research center personnel (see Section 6, Study Management). After the completion of each survey, each study participant will be paid $20. Such payments are required to maximize recruitment and retention and demonstrate appreciation for participants' efforts[69, 70].

4.3.7 Participant selection

All individuals approved as liver donor candidates and who are recruited for enrollment into A2ALL-2 will be eligible for this study.

After informed consent is obtained by staff at individual centers, all assessments will be conducted by telephone; no visits will be required. As noted above, respondents will complete a total of five assessments.

4.3.8 Data elements

Tables 2 and 3 below list the measures to be included in each of the telephone assessments. Table 2 includes measures for the pre-donation assessment, and Table 3 includes measures for the 3-month and 6-month post-donation assessments. (Subsequent assessments at 1-year and 2-years post-donation are identical to the earlier post-donation assessments except that the 10-item Posttraumatic Growth Inventory is included.) Our approach to the selection of specific instruments is identical to that employed for the long-term follow-up cohort, namely that measures were retained when possible (rather than replacing them with new measures of identical concepts and—where required—new measures are added to augment existing measures or assess domains not previously assessed).

874 **4.3.8.1 Table 2: HRQOL measures for prospective donor cohort, pre-donation**

Domain	Specific Items in Survey	Total No. of Items
Demographic items	63-68	6
Predonation factors/Risk factors		
• Simmons Psychosocial Background items (volunteer/donation history, importance of religion)	22-27	6
• Simmons Donation Decision-Making items/scales (decision process, ambivalence, others' influence, anticipated outcomes, black sheep donor)	1-13, 15-19, 30, 31, 50, 52, 57a-c, 58a-b, 59-61	30
• Simmons Preparedness for Donation item	62	1
• General QOL pressure to donate items	14	1
• Simmons Motivation for Donating Scale items	28a-k	11
Mental health		
• PRIME-MD Brief Patient Health Questionnaire (depression, anxiety, alcohol)[63]	54a-i, 55a-g, 56, 56a-e	11 to 22*
Somatic complaints		
• FACIT-Fatigue[64]	47a-m	13
• Brief Pain Inventory Short Form: numeric rating + activity impairment subscale[65]	46, 46a-g	1 to 8**
• Donation concerns about health and well-being (Simmons Concerns about Donation items, general physical item)	34, 48, 49, 51, 69	5
Interpersonal relationships		
• Relationship with Recipient items (Simmons items)	29a-d	4
• Simmons Family Support items	32, 33	2
Positive psychological status		
• Simmons Better Person scale items	20-21	2
• Campbell Global Life Satisfaction item	51	1
Generic HRQOL		
• SF-36v2	35, 36, 37a-j, 38a-d, 39a-c, 40-42, 43a-i, 44, 45a-d	36
Total No. of items/duration of assessment		130 to 148/** 23 to 29 min***

**depending on whether respondent skips out of sections
***estimate based on pilot testing

875 **4.3.8.2 Table 3: HRQOL measures for prospective donor cohort, 3 months and 6 months**
876 **post-donation**

Domain	Specific Items in Survey	Total No. of Items
Demographic items	34, 41, 42, 56, 57	5
Mental health • PRIME-MD Brief Patient Health Questionnaire (depression, anxiety, alcohol)[63]	38a-i, 39a-g, 40, 40a-e	11 to 22**
Somatic complaints • FACIT-Fatigue[64] • Brief Pain Inventory Short Form: numeric rating + activity impairment subscale[65] • Post-Donation Symptom Checklist[20,25] • Post-Donation concerns about health (Simmons Worries about Donation items, Simmons Donation Stressfulness items; general QOL physical items)	 29a-m 28, 28a-g 27a-s 1, 9-15, 50, 51, 53, 58	 13 1 to 8** 19 12
Interpersonal relationships • Relationship with Recipient items (Simmons and general QOL items) • Simmons Family Support items • Simmons Worry about Recipient item • Toronto Recipient Behavior item • Simmons Preoccupation items • Simmons Grief items	 30, 32, 32e-j 33, 35 32d 32k 7, 31 32a-c	 2-14** 1-2** 1** 1** 2 4**
Financial concerns • Financial Burden of Donation items[28,66]	 43-47, 48a-d, 49	 10
Positive psychological outcomes • Simmons Better Person scale items • Simmons Satisfaction with donating items • Campbell Global Life Satisfaction item • Regret item from general QOL items • Posttraumatic Growth Inventory (10 items)[67]	 2-6, 36a-c, 54, 55 8a-g 37 52 Not asked at these time points	 10 7 1 1
Generic HRQOL • SF-36v2	 16, 17, 18a-j, 19a-d, 20a-c, 21-23, 24a-i, 25, 26a-d	 36
Total No. of items/duration of assessment		136 to 166/** 24 to 38 min***

**depending on whether respondent skips out of sections
***estimate based on pilot testing

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For the prospective donor cohort HRQOL studies at 1 year and 2 years post-donation, the assessments are identical to those at 3 months and 6 months in the prospective cohort, except that the 10-item Posttraumatic Growth Inventory is included. This will increase the estimate time to 26 to 40 minutes.

4.3.9 Sample size and power calculations

We anticipate a total sample size of 375 liver donors. This sample size estimate is based on the numbers of living liver donor transplants performed at A2ALL-2 sites during the past 3 years and the expectation that we would enroll subjects for a total of two years going forward (allowing for follow-up of the last subjects enrolled before the end of A2ALL-2 funding). It also assumes 20% to 30% of prospective donors will refuse to enroll. Finally, across the study period, we assume that attrition will range between 10% to 15% (based on our past experience with donor and other transplant-related samples using the type of survey strategies proposed). Thus, by the final assessment wave, we expect to have a sample of 319 to 337 liver donors.

Given expected refusals to enroll and expected attrition, even with 319 liver donors (the worst-case scenario) we would have power exceeding .995 to detect small differences of less than 4% between a "case" rate of problems in a given HRQOL domain (e.g., rate of clinically significant psychiatric symptomatology) and a population/normative rate (Primary Aim 2, Objectives b.1. and b.2.). For Objective b.3., we would utilize the same strategies as those described for the long-term follow-up cohort. With a sample of 319, utilizing a regression approach to examine donor outcome status at a given time point (see also Section 4.3.10 below), with two-tailed alpha at .05, as many as 8 covariates controlled, and allowing the covariates themselves to have moderate-sized associations with the outcome, then our power to detect even conventionally small[68] differences in proportions or means will exceed .80. We note that we will not restrict our analyses to consideration of outcomes at only individual time points but will also utilize a mixed effects approach (which is appropriate both for interval and discrete outcomes). Power will be even greater under a mixed effect approach because such models allow for the inclusion of cases with incomplete data, and thus our effective sample size will be the total cohort enrolled. Therefore, even if we apply corrections for multiple comparisons (given the fact that we will examine multiple domains of HRQOL), our power will continue to exceed .80 for examining risk factor-outcome associations.

4.3.10 Statistical analysis

Similar to the long-term follow-up cohort, a chief aim of the analyses is to provide descriptive information about the new prospective cohort at each assessment time point post donation (Objectives b.1. and b.2.). Standard approaches to examine distributions of responses to survey measures will be examined (e.g., descriptive statistics, box plots, histograms). To examine prevalence of poor HRQOL outcomes in each identified domain, we will calculate the percentage of the sample at each time point that report clinically significant difficulties within a given domain. These rates, as well as mean scores on continuous measures, can be compared to norms for the measures.

To examine temporal patterns over time, we will use both survival analysis and mixed effects strategies. We will examine time to specific outcomes (e.g., onset of specific mental health problems) via survival analysis. We will examine temporal patterns of responses in each outcome domain with mixed effects models. We will evaluate assumptions regarding missing data patterns

and mechanisms and engage in sensitivity analyses to test the stability of our models. To examine risk factors for poor outcomes in the identified domains at (or by) a particular time point post-donation, we will initially utilize regression-based strategies (linear, logistic, or Cox proportional hazard, depending on the outcome measure of interest) (Objective b.3.). We will also apply mixed effects models to examine risk factors in relation to the trajectory of change in a given HRQOL outcome over time.

4.4 Primary Aim 4: To study the effects of pressure and flow on the outcomes of LDLT

4.4.1 Study Methods:

Baseline assessment will include the standard clinical and demographics required for the Core Protocol. Donor and recipient height, weight, and BMI will be recorded to normalize graft size and the extent of resection. Special attention will be paid to recipient parameters associated with the presence of portal hypertension including ascites and varices. Baseline recipient cross-sectional imaging will define liver and spleen volumes.

Standard surgical techniques will be used for the donor and recipient operations. Right lobe, left lobe, or left lateral segment donation and transplantation will be performed based on clinical parameters for graft selection.

The following will be recorded for donors: duration of surgery, hemodynamics, blood, and fluid replacement. Liver biopsy will be obtained at baseline and after parenchymal transection before devascularization of the graft. The liver graft will be weighed upon extraction. Donor pressure and flow measurements were collected as part of the A2ALL Core protocol, V1.9. We sought to define the values and variability of these observations in healthy livers. The value of these data was weighed against the intrusiveness of the probe insertion and portal vein puncture. From the outset we planned interim analyses with the expectation that we would stop collecting donor data after an adequate sample of reliable data was collected. The Surgical Innovations Committee met in Nov. 2011 and determined that the amount and quality of data was inadequate and donor collection should continue. A follow-up review was conducted on April 16, 2012 with data on 90 subjects. Key values were reviewed and deemed satisfactory for the purposes of the study and the Committee recommended that further data collection be suspended in the interest of donor safety. This was supported unanimously by the Steering Committee the following day and collection has been suspended.

The following will be recorded for recipients: duration of surgery, hemodynamics, blood, and fluid replacement. Anatomical details of the reconstructions will be recorded. Portal flow and pressure and arterial flow will be measured at the completion of the dissection. Central Venous Pressure (CVP), cardiac index, and mean arterial pressure (MAP) will be recorded. After revascularization of the graft, pressures and flows will be measured. CVP, cardiac index, and MAP will be recorded. A liver biopsy will be collected on the back table before implantation of the graft and after revascularization of the graft. The appropriate cutoff values for portal vein flow modulation have not yet been established. In the current protocol, center-based clinical preference will be the basis for flow intervention. If the recipient meets local criteria for portal flow modulation, pressure and flow measurements will be repeated after completion of each portal flow modulation and the type(s) of surgical and/or medical portal flow modulation(s) will be recorded.

4.4.2 Participant selection

All potential subjects will be presented with information and approached for consent.

4.4.2.1 Inclusion Criteria

- Recipients
  - Age 18 or older at the time of consent
  - Has had a living donor identified and accepted and LDLT is planned
  - Informed consent obtained
  - Is listed for single organ (liver) transplantation
- Donors
  - Age 18 or older at the time of consent
  - Has undergone donor evaluation process and was accepted and donation surgery is planned
  - Informed consent obtained

4.4.2.2 Exclusion criteria

  - None

4.4.3 Data elements

In addition to the data elements listed in Section 4.1.3, the following additional data will be collected:

- **Recipients**
  - Pre-operative imaging studies for measurement of liver and spleen volume
  - Intraoperative data
    - Portal pressure and flow measurements
    - Hepatic artery pressure and flow measurements
    - CVP
    - Mean arterial pressure
    - Cardiac output
  - Early postoperative period – Weeks 1 and 2, Month 1 -
    - Portal vein peak systolic flow velocity via Doppler on Day 1
    - Encephalopathy grade
  - Drain output
  - Liver MRI/CT at Month 3 for measurement of liver and spleen volume
- **Donors**
  - Pre-operative imaging studies for measurement of liver and spleen volume

4.4.4 Sample size and power calculations

We anticipate enrollment to average 10 recipients annually per site with a potential enrollment of 180 recipients over a 2-year period. This sample size estimate is based on the numbers of living liver donor transplants performed at A2ALL-2 sites during the past 3 years and the expectation that we would enroll subjects for a total of two years going forward (allowing for follow-up of the last subjects enrolled before the end of A2ALL-2 funding). It also assumes 20% to 30% of prospective recipients will refuse to enroll. Statistical analysis

The chief aim of the analyses is to provide descriptive information about relation between hepatic hemodynamics and graft size and functional outcomes. Standard approaches to examine distributions (e.g., descriptive statistics, box plots, histograms). We will attempt to identify correlations using regression analysis. Categorical comparisons between graft types will be examined to detect the effect of left lobe grafting.

4.5 Primary Aim 5: To compare the long-term histological outcomes in recipients of LDLT and DDLT with recurrent HCV infection

4.5.1 Study methods

The primary focus of this aim is to compare long-term outcomes (cirrhosis) of HCV recurrence in recipients of DDLT vs. LDLT. All participants from the Cohort A2ALL-1 study, including those whose donor was evaluated during the Retrospective era, will be eligible for inclusion. LDLT and DDLT recipients from the new A2ALL sites will be eligible if they had at least one potential donor present to the transplant center for evaluation, as per the original A2ALL-1 inclusion criteria. For these patients identified by the new sites, a waiver of consent for data extraction will be sought from their respective IRBs. for chart review if the patient is deceased or no longer followed. Subjects who received a transplant during the GAP era and meet the inclusion criteria will also be approached for consent or have their data collected under a Waiver of Consent as described above.

With the goal of focusing on longer-term outcomes, surviving non-retransplanted recipients (LDLT and DDLT) will return to their transplant center at least 3 years post-LT for a comprehensive evaluation, including collection of blood for DNA (if not already collected as part of Aim 2) and serum/plasma and liver biopsy. Retrospective data will be retrieved from all recipients, including those who undergo the protocol biopsy, those who are not biopsied because they are already deceased, have clinically decompensated cirrhosis, had been re-transplanted, refused biopsy, had a biopsy in the previous 12 months, have cirrhosis on a previous biopsy, or have a documented post-transplant Sustained Virologic Response (SVR). For deaths and re-transplants, the data up to the time of death or re-transplant will be collected. Clinical data, completed for all HCV patients, will be verified by the site hepatologist if recent biopsy data are not available.

Liver biopsies will be used for assessment of advanced disease and/or cirrhosis due to HCV recurrence. For recipients from the continuing A2ALL centers, demographic and clinical data will be collected as indicated in Section 4.1.3. For recipients from new A2ALL centers, a limited set of demographic and clinical data will be collected for Aim 5 only. For recipients from all A2ALL centers, data from previous liver biopsies documenting progression to cirrhosis or not will be collected – date of first biopsy documenting cirrhosis (for those who have cirrhosis) and date and fibrosis score of last biopsy documenting no cirrhosis (for all patients with and without cirrhosis).

The primary outcome of interest is the development of cirrhosis, defined by Ishak fibrosis stage ≥ 5 based on histology, or liver stiffness >12.5 kPa by transient elastography, or advanced HCV disease based on clinical criteria.
Liver biopsies will be obtained by the transjugular or percutaneous route (per site practice and PI discretion). In addition to unstained slides, additional slides will be stained with hematoxylin/eosin and trichrome. The Ishak scoring system will be used for staging of fibrosis to remain consistent with the central reading of A2ALL-1 biopsies. Inflammation, necrosis, steatosis, steatohepatitis and

evidence of fibrosing cholestatic hepatitis C (pericellular/sinusoidal fibrosis, cholestasis) will be assessed by the central pathologist. Concurrent conditions including acute and chronic rejection and histologic evidence of biliary disease will be noted. The central pathologist will also assess for biopsy adequacy by counting the number of complete portal triads present.

The central pathologist will also evaluate biopsy slides for those subjects who underwent a biopsy in the past 12 months, if that biopsy is serving as a surrogate for the protocol biopsy.

Recipients who met the endpoint of histological cirrhosis during the A2ALL-1 era will be included in this analysis. In order to verify concordance between the A2ALL-1 and A2ALL-2 central pathologists, all biopsies read by the A2ALL-1 pathologist will be re-read by the A2ALL-2 central pathologist. Similarly, biopsies performed during the A2ALL-1 era which were read locally as cirrhosis and the biopsy showing no cirrhosis immediately preceding that biopsy, that had not been reviewed centrally, will also be forwarded for re-read by the A2ALL-2 pathologist. For new A2ALL-2 sites, the latest liver biopsy from patients who do not undergo the ≥3 year protocol biopsy because they have already developed cirrhosis (either by clinical evidence and/or biopsy), the earliest biopsy read locally as cirrhosis, and the biopsy showing no cirrhosis immediately preceding that will also be re-read by the A2ALL-2 central pathologist.

Non-invasive assessment of fibrosis will be made for patients who refuse a biopsy or cannot have a biopsy due to safety concerns at UCSF, Toronto or Northwestern, or centers who acquire transient elastography equipment in the future. In addition, all patients who undergo biopsy at these centers will undergo transient elastography within 90 days of the liver biopsy for the purpose of validating liver stiffness with Ishak fibrosis score.

All subjects' clinical data will be reviewed by members of the HCV Sub-Committee for evidence of having met the clinical end-points of cirrhosis or advanced disease. The review will include assessment of the primary etiology of advanced disease (e.g., HCV disease or non-HCV factors including bile duct stricture, chronic rejection and vascular complications) or documentation of SVR after transplantation (based on undetectable HCV RNA at least 6 months after end of treatment).

4.5.2 Participant selection

In this study, we will recruit approximately 500 male and female HCV-infected adult liver transplant recipients from the 6 continuing A2ALL-1 centers (from those patients enrolled in the A2ALL-1 Cohort study), and from those concurrently transplanted at new A2ALL-2 centers (University of Toronto, University of Pittsburgh, Lahey Clinic).

In addition to those listed in Sections 4.1.2.1 and 4.1.2.2, the following inclusion and exclusion criteria apply to potential subjects with recurrent HCV.

4.5.2.1 Inclusion criteria

- Continuing centers will include LDLT and DDLT recipients enrolled in A2ALL-1 with evidence of HCV at transplantation.
- New centers will include transplanted patients (between January 1998 and August 31, 2010) who had at least one potential living donor who underwent an initial evaluation history and physical examination at the center and had evidence of HCV at transplantation.

- Recipients must have survived at least 90 days without retransplantation.

4.5.2.2 Exclusion criteria

- Documented SVR prior to transplant (non-detectable HCV RNA at least six months after end of treatment)
- Co-infection with hepatitis B virus (HBsAg-positive) before transplant
- Co-infection with HIV
- Receipt of a graft from an HCV-infected donor
- LDLT was one of the first 20 cases at the site

4.5.2.3 Subjects who will be approached for ≥3 year post-transplant liver biopsy

Surviving subjects who meet the inclusion criteria and none of the exclusion criteria listed in Sections 4.5.2.1 and 4.5.2.2 will be approached for a liver biopsy unless they have one of the following conditions: re-transplantation, clinical evidence of decompensated cirrhosis, cirrhosis documented on previous biopsy, liver biopsy performed within the past 12 months, or coagulopathy precluding a liver biopsy. Those subjects who had a biopsy in the past 12 months or had cirrhosis on a previous biopsy will have the biopsies re-read by the A2ALL-2 central pathologist.

4.5.2.4 Inclusion of deceased subjects, retransplanted subjects, and those who do not undergo the ≥3 year post-transplant liver biopsy

Inclusion of these subjects will be critical to avoid a survivor bias and also to meet the required sample size (Table 4). In order to collect the most robust representation of outcomes in LDLT and DDLT recipients, clinical information as well as liver histology data obtained post-transplant will be extracted. Data from recipients who are already deceased, are lost to follow-up, re-transplanted or have clinical evidence of graft failure will be collected retrospectively under a Waiver of Consent. Former Cohort subjects who have been re-transplanted and were ineligible for the main core protocol will be approached and consented for the HCV aim only. Those that are found to be deceased or lost-to-follow-up will have chart review conducted under a Waiver of Consent as described above. Gap-era Core subjects who had previously reached the endpoint of re-transplant will be approached for consent into the HCV sub-study so that their charts can be reviewed. If they are lost to follow-up, their charts will be reviewed under a Waiver of Consent as described above.[

4.5.3 Data elements

Since we have previously shown that center experience is an important determinant of outcome after LDLT for HCV, statistical analysis of outcome will adjust for center experience. New A2ALL sites will therefore identify those LDLT recipients done with center experience >20 cases.

In addition to the data elements listed in Section 4.1.3, the following additional data will be collected:

- **Living Donors (characteristics at donation)**
  - Age, race, gender, diabetes, BMI, relationship to recipient
- **Deceased Donors (characteristics at transplant)**
- Age, race, gender, diabetes, BMI, relationship to recipient, cause of death, donation after cardiac death (DCD) status

- **Recipients**
  - Labs (albumin, AST, ALT, bilirubin, creatinine, INR) at the time of transplant, diabetes, BMI, cold and warm ischemia times, treated acute rejection episodes (dates/treatment), CMV disease (dates/treatment), HCV treatment (dates, drug regimen, date of SVR if applicable), immunosuppression regimen at day 0-7, at 12 months post-transplant, and at time of biopsy, case number (for LDLTs).
  - Biosamples – collected once, at the time of liver biopsy or after activation into the HCV component of the study (> 3years post-txp) – serum, plasma, whole blood for DNA extraction (if not previously collected as part of Aim 2). These samples will be stored at the NIDDK Biosample Repository for future studies on HCV recurrence after liver transplantation.
- **Outcomes: Severity measures (with dates)**
  - Liver biopsy (Ishak score)
  - Measurement of liver stiffness by transient elastography
  - Graft survival: date and cause of graft loss, date of retransplant, explant pathology report, dates of development of complications of liver failure (ascites, encephalopathy, variceal bleeding)
  - Patient Survival: date and cause of death, autopsy report (if available)
  - Hepatic venous pressure gradient (mmHg), if available, as part of obtaining liver biopsy via the transjugular route, including free and wedged hepatic vein pressures[74,75]
  - Clinical Data: presence of ascites, hepatic encephalopathy, bleeding esophageal varices

4.5.3.1 Table 4: Schedule of data and biosamples for HCV study

Study Population	Data Collected	OLT Admission	post-OLT
1. A2ALL-1 Cohort Study enrollees*	Demographics	+	+
	Transplant data (e.g., CIT, WIT)	+	
2. Concurrently transplanted DDLT recipients from New A2ALL-2 Sites** with ≥ 1 potential donor	Outcomes		+
	Diabetes (medication-treated)	+	+
	Rejection/treatment		+
	CMV/treatment		+
	HCV treatment and response		+
	Biliary complications		+
	Immunosuppression	+	+
3. Concurrently transplanted LDLT recipients from New A2ALL-2 Sites**	Liver Biopsy		+
	Lab values	+	
	Serum		+
	Plasma		+
	Whole blood for DNA (if not previously collected for Aim 2)		+

*A2ALL-1 Sites continuing in A2ALL-2 Study: Columbia University, University of Colorado, Virginia Commonwealth University, Northwestern University, University of Pennsylvania, University of California at San Francisco

** Patients transplanted during the A2ALL-1 Era from New A2ALL-2 Sites: Lahey Clinic, University of Toronto, University of Pittsburgh.

4.5.4 Sample size and power calculations

All sample size calculations below assume a significance level of 0.05, two-sided testing, and an exponential distribution of times to cirrhosis. A clinically meaningful difference in risk of cirrhosis after a median follow-up of 5 years will be defined as ≥15%. The predicted proportion with cirrhosis (Ishak 5-6 or cholestatic hepatitis on biopsy, liver stiffness measurement ≥12.5 kPa by transient elastography, or clinical criteria of cirrhosis per HCV disease form) at 5 years for DDLT is estimated to be 5%. To detect a greater proportion in LDLT than DDLT (12% vs. 5%, hazard ratio=1.41) with 92% power will require a sample size of 200 per group. As depicted in Table 5, such a sample size should be reached by patients currently in Retro/Cohort A2ALL-1 with the participation of new A2ALL sites (Toronto, Lahey, Pittsburgh); we estimate that there are currently 221 DDLT recipients with at least one donor evaluated and more than 304 LDLT recipients currently alive and ≥ 3 years post-transplant. Inclusion of almost all DDLT recipients into the study will be needed to reach sample size, although any shortfall may be offset by the extra power gained by the likely occurrence of more than 200 LDLT enrollees.

4.5.4.1 Table 5: Number of LDLT and DDLT recipients from each study site known to be alive at least 3 years post-transplant from the A2ALL-1 Cohort Study (continuing sites) and the A2ALL-1 Cohort Study era (new sites)

	Columbia	NW	Penn	Colorado	Lahey	UCSF	Toronto	Pitt	VCU	Total
DDLT	16	4	3	21	14	29	112	21	10	221
LDLT*	44	13	6	31	60	20	70	44	27	304

*DDLT recipients are those who had at least one potential living donor evaluated.

4.5.5 Statistical analysis

The primary outcome is cirrhosis based on liver biopsy, or in cases without biopsy, based on transient elastography and clinical and laboratory criteria of advanced disease. In general, if information from more than one source is available, the order of preference of information is: biopsy, transient elastography, and clinical and laboratory criteria. The biopsy measures include fibrosis score (standardized to 6-point ordinal scale, 0-6), or cholestatic hepatitis (scored as 6), or advanced disease as determined from the HCV Disease Form (scored as 6).

Patients with a biopsy documenting cirrhosis will be considered to have met the primary endpoint at some time prior to biopsy (i.e., left-censored data). Those with a biopsy documenting no cirrhosis will not yet have crossed the threshold (i.e., right-censored data). If additional biopsies are available, then we may be able to isolate the interval in which cirrhosis occurred as between the last biopsy documenting no cirrhosis and the first biopsy documenting cirrhosis (interval-censored data). If biopsy is not available, liver stiffness measurement by transient elastography will be used to determine if primary endpoint of cirrhosis was met. In the absence of both biopsy and liver stiffness measurement, primary endpoint will be determined based on clinical and laboratory criteria contained in the data elements listed in Section 4.5.3. This information will also be used to determine if the primary endpoint was reached in patients who died or who had been re-transplanted. Data will be reviewed by the HCV Adjudication Committee to determine if criteria for cirrhosis were met and if death or graft loss was HCV-related. The cumulative distribution (or survival) function for time from transplant to cirrhosis will be estimated using either parametric models or nonparametric (Turnbull estimator) methods. To test for a difference in this distribution between

LDLT and DDLT, adjusting for covariates such as age and MELD score, parametric regression models (e.g., using SAS Proc Lifereg), or discrete survival analysis methods (e.g., using SAS Proc Genmod) will be used.

In addition, times to patient death and graft failure will be analyzed as right-censored outcomes, using standard survival methods (Kaplan-Meier estimates, log rank tests, and Cox regression). Non-Markov multistate models[73] will be considered if feasible with the available data.

Validation of transient elastography will be performed based on the subset of patient who undergo both transient elastography and biopsy within 90 days of each other. The correlation coefficient between transient elastography measure and Ishak score from biopsy will be calculated. A calibration model will be fit to convert transient elastography values into Ishak equivalents. A strong correlation (e.g., 0.7 or higher) would be expected if the two methods are to be considered interchangeable. A transient elastography cutpoint of values above 12.5 kPa are indicative of cirrhosis.

4.6 Primary Aim 6: To understand the history of pain management and to measure quality of care in pain control in living donors following partial hepatectomy.

4.6.1 Study Methods

The study uses two surveys to collect information about live donor pain management. The first survey collects information from care providers in the A2ALL Consortium regarding the details of their choice of pain management and their opinions/beliefs.

4.6.1.1 Study Methods – Retrospective Component

We used the APS-POQ-R as a template to develop the survey questions. The survey addresses aspects of practice that are linked to outcome, including: resources and personnel participating in pain management, methods used to assess pain, and opinions about the efficacy of pain management. An electronic retrospective survey (see Appendix E) will be distributed to the transplant research coordinator and completed by a surgeon, nurse and anesthesiologist (if the latter is involved in pain management) at each of the nine A2ALL clinical centers. The survey measures the methods and personnel used in postoperative pain management, how pain was assessed and what quality indicators were used assess performance. Data will be collected via a commercial web-based survey application .

4.6.1.2 Study Methods – Prospective Component

All sites will utilize the APOS-POQ-R (see Appendix F) to collect information about the outcome of pain management from the post-op liver donors' perspective. A study coordinator will read the questions to the subjects and record their answers 48 hours following liver donation surgery. A database will be constructed from the subjects' answers to the APS-POQ-R that is not biased by the source of the data or the technique used for pain management. Data will be analyzed for overall effect by measuring patient satisfaction (how living donors rate the quality of their pain care). Answers to the survey questions assess overall patient satisfaction. The responses to individual questions that identify specific areas of pain management also relate to patient satisfaction.

Collection and analysis of this data corresponds to our study's objectives summarized in Section 3.6.1.

4.6.1.3 Participant Selection – Retrospective Component

The lead investigator at each site will select up to three health care providers involved in post liver donation pain management: a liver transplant surgeon, an anesthesiologist, and the nurse transplant coordinator.

4.6.1.4 Participant Selection – Prospective Component

Inclusion Criteria

- Adult living liver donors

Exclusion Criteria

- History of chronic pain
- History of narcotic use (routine scheduled narcotic use for treatment of a pain disorder diagnosed and treated by a physician)
- Medically unstable at 48 hours post-donation surgery
- Language barrier

4.6.1.5 Data elements

Retrospective Component:

- Responses to retrospective survey (see Appendix E)

Prospective Component

- Demographic information as described in Section 4.1.3
- Intraoperative, perioperative and post-operative complication and hospitalization information as described in Section 4.1.3
- Responses to screening questions regarding history of chronic pain and narcotic use
- Responses to the APS-POQ-R survey (see Appendix F)

4.6.1.6 Sample size and power calculations

Retrospective Component: The unit of analysis is the clinical center, with a sample size of 9. This analysis will describe clinical practice at the 9 A2ALL centers and will not attempt to make inference to a larger population.

Prospective Component: We anticipate that approximately 200 future donors will be enrolled in A2ALL-2. Although it is unlikely that more than 200 donors will be accrued, enrollment will remain open during A2ALL-2 to allow as much power as possible to assess center effects and variables predictive of satisfaction with pain management. Because many of the study measures will be presented descriptively, we first give the confidence interval (CI) width for, e.g., the true mean satisfaction score (0-10 scale) assuming a standard deviation of 2.0. With n=200, we will have 93% probability that the width of this CI will be no greater than +/- 0.30. For comparing the satisfaction scores at two of the 9 centers, say each with n=30 donors, we will have 90% power to detect a difference in means of 1.7. Sample size calculations were made using the SAS Power procedure (SAS Institute, Inc., Cary, NC).

4.6.1.7 Statistical Analysis

Retrospective Component:
The methods and personnel that each center uses to manage postoperative pain in live liver donors and methods they have stopped using, will be presented using descriptive statistics. If possible, graphical methods will be used to display the changes over time.

The medical specialty of care providers responsible for pain management and assessment will also be described for the 9 A2ALL centers. This summary will include both the type of specialists involved, and whether pain management involved an Acute Pain Team or not. Both the proportion of centers with Acute Pain Teams and the composition of these teams will be described. The continuity of pain management through phases of patient locations (e.g., ICU, surgical ward) will also be reported. Finally, the opinion of the medical care providers on the adequacy of pain control at their center will be described, and will also be compared to patient reports at that center (using data from prospective component of the study).

Prospective Component:
Satisfaction will be assessed using (a) the single question (P9), measuring overall satisfaction, and (b) the individual items of the pain questionnaire (P1-P8 and P10-12). These outcomes will be presented using descriptive statistics, including frequencies, means and standard deviations. Histograms and/or boxplots will be used to identify the forms of the distributions and to identify outliers. Aspects of care with low scores or a large standard deviation will be identified as practices that require overall improvement. Boxplots and analysis of variance will also be used to display and compare quality indicators from the APS-POQ-R measures by center.

To identify aspects of care that account for differences in patient satisfaction, we will evaluate predictors of overall satisfaction (P9) using linear regression. Predictors of overall satisfaction to be tested will include the pain relief variables (P1-P7), participation in decisions about pain treatment (P8), helpfulness of information received (P10), non-medicine methods of treatment (P11, P12), demographic variables, and donor relationship.

The complications outcomes (P6) will be analyzed using descriptive statistics as described above. Pain questionnaire data will also be linked to A2ALL-2 donor complication data to assess whether aspects of the donor pain experience, based on questions from the APS-POQ-R, are predictive of subsequent complications.

5 Human Subjects

5.1 Protection of human subjects

5.1.1 Institutional review board

This study and analysis will be performed under Institutional Review Board (IRB) oversight. Prior to the initiation of the study, an IRB approval for study of human subjects will be obtained separately from the IRB of each of the participating transplant centers and the DCC. Revisions to the study protocol and changes in the study design will also be submitted to the individual IRBs for approval prior to implementation.

Subjects will be enrolled in the core protocol with full informed consent which will include the gathering of privileged health information (PHI), the collection of blood and tissue specimens beyond that normally performed for transplant/donation clinical care as well as samples for genetic studies, and the collection of medical and quality of life information at defined intervals prior to and after the transplant in donors and recipients.

Each participating center will be responsible for obtaining such human subjects research authorization and will create an informed consent document detailing the procedures described above in the language required by their respective institutes. All key personnel at the participating centers will have successfully completed their IRB-required training and certification for human subject's research and HIPAA researchers' privacy requirements.

5.1.2 Patient confidentiality

5.1.2.1 Core Protocol

Special procedures for ensuring patient confidentiality will be implemented. Data transmission and the distributed data systems have multiple layers of security as discussed below in Section 6, Study Management. Each study subject will be assigned an identification number. Only this number will be used to identify subjects in any individual tabulation. The PHI that is collected will represent the minimum necessary to successfully execute the study. The DCC plans to periodically update outcomes and mortality information (graft failure, liver failure, mortality) in the study population by linking to the Scientific Registry of Transplant Recipients (SRTR). The DCC maintains a Data Use Agreement with the SRTR's contractor and adheres to the requirements set forth to protect subjects' privacy and confidentiality. Links to the SRTR database will be destroyed when the study has ended.

PHI entered into the database at the site level will only be visible to study personnel accessed through a triple password regimen. The PHI is encrypted at the site level. Site personnel have the decryption key, and it is not available to the DCC. It is expected that only group data will be published. If individual subject data are to be published, no identifying information will be included. The study files will be maintained in a secure location as described above. Access to computerized data will be restricted to study personnel. Password authorization will be enforced. Previous use of this security system and secured server indicates that this technique is very successful in assuring the protection of confidential information.

Authorized representatives of the Sponsor, the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), participating clinical institution, DCC monitoring staff, as well as the IRB, have access to medical records and records from participation in this study. Such access is necessary to ensure the accuracy of the findings.

5.1.2.2 HRQOL Substudy

Potential risks of the HRQOL substudies include a possible breach of confidentiality. Care will be taken at all stages of the protocol to ensure and protect study participants' confidentiality. Individual A2ALL sites will each assure, and their consent forms will explain, that the living donor transplant team and program will not be informed as to the contents of any completed HRQOL assessment instruments by study participants. No materials gathered during the research will become part of

participants' medical records, including any records maintained by the living donor programs. No individual participant will be identified in any published report. Data collected during the research will be entered into password-secured databases by research staff authorized by the survey center PIs at Northwestern University (NWU) and the University of Pittsburgh (Pitt) to do this (see Section 6, Study Management, for further discussion of survey research center management issues). Research records and documents will be kept in a locked file. No research documents will contain the names of study participants. Instead, identification numbers will be assigned to each study participant to mask their identity, and the list linking participant names and IDs will be stored in a separate locked file in the survey center PI's office. The study interviewers at the centralized survey research centers, who will perform HRQOL study assessments, will have study participant contact information but they will not be employed by the living donor programs and they will all sign a statement indicating that they will abide by HIPAA and IRB confidentiality regulations.

5.1.3 Risks to the study participant and adequacy of protection against risk

Patients enrolled in this study will experience more than the normal amount of testing which is customary for this complicated medical and surgical procedure. Additional time will be required both before and after the transplant for the gathering of medical and quality of life information. Blood and liver tissue will be collected and stored for special tests which are not normally required for clinical care. Venipuncture carries risks of pain and bruising at the puncture site. Intraoperative biopsy carries the risk of increased bleeding. Percutaneous liver biopsy carries the risks of: pain (20%), severe bleeding requiring a blood transfusion or an operation to stop the bleeding, infection, puncture of the gallbladder, lung or kidney (~1 per thousand), and death (~1 per 10,000). In addition to the risks associated with a percutaneous liver biopsy, a liver transjugular liver biopsy carries the following risks: collection of hemotoma in the neck, temporary problems with the facial nerves, and temporary voice problems. Portal and hepatic vein pressure and flow measurement also carries the risk of bleeding and damage to the vein(s). All research procedures will be carried out by qualified personnel who are experienced in performing the tasks.

The study participant interviews and the HRQOL instruments do not involve any known physical risks. Individuals may experience psychological discomfort in answering repeated, longitudinal assessment questions related to their emotional well-being, health concerns and worries, relationship problems, or financial hardships. With respect to potential discomfort developing during interviewing, we note that the interviewers will be trained by the investigators to be sensitive to participant discomfort and concerns. Regarding the post-donation assessments in particular, we have found in our previous studies involving living donors that they often report that, rather than being stressful, post-donation assessments are a source of support to them and that they are glad to have had the chance to discuss the donation experience and post-donation issues. There is a potential risk of breach of confidentiality that is inherent in all research protocols and steps to minimize this risk are described above. Steps to minimize risk and address any psychological discomfort are addressed below.

> Recruitment and Informed Consent. At each A2ALL site, individuals eligible for study (based on criteria described in Section 4.1.2 above) will be approached by a member of the living donor transplant team for release of their protected health information and contact information so that study staff may approach them to describe the study and obtain informed consent. All consent forms will be HIPAA compliant. A copy of the signed consent forms

will be kept by the study participant, and one will be kept in the research records at the site where the participant was enrolled. Participants will be informed verbally and in the informed consent form that their contact information will be released to a centralized survey research center which will contact them and conduct the interviews by telephone. They will be informed of the assessment time points and the payments they will receive for participating in the HRQOL assessments.

Psychological discomfort during study procedures (i.e., during study assessments). With regard to participants' psychological discomfort and overall well-being, we noted above that the interviewers will be specifically trained to be sensitive to subjects discomfort and concerns. These issues will be of central focus during their training. If a participant finds the research procedures to be upsetting or aversive, he/she will have the option to withdraw from the study. We will refer participants to an appropriate clinical setting for evaluation and/or treatment (a) in the unlikely event that an interviewer judges a participant to immediately require such care for psychological distress, or (b) if the participant him- or herself inquires about receiving such care. The criteria for establishing that a participant immediately requires care are that the participant expresses thoughts or an intention to harm him/herself or others. During the HRQOL assessment interviewers will be alert for any statements volunteered by the participant regarding thoughts or intent for harm or for the participant's affirmative response to the PRIME-MD items that refer to thoughts or intent of harming self or others. In this situation, confidentiality would have to be broken in order to protect the participant. The participant will be made aware of this contingency in the informed consent form. If this circumstance arises, the interviewer will initially consult the specific center study coordinator to arrange for an evaluation at the respective institute, or at a local facility in the geographical area where the participant resides if he/she lives a long distance from the living donor transplant program and prefers a local referral. This approach meets IRB guidelines, and these procedures have successfully facilitated such local and long-distance arrangements in our past studies. We have had to invoke these procedures with any transplant-related population extremely rarely.

5.1.4 Unauthorized data release

5.1.4.1 Core Protocol

The data sets will be stored on a secure server with restricted access (requires a unique username and password) at the DCC and every precaution will be taken to keep the information private. However, there is always the possibility of unauthorized release of data about subjects. Such disclosure would be extremely unlikely to involve a threat to life, health, or safety, since the only PHI that will be collected is month and year of birth. It is conceivable that such disclosure could have psychological, social, or legal effects on the patient. Using the standard security procedures (described above under patient confidentiality) can effectively minimize the risk of unauthorized disclosure of data. All study personnel who have access to patient data will be educated regarding the need to protect confidentiality and the procedures to be followed to ensure such protection. All staff will also be required to sign a standard medical record confidentiality agreement. The computer system on which data are maintained uses standard password protection procedures to limit access to authorized users.

5.1.4.2 HRQOL Substudy

The protection of study participant privacy is especially important as it relates to access and transmission of research data. We will take the following steps to assure the confidentiality of research data during storage and transmission via the internet. First, participants' names and identifying information will not be transmitted with study assessment information. Instead, an identification number will be used for data transmittal. Secondly for the handling and transmittal of data, the centralized survey research centers will provide computer and web page security and data transmission between their web servers to World Wide Web users and thus provide secure transmission of data to the DCC (using such protections as Secure Sockets Layer (SSL), SSL Certificate authentication, data encryption and password protection). Each individual needing to access the web sites will be provided with a unique Username and a Password.

At the survey research center responsible for data collection from a given participant, only the PI and authorized study staff will be allowed access to participant information and all computerized data will be password protected. In addition, the center will monitor individuals who are accessing participant information to assure that strict authorized access only is maintained. At the individual A2ALL sites responsible for enrolling study participants, similar procedures will be used to ensure that informed consent forms are maintained (e.g., locked files accessible only to authorized study staff).

5.1.5 Adverse event monitoring and reporting

5.1.5.1 Definition of adverse event

An adverse event (AE) is any untoward medical occurrence or unfavorable and unintended sign in a research subject that occurs during or as a result of a research procedure.

For this observational study, the majority of the procedures are standard clinical care and adverse effects of clinical care will be tracked as complications but will not be considered adverse study events. Each center will review the list of study procedures and identify the specific procedures that are not standard-of-care at their institution and these will be considered research procedures. Complications that are a result of research procedures will be reported and tracked as adverse events.

5.1.5.2 Assessment of event severity and relationship to treatment

The modified World Health Organization (WHO) grading system will be used for grading severity of AEs (Appendix C). For AEs not covered by the modified WHO grading system, the following definitions will be used:

Mild:	awareness of sign, symptom, or event, but easily tolerated
Moderate:	discomfort enough to cause interference with usual activity and may warrant intervention
Severe:	incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention

Life-threatening:	immediate risk of death

The investigator must also assess the relationship of any adverse event to the research procedure, based on available information, using the following guidelines:

Unlikely related:	no temporal association, or the cause of the event has been identified; or the procedure cannot be implicated
Possibly related:	temporal association, but other etiologies are likely to be the cause; however, involvement of the procedure cannot be excluded
Probably related:	temporal association; other etiologies are possible, but unlikely

5.1.5.3 Definition of serious adverse events

A serious adverse event (SAE) is any adverse experience that results in any of the following outcomes:

- Death;
- Life-threatening AE (i.e., one that places the subject, in the view of the investigator, at immediate risk of death from the AE as it occurs);
- Persistent or significant disability/incapacity;
- Required in-patient hospitalization, or prolonged hospitalization;
- Congenital anomaly or birth defect.

Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event when, if based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

5.1.5.4 Reporting responsibility

All adverse events must be recorded. The onset and end dates, severity and relationship to study procedure(s) will be recorded for each adverse event. Any action or outcome (e.g., hospitalization, additional therapy, etc.) will also be recorded for each adverse event. Subjects will be questioned and/or examined by the investigator or his/her designee for evidence of adverse events.

All AEs and SAEs must be reported by the investigator to the A2ALL Data Coordinating Center (DCC). The DCC will review reports of all related SAEs and other relevant information immediately, and may request additional information from sites for analysis of these events. Sites will report serious adverse events according to the time frames outlined below.

All events that are serious and related (possibly or probably) must be reported to the DCC within 24 hours of the investigator being informed of the event. Follow-up information about a previously reported serious and related adverse event may be reported to the DCC within 7 working days of the investigator receiving the information; however, important follow-up information must be submitted

within 24 hours. All deaths connected to a study procedure must be reported to the DCC within 24 hours of the investigator being informed of the event.

5.2 Benefits to the patients

There are no direct benefits to the patients for participation in the study.

5.3 Inclusion of women

This is a multi-center study drawing on a clinical population from nine transplant institutions across the United States and Canada. The demographics of the study population are pre-determined due to the all-inclusive nature of the study. Women will be included in the study as living liver donors or as recipients. It is anticipated that the representation of women will correspond to the fraction of females in the living liver donor and recipient population.

5.4 Inclusion of minorities

This is a multi-center study drawing on a clinical population from nine transplant institutions across the United States and Canada. The demographics of the study population are pre-determined due to the all-inclusive nature of the study. Racial and ethnic minority groups will be included in the donor and recipient components of the study and will be proportional to their representation in the living liver donor and recipient population.

5.5 Inclusion of children

The study specifically excludes children. By definition this study is designed to examine the risks, benefits and outcomes of Adult-to-Adult living donor liver transplantation. However, eligible subjects between the age of 18 and 21 years will be enrolled.

5.6 Data and safety monitoring plan

Accepted principles of data and safety monitoring will be observed throughout the conduct of the A2ALL study. The NIH will appoint an independent Data Safety and Monitoring Board (DSMB) that will provide study oversight. The DSMB will approve the study protocol prior to enrollment and will also approve all subsequent protocol revisions.

Each transplant center principal investigator will be responsible for monitoring the enrollment of subjects and submission of data to the DCC. The DCC will be responsible for monitoring for effective conduct of the protocol and accurate and timely data submission.

IRBs will be provided feedback on a regular basis.

Training of study coordinators and study monitoring activities will be conducted by the DCC to ensure patient confidentiality and privacy and to maximize the reliability, accuracy, and timeliness of study data.

The HRQOL substudy committee and relevant survey research center staff will conduct quarterly meetings to review recruitment/enrollment progress, data collection activities, review participant complaints and any adverse events (see adverse event procedures above). As a part of these meetings the centralized survey research centers will generate quarterly reports to the HRQOL

substudy committee on the tracking and management of all substudy participants. In particular, the centralized survey research centers report monthly retention rates, outstanding interviews/surveys, and data entry progress. The centers will use electronic tracking systems to monitor numbers of interviews scheduled, completed, refused, pending, etc. Data will be routinely exported from the system, examined for accuracy and completeness, and backed up to secure storage devices. Upon completion of data collection, final processing and cleaning of data will be conducted. A technical report detailing specific project methodology, response rates, and other details will be produced. The HRQOL substudy committee will supervise these activities and provide additional assistance as may be required.

5.7 Study organization

5.7.1 Clinical transplant centers

The participating Clinical Centers will have primary responsibility for developing the study protocol, maintaining high rates of follow-up and data collection, obtaining data of high quality, and interpreting, presenting, and publishing findings from the study.

Columbia University Medical Center
New York, NY
Principal Investigator: Jean Emond, MD (Steering Committee Co-Chair)

Northwestern University
Chicago, IL
Principal Investigator: Michael Abecassis, MD

University of Pennsylvania
Philadelphia, PA
Principal Investigator: Kim Olthoff, MD

University of Colorado Denver
Aurora, CO
Principal Investigator: James Burton, MD

University of California, San Francisco
San Francisco, CA
Principal Investigator: Christopher Freise, MD

Virginia Commonwealth University – Medical College of Virginia
Richmond, VA
Principal Investigator: Robert Fisher, MD

Lahey Clinic
Burlington, MA
Principal Investigator: Elizabeth Pomfret, MD

University of Pittsburgh Medical Center
Pittsburgh, PA
Principal Investigator: Abhinav Humar, MD

University of Toronto
Toronto, Canada
Principal Investigator: David Grant, MD

5.7.2 Data coordinating center

The Data Coordinating Center (DCC) contributes content area expertise and shares in scientific leadership of the research group. The DCC has developed a communication infrastructure that includes meetings, teleconferences, electronic mail and bulletins, interactive web-based encounters and written correspondence. The DCC assists in protocol development and preparation of scientific publications. The DCC has the major responsibility of creating a database and data collection systems for the transplant centers, ongoing evaluation of data quality and performance monitoring of the transplant centers and statistical analyses of the data. The DCC will also create a comprehensive Manual of Operations (MOO) that will govern the conduct of the study. The manual will detail the protocols, protocol clarifications and amendments, summary of the regulatory requirements for the study, instructions for enrollment, data collection, data management, visit schedules and detailed instructions on the use of the electronic data submission. The DCC is responsible for clinical monitoring of the study.

University of Michigan
Ann Arbor, MI
Principal Investigator: Robert M. Merion, MD (Steering Committee Chair)

5.7.3 Steering committee

The primary governing body of the study is the Steering Committee, comprised of each of the Principal Investigators of the transplant centers, the Principal Investigator of the DCC and the NIDDK Project Officers. The Steering Committee develops policies for the study pertaining to access to patient data and specimens, ancillary studies, performance standards, and publications and presentations. They develop the study protocol and meet to discuss the progress of the study and to consider problems arising during its conduct. The Steering Committee may establish subcommittees to further develop specific components of the study protocol and propose ancillary areas of study. Small working groups may be established to prepare manuscripts and presentations.

5.7.3.1 Workgroups and subcommittees

The following subcommittees have been established to address specific issues, develop protocols and provide administrative guidance to the project:

- Protocol Design
- Hepatitis C Virus (HCV) Workgroup
- Hepatocellular Carcinoma (HCC) Workgroup
- Regeneration and Function Workgroup
- HRQOL Workgroup
- Surgical Innovations Workgroup

- Publications Committee
- Ancillary Studies Committee

6 Study Management

6.1 Data collection, case report forms, and data entry: Aims 1, 2, 4, and 5

The DCC will utilize the web-based *A2ALL-Link* as the data management nucleus for the A2ALL-2 studies. *A2ALL-Link* is a database platform developed by Arbor Research Collaborative for Health (Arbor Research). The research team at Arbor Research has successfully collaborated with the University of Michigan DCC team on another NIH-sponsored study researching outcomes of living kidney and lung donors. *A2ALL-Link* provides many improvements over the database application employed during the first iteration of the A2ALL study.

The DCC will utilize the *A2ALL-Link* to create electronic case report forms to capture all relevant study data for the core study and all investigational/research protocols that are developed and implemented during the course of A2ALL-2. The *A2ALL-Link* system allows real-time monitoring of study data for protocol adherence, quality assurance, adverse event reporting, discrepancy reporting, and other trends.

The DCC plans to periodically update outcomes and mortality information (graft failure, liver failure, mortality) in the study population by linking to the SRTR. The DCC maintains a Data Use Agreement with the SRTR contractor and adheres to the requirements set forth to protect subjects' privacy and confidentiality. Links to the SRTR database will be destroyed when the study has ended.

6.2 Data collection, case report forms, and data entry: HRQOL Substudy

For the HRQOL Substudy, data collection for both the long-term follow-up and the prospective cohort study will be accomplished through the involvement of the study's two survey research centers, with Northwestern (NWU) taking responsibility for continuing A2ALL sites (UCSF, NWU, VCU, Colorado, Columbia, Penn) and the University of Pittsburgh taking responsibility for the three new sites (Pittsburgh, Lahey, Toronto).

We will utilize telephone survey methods in order to collect the data because these methods are known to produce higher response rates than mailed questionnaires.[43,71,72]. To ensure uniformity, accuracy and consistency of data collection, we will employ training and monitoring of interviewers, and we will use computer assisted telephone interviews (CATI). Interviewers will be trained in general and project-specific interviewing techniques using a combination of didactic presentations, written handouts, video instruction, and hands-on experience. Interviewers will be continuously monitored during data collection for quality assurance, and periodic retraining sessions will occur as necessary. We will employ real-time data collection and entry through CATI. CATI systems involve survey instruments programmed into an electronic data system, interviewers reading the questions directly from the computer screen, and responses being directly entered into the database. This eliminates the need for independent data entry and minimizes transcription and coding errors. It is also cost-efficient.

6.3 Data management

All core study data will be entered into the electronic data entry system by study coordinators at each study site. These data will be encrypted and transferred to the DCC and stored on a secure server at the University of Michigan's subcontractor (Arbor Research). Access to the server and data entry system is limited and requires a unique username and password combination. The servers are backed up daily and physically stored in a locked facility.

For the HRQOL study, both the NWU and Pittsburgh survey research centers will provide secure transmission of electronic files containing all survey responses to the DCC. Both centers will institute electronic tracking systems to ensure that interviews are scheduled and completed in a timely manner and that data is efficiently transmitted to the DCC.

All analysis of the data sets will utilize de-identified (coded) data sets.

6.4 Quality control and database management

The first steps in ensuring protocol compliance are good protocol design and careful orientation of study personnel. Following final agreement on protocols, and prior to study initiation at any of the transplant centers, the DCC will organize a Training and Certification session for transplant center study coordinators/data entry personnel.

The electronic data entry system will have built-in data checks as part of study quality assurance. Protocol compliance will be assessed by monitoring the submission of data at required intervals. Data inconsistencies and discrepancy reports will be reviewed by the Clinical Monitors so that necessary queries can be generated and sent to the transplant center study sites for verification and resolution.

Periodic requests may be generated for the submission of random source documents to assess the quality of data acquisition and data entry at each site. In addition, the Clinical Monitor or Project Manager will visit each site at least once a year to review source documents, monitor regulatory compliance, and assess protocol adherence.

In addition to source document verification, the Clinical Monitor and Project Manager will produce reports from the database to look for inconsistencies in submitted data, particularly for repeated measures data elements, even if data do not fall outside of built-in validation routines.

Studies of intra-subject and inter-subject data variability by transplant center as well as intra-transplant center and inter-transplant center data variability will be used to further ascertain random or systematic data quality issues.

Comparisons of major endpoints from the current study to national data from the SRTR will be used to assess the extent to which participants in the A2ALL study are representative of the general population of patients undergoing these procedures in the United States.

6.5 Data security/data transfer

For the Core Protocol, personnel at each study center will collect and enter data into the web-based data entry system. The following data security contingencies are in place:

- Compliance with Industry Standards Regarding Data Security (HIPAA and 21 CFR Part 11)
- Audit trails are maintained for all activity and all changes to any data element
- All servers, web servers, firewalls, etc. are configured and maintained according to industry best practice guidelines for backup, security, continuity of operations, and protection of PHI
- All data are available only to authorized users from each site after secure login with encryption, with all site activity audited at the user level
- All transmissions between the Internet and the database are encrypted using a 128-bit encryption algorithm
- There is a comprehensive security plan in place

Detailed instructions on the use of the database platform, data element definitions and a code list will be provided in a Manual of Operations (MOO). Each study site will be provided a copy of the MOO and the entire manual will be available on the study web site, and in the Help area of the database user interface.

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8 APPENDICES

8.1 APPENDIX A: Donor schedule of events

Event	Time Point											
	Pre-Donation	At Donation										
	Shortly Pre-Donation	Just Prior to Resection	1° Post Resection	Day 2	Week 1	Month 1	Month 3	Month 6	Year 1	Year 2	Year 3	Year 4
LFTs	**X**				**X**	**X**	**X**		**X**	**X**	**X**	**X**
CBC	**X**				**X**	**X**	**X**		**X**	**X**	**X**	**X**
Creatinine & BUN	**X**				**X**	**X**						
PT/INR	**X**				**X**	**X**	**X**		**X**	**X**	**X**	**X**
CT/MRI	**X**						**X**					
Liver Bx - Biorepository		**X**	**X**									
Whole Blood – DNA Biorepository	**X*** **											
Serum - Biorepository	**X**				**X**	**X**	**X**		**X**			
Plasma & Peripheral Cells - Biorepository	**X**					**X**	**X**		**X**			
Whole Blood - RNA Extraction for future study	**X**					**X**	**X**		**X**			
Post-Donation Pain Survey				X								
Long - term Follow-up Cohort* HRQOL BATTERY (Table 1 in Protocol)										**X**	**X**	**X**
Prospective Cohort** HRQOL BATTERY (Table 2 in Protocol)	**X**						**X**	**X**	**X**	**X**		

* Old donors from new sites will not be getting labs or non-HRQOL-related study visits.
** All new donors from all sites.
***Can be collected at any timepoint during the study.
SUBJECTS JOINING THE STUDY FROM THE PREVIOUS A2ALL COHORT STUDY WHO ARE MORE THAN 4 YEARS POST-TXP WILL FOLLOW AN ANNUAL SCHEDULE OF EVENTS WITH THE SAME ASSESSMENTS AND SAMPLES AS YEAR 4.

8.2 APPENDIX B: Recipient schedule of events

Event	Time Point																									
	Pre-TXP	At TXP						Post TXP																		
	Shortly Pre-TXP	Pre-op	After Portal Dissection	Back Table	After completion of the arterial anastomosis	After portal flow modification*	1° Post Reperfusion	Day 1	Day 2	Day 3	Day 4*	Day 5*	Day 6*	Day 7	Day 8*	Day 9*	Day 10*	Day 11*	Day 12*	Day 13*	Wk 2	Mon 1	Mon 3	Yr 1	Yr 2	Yr 3	Yr 4
LFTs	X							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC	X							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Creatinine	X							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PT/INR	X							X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sodium	X							X	X	X	X	X	X	X	X	X	X	X	X	X	X					
BUN	X							X	X	X	X	X	X	X	X	X	X	X	X	X	X					
HCV RNA																									X ***	
Pressure & Flow Measurements			X		X	X																				
Doppler Portal Vein Flow Rate								X																		
CT/MRI	X																					X				
Liver Bx - Biorepository				X			X																		X ***	
Whole Blood – DNA BioRepository	X**																									
Serum - Biorepository	X													X							X	X	X	X	X	X
Plasma & Peripheral Cells - Biorepository	X																					X	X	X	HCV Plasma Only	
Whole Blood - RNA Extraction for future study	X																					X	X	X	X	

* Record if done clinically
**Can be collected at any time point in the study
***HCV RCP only; Bx performed if no clinical Bx was performed at this timepoint
SUBJECTS JOINING THE STUDY FROM THE PREVIOUS A2ALL COHORT STUDY WHO ARE MORE THAN 4 YEARS POST-TXP WILL FOLLOW AN ANNUAL SCHEDULE OF EVENTS WITH THE SAME ASSESSMENTS AND SAMPLES AS YEAR 4.

8.3 APPENDIX C: Modification WHO grading and management of adverse events

Recommendations for Grading of Adverse Events (Modification of WHO Recommendations)				
	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)
Hematologic (Adults)				
Hemoglobin (g/100 mL)	9.5-10.9	8.0-9.4	6.5-7.9	<6.5
Leukocytes 1000/cmm	2.0-2.9	1.5-1.9	1.0-1.4	<1.0
Neutrophils 1000/cmm	1.0-1.5	0.75-0.99	0.5-0.74	<0.5
Platelets 1000/cmm	70-100	50-69	25-49	<25
Lymphocytes (1000/cmm)	0.5>0.20	0.2>0.10	0.10	
Hemorrhage*	-	mildly symptomatic, no Rx required	gross blood loss or 1-2 units transfused	massive blood loss or >2 units transfused
Gastrointestinal				
Total Bilirubin*	1.26-2.5 x N[§]	2.6-5 x N	5.1-10 x N	Evidence of hepatic failure
AST/ALT (SGOT/SGPT)	2 x Baseline	2.1-5 x Baseline	5.1-10 x Baseline	Evidence of hepatic failure
Alkaline phosphatase	2 x Baseline	2.1-5 x Baseline	5.1-10 x Baseline	Evidence of hepatic failure
Oral/stomatitis	painless ulcers, erythema, or mild soreness	painful erythema, edema or ulcers, but can eat	painful erythema, edema or ulcers, and can not eat	requires parenteral or enteral support
Diarrhea	increase of 2-3 stools/ day of pre-Rx	increase of 4-6 stools/day or nocturnal stools, or moderate cramping	increase of 7-9 stools/day, or incontinence, or severe cramping	increase of 10 stools/day or grossly bloody diarrhea, or need for parenteral support
Constipation	mild	moderate	abdominal distention	distention and vomiting
Renal, Bladder				
BUN or blood urea*	1.26-2.5 x N	2.6-5 x N	5.1-10 x N	>10 x N
Creatinine	>1.5 mg/dL <2.0 mg/dL	2.0 <4.0 mg/dL	4.0 <8.0 mg/dL	>8.0 mg/dL
Proteinuria*	1+, <0.3 g/100 mL	2-3+, 0.3-1.0 g/100 mL	4+, >1.0 g/100 mL	nephrotic syndrome
Hematuria	micro only	gross, no clots	gross + clots	requires transfusion
Pulmonary[¶]	asymptomatic, with abnormality in PFTs	dyspnea on significant exertion	dyspnea at normal level of activity	dyspnea at rest
Allergic*	transient rash	urticaria, mild bronchospasm	serum sickness, bronchospasm, required parenteral meds	anaphylaxis

Recommendations for Grading of Adverse Events (Modification of WHO Recommendations)				
	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)
Cutaneous/Rash/Dermatitis	erythema, pruritus	diffuse maculopapular rash or dry desquamation	vesiculation or moist desquamation, or ulceration	Any one: mucous membrane involvement, suspected Stevens-Johnson (TEN), erythema multiforme, necrosis req. surgery, exfoliative dermatitis
Hair*	minimal hair loss	moderate, patchy alopecia	complete alopecia but reversible	nonreversible alopecia
Infection (specify site)*	minor infection	moderate infection	major infection	major infection with hypotension
Cardiac				
Cardiac dysrhythmias	asymptomatic, transient, requiring no therapy	recurrent or persistent, no therapy required	requires treatment	requires monitoring or causes hypotension, or ventricular tachycardia, or fibrillation
Function*	asymptomatic, but abnormal cardiac sign	transient symptomatic dysfunction, no therapy required	symptomatic dysfunction responsive to therapy	symptomatic dysfunction nonresponsive to therapy
Cardiac-ischemia	nonspecific T-wave flattening (new ECG changes)	asymptomatic, ST and T-wave changes suggesting ischemia (new ECG changes)	angina without evidence for infarction	acute myocardial infarction
Cardiac-pericardial	asymptomatic effusion, no intervention required	pericarditis (rub, chest pain, ECG changes)	symptomatic effusion; drainage required	tamponade; drainage urgently required
Blood Pressure				
Hypertension	asymptomatic transient increase by greater than 20 mm Hg (0) or to >150/100 if previously WNL; no treatment required	recurrent or persistent increase by greater than 20 mmHg (0) or to >150/100 if previously WNL; no treatment required	requires therapy	hypertensive crisis or hospitalization required for hypertension
Hypotension	transient orthostatic hypotension, no Rx	symptoms correctable with oral fluid Rx	IV fluid req, no hospitalization req.	requires hospitalization
Neurotoxicity*				
Peripheral*	paresthesias and/or decreased tendon reflexes	severe paresthesias and/or mild weakness	intolerable paresthesias and/or marked motor loss	paralysis
Neuromotor (Asthenia)	subjective weakness; no objective findings	mild objective weakness without significant	objective weakness with impairment of function	paralysis, or confined to bed or wheel chair because of

Recommendations for Grading of Adverse Events (Modification of WHO Recommendations)				
	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)
		impairment of function		muscle weakness
Neurocortical	mild somnolence or agitation	moderate somnolence or agitation	severe somnolence, agitation, confusion, disorientation, or hallucinations	coma, seizures, toxic psychosis
Neurocerebellar	slight in coordination or dysdiadochokinesias	intention tremor or dysmetria, or slurred speech, or nystagmus	ataxia requiring assistance to walk or arm incoordination interfering with ADLs	unable to stand
Neuromood	mild anxiety or depression	moderate anxiety or depression	severe anxiety or depression	suicidal ideation
Neurohearing	asymptomatic hearing loss on audiometry only	tinnitus	hearing loss interfering with function but correctable with hearing aid	deafness not correctable
Neurovision	--	--	Symptomatic subtotal loss of vision	blindness
Pain (specify site)	mild	moderate	severe	intractable, requires use of narcotics
Local (specify site)	pain	pain and swelling with inflammation or phlebitis	ulceration	plastic surgery indicated, intractable pain
Flu-like Symptoms				
Fever	up to 38.6 C (101.5 F)	38.7 C-39.9 C (101.7 F-103.8 F)	>40 C (104 F)	Fever with hypotension
Chills	Mild to Moderate Shaking	Severe Shaking	Rigors that incapacitates patient's daily function	--
Headache	<2 hours not requiring analgesic	2 hours, but less than 24 hrs requires analgesic	24 hrs requires multiple doses of analgesic	intractable, requires repeated narcotics
Fatigue	fatigue reported but no effect on daily function	moderate decrease in daily function	fatigue that incapacitates patient's daily function	--
Malaise	<24 hours duration	24-48 hours duration	persistent >48 hours duration	--
Nausea	occasional and transient	persistent >24 hours	persistent >24 hours with daily vomiting	--
Vomiting	sporadic not occurring daily	daily emesis	daily emesis intolerable requiring therapy	intractable vomiting
Weight gain/loss	5.0-9.9%	10.0-19.9%	20.0%	--

Recommendations for Grading of Adverse Events (Modification of WHO Recommendations)				
	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Life-threatening)
Arthralgia	joint pain reported but no effect on daily function	moderate decreases of daily function	joint pain incapacitates patient's daily function	--
Myalgia	muscle pain reported but no effect on daily function	moderate decrease of daily function	muscle pain that incapacitates patient's daily function	--
Thyroid Abnormality[#]				
Hypothyroid	Borderline Elevation TSH (<1.5 N)	Elevated TSH (1.5N), low T_4, no clinical signs or symptoms	Elevated TSH, low T_4 with clinical signs or symptoms requiring thyroid replacement medication	Myxoedema or Myxoedema coma
Hyperthyroid	low TSH	Low TSH, elevated T_4, no clinical signs or symptoms	Low TSH, elevated T_4 with clinical signs or symptoms requiring anti-thyroid medication	thyroid storm, hyperthyroidism poorly or not controlled by antithyroid medication
Metabolic				
Hyperglycemia (mmol/L)	6.4-8.8	8.9-13.7	13.8-27.5	>27.5 or ketoacidosis
Hyperuricemia	ULN 1.5 x N	>1.5 x N, no clinical signs or symptoms	clinical gout	
Hypoglycemia (mmol/L)	3.0-3.5	2.2-2.9	1.7-2.1	<1.7
Amylase	<1.5 X N	1.5-2.0 X N	2.1-5.0 X N	>5.1 X N
Hypercalcemia (mmol/L)	2.6-2.89	2.9-3.09	3.1-3.3	>3.3
Hypocalcemia (mmol/L)	1.9-2.14	1.7-1.89	1.5-1.69	<1.5
Hypomagnesemia (mmol/L)	1.4-1.2	1.1-0.9	0.8-0.6	0.5
Coagulation				
Fibrinogen	0.99-0.75 X N	0.74-0.50 X N	0.49-0.25 X N	0.24 X N
Prothrombin time	1.01-1.25 X N	1.26-1.50 X N	1.51-2.00 X N	>2.00 X N
Partial thromboplastin time	1.01-1.66 X N	1.67-2.33 X N	2.34-3.00 X N	>3.00 X N
Other	reported but no effect on daily function	moderate decrease in daily function	incapacitates patient's daily function	clinical judgment of the investigator with documentation of the clinical criteria used to make the decision

* Miller AB, et. al.: Cancer 47:210-211, 1981 (Items taken from WHO are indicated with an asterisk).

§ N = Upper limit of normal. Therapy should be discontinued for subjects developing thyroid abnormalities during treatment, whose thyroid function can not be normalized by medication.

8.4 APPENDIX D: Potential Subjects for Enrollment into the Core Protocol

Subject Type	Enroll into Core Protocol?	Enroll into HRQOL Sub-study?	HCV Study	Donor Pain Study	Existing Data Sources	Potential Data Entry Methods
Former A2ALL Subjects (continuing centers only)						
Full Cohort Donors Post-donation at the end of Cohort enrollment*	YES	YES	NO	NO	BioDBx***	Upload/New Data Entry
Full Cohort LDLT Recipients Post-transplant at the end of Cohort enrollment*	YES	NO	YES	NO	BioDBx***	Upload/New Data Entry
Full Cohort DDLT Recipients Post-transplant at the end of Cohort enrollment*	YES	NO	YES	NO	BioDBx***	Upload/New Data Entry
Cohort Lite Donors Post-donation at the end of Cohort enrollment* (donation occurred from 2002 – 2008)	YES	YES	NO	NO	BioDBx***	Upload/New Data Entry
Cohort Lite LDLT Recipients Post-transplant at the end of Cohort enrollment*	YES	NO	YES	NO	BioDBx***	Upload/New Data Entry
Cohort Lite DDLT Recipients Post-transplant at the end of Cohort enrollment*	YES	NO	YES	NO	BioDBx***	Upload/New Data Entry
Donors whose donation occurred in the Gap Era**	YES	NO	NO	NO	BioDBx***	Upload/New Data Entry
LDLT Recipients whose transplant occurred in the Gap Era**(must be three years post-transplant for the HCV Study)	YES	NO	YES	NO	BioDBx***	Upload/New Data Entry
DDLT Recipients whose transplant	YES	NO	YES	NO	BioDBx***	Upload/New Data Entry

occurred in the Gap Era**(must be three years post-transplant for the HCV Study)						
New Subjects (all centers)	**Enroll into Core Protocol?**	**Enroll into HRQOL Sub-study?**	**HCV Study**	**Donor Pain Study**	**Existing Data Sources**	**Potential Data Entry Methods**
Actual Donors shortly Pre-donation	YES	YES	NO	YES	NONE	New Data Entry
LDLT Recipients shortly Pre-transplant	YES	NO	NO	NO	NONE	New Data Entry
Donors whose donation occurred in the Gap Era**	YES	NO	NO	NO	NONE	Upload/New Data Entry
LDLT Recipients whose transplant occurred in the Gap Era**(must be three years post-transplant for the HCV Study)	YES	NO	YES	NO	NONE	Upload/New Data Entry
Donors that Donated Prior to the Gap Era** (new centers only)	NO	YES	NO	NO	NONE	Upload/New Data Entry
LDLT Recipients whose transplant occurred during the Cohort Era****	NO	NO	YES	NO	NONE	Upload/New Data Entry
DDLT Recipients with HCV whose transplant occurred during the Cohort Era**** AND had a living donor evaluated(must be three years post-transplant for the HCV Study).	NO	NO	YES	NO	NONE	Upload/New Data Entry

* End of Cohort Enrollment = August 31, 2009
** Gap Era = September 1, 2009 - Site Initiation for Core Protocol (will vary by site)
*** Data for former A2ALL subjects exists in BioDBx up through August 31, 2010. All subjects will be post-transplant/donation. Additional data for the time period September 1, 2010-Site Initiation for Core Protocol will have to be manually entered or uploaded via spreadsheet.
****Cohort Era = March 1, 2003 – Sept. 1, 2010

8.5 APPENDIX E: Retrospective Institutional Pain Management Practice Survey

Introduction

There are a number of ways to treat postoperative pain in live liver donors. However, there is little information available to help physicians choose the best approach. We are conducting a survey to collect information about methods of pain control used for live liver donors and the type of personnel who administer them.

The survey asks about current and past methods used to control pain and your perceptions of their effectiveness. If you do not know the answer to a question, please check "Don't Know" response.

Responses will be reported in aggregate form; individual responses will remain anonymous. You will be asked to indicate the center where you work. This will allow us to determine center-specific practices, but no individual response will be identified.

A. Personnel, Training, and Facility Resources

1. At which transplant center do you work?

- ◯ UCSF
- ◯ University of Colorado
- ◯ Northwestern
- ◯ Toronto
- ◯ University of Pittsburgh
- ◯ University of Pennsylvania
- ◯ VCU
- ◯ Columbia
- ◯ Lahey

2. What is your clinical training?

- ◯ Anesthesiologist
- ◯ Surgeon
- ◯ Nurse
- ◯ Other

Other (please specify)

3. For how many years have you provided acute pain care for live liver donors?

- ◯ <2 years
- ◯ 2-6 years
- ◯ 7-10 years
- ◯ >10 years

4. How many live liver donors did you provide pain care for in the last 12 months?

- ◯ 1-5
- ◯ 6-10
- ◯ 11-15
- ◯ 16-20
- ◯ More that 20

5. Does your hospital have a dedicated Acute Pain Team?

- ◯ Yes
- ◯ No
- ◯ Don't know

6. Are you a member of the Acute Pain Team?

- ◯ Yes
- ◯ No

7. Does the Acute Pain Team provide postoperative pain management to live liver donors?

- ◯ Yes
- ◯ No

8. If the Acute Pain Team does not provide postoperative care, why not? Check all that apply.

- ☐ There is no Acute Pain Team
- ☐ The Acute Pain Team does not have enough expertise with live liver donors
- ☐ The Acute Pain Team is not available enough to provide continuity of care
- ☐ The liver transplant team has not developed a collaboration with the Acute Pain Team
- ☐ Use of the Acute Pain Team takes away control of the patient from the surgical team
- ☐ It is too complicated to have so many care providers
- ☐ Don't Know

9. If there are reasons other than the ones listed above related to why the Acute Pain Team is not used, please specify.

10. What Departments are members of the Acute Pain Team at your institution? Check all that apply.

- ☐ Anesthesiology
- ☐ Surgery
- ☐ Don't Know

Other (please specify)

11. Does the Acute Pain Team provide 24 hour coverage?

- ○ Yes
- ○ No
- ○ Don't know

12. Is there a dedicated team of anesthesiologists that cares for live liver donors in the operating room?

- ○ Yes
- ○ No
- ○ Don't Know

13. Do any of the dedicated live donor intraoperative anesthesiologists serve on the Acute Pain Team?

- ○ Yes
- ○ No
- ○ Don't Know

14. Where are donors admitted for immediate postoperative care?

- ○ ICU (Intensive Care Unit)
- ○ PACU (Post Anesthesia Care Unit)
- ○ Don't Know
- ○ Other, please specify

Other (please specify)

15. What is the average number of days in ICU and/or PACU? Please indicate number for each unit in box, or indicate DNK (do not know)

Care Providers Opinions About Pain Care

This set of questions is about your perceptions pain and pain management for live liver donors. Please indicate how much you agree or disagree with the statements that follow.

21. Our live liver donors receive enough monitoring on the ward for early identification of adverse events.

- ◯ Strongly agree
- ◯ Somewhat agree
- ◯ Uncertain
- ◯ Somewhat disagree
- ◯ Strongly disagree

22. Pain is assessed frequently enough on the ward.

- ◯ Strongly agree
- ◯ Somewhat agree
- ◯ Uncertain
- ◯ Somewhat disagree
- ◯ Strongly disagree

23. The severity of pain experienced by live liver donors is greater than other liver resection patients.

- ◯ Strongly agree
- ◯ Somewhat agree
- ◯ Uncertain
- ◯ Somewhat disagree
- ◯ Strongly disagree

24. The amount of emotional distress experienced by live liver donors due to pain is greater than other liver resection patients.

- ◯ Strongly agree
- ◯ Somewhat agree
- ◯ Uncertain
- ◯ Somewhat disagree
- ◯ Strongly disagree

16. After ICU/PACU stay is complete, where are donors transferred to?

- ◯ A surgical ward that specializes in transplant care
- ◯ A general surgical ward
- ◯ A step-down unit
- ◯ Don't know

17. Do the nurses on the ward where the live donor is admitted receive formal teaching about postoperative pain management?

- ◯ Yes
- ◯ No
- ◯ Don't know

18. If yes, who provides their formal education?

- ◯ Acute Pain Team
- ◯ Nursing
- ◯ Surgery

Other (please specify)

19. Do live liver donors routinely have continuous monitoring of any vital signs that can be seen at the main nursing desk during their ward stay?

- ◯ Yes
- ◯ No
- ◯ Don't Know

20. If YES, what kind of continuous monitoring is used? Check all that apply.

- ☐ Pulse oximitry
- ☐ EKG
- ☐ Blood pressure
- ☐ Other

Other (please specify)

Care Providers Opinions About Pain Care

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21. Our live liver donors receive enough monitoring on the ward for early identification of adverse events.

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- ◯ Uncertain
- ◯ Somewhat disagree
- ◯ Strongly disagree

24. The amount of emotional distress experienced by live liver donors due to pain is greater than other liver resection patients.

- ◯ Strongly agree
- ◯ Somewhat agree
- ◯ Uncertain
- ◯ Somewhat disagree
- ◯ Strongly disagree

25. Health care providers often under treat pain in live liver donors because they are worried about complications of pain medications.

- ◯ Strongly agree
- ◯ Somewhat agree
- ◯ Uncertain
- ◯ Somewhat disagree
- ◯ Strongly disagree
- ◯ Don't know

26. Your live liver donors are currently satisfied with their pain management.

- ◯ Strongly agree
- ◯ Somewhat agree
- ◯ Uncertain
- ◯ Somewhat disagree
- ◯ Strongly disagree

C. Approach to Pain Assessment

The following questions ask about how your institiuion evaluates patients' pain.

27. Indicate all health care providers that routinely perform pain assessment in the ICU.

- [ ] Nursing
- [ ] Acute Pain Team
- [ ] Surgery
- [ ] Attending anesthesiologist
- [ ] ICU physician
- [ ] Don't know

Other (please specify)

28. Indicate all health care providers that routinely perform pain assessment in the PACU.

- [ ] Nursing
- [ ] Acute Pain Team
- [ ] Surgery
- [ ] Attending anesthesiologist
- [ ] ICU physician
- [ ] Don't know

Other (please specify)

29. Please indicate all health care providers that routinely assess pain on the surgical ward.

- [ ] Nursing
- [ ] Acute Pain Team
- [ ] Surgery
- [ ] Attending anesthesiologist
- [ ] Don't know

Other (please specify)

30. What pain related information is routinely recorded? (only data that would be retrievable by chart review)

- ☐ Visual/numerical pain score at rest
- ☐ Visual/numerical pain score with movement
- ☐ Sedation scores
- ☐ Comfort goal
- ☐ Don't know

31. Does your instituion routinely use a standard patient satisfaction survey to assess the efficacy of pain management?

- ◯ Yes
- ◯ No
- ◯ Don't Know

32. If your institution does not use a standard survey to assess satisfaction of live donors with their pain management, how do you assess this information?

Preoperative Preparation, Patient Input and Ongoing Assessment

These questions are about types of interaction that health care providers have with live liver donors prior to surgery. Area of interest include personal interactions and the development and use of protocols for pain management.

33. Does an anesthesiologist see all live liver donors prior to the day of surgery?

- ◯ Yes
- ◯ No
- ◯ Don't Know

34. Does the Acute Pain Team offer to see all live liver donors prior to the day of surgery?

- ◯ Yes
- ◯ No
- ◯ Don't Know

35. Does your institution have a single protocol for pain management in live liver donors?

- ◯ Yes
- ◯ No
- ◯ Don't Know

36. Please check all types of health care providers that participated in the development of this protocol.

- ☐ Anesthesiology
- ☐ Acute Pain Team
- ☐ Surgery
- ☐ Nursing
- ☐ Other, please specify

Other (please specify)

37. If there is no institutional protocol, who decides what pain technique is used? Please check all that apply.

- ☐ Attending Anesthesiologist
- ☐ Surgeon
- ☐ Acute Pain Team
- ☐ Not always the same provider

Other (please specify)

38. Is each live liver donor typically given a choice of pain therapies?

- ◯ Yes
- ◯ No
- ◯ Don't Know

39. Please check all pain management options that are discussed with live liver donors PRIOR TO surgery.

- ☐ Epidural
- ☐ Intrathecal medication
- ☐ Intravenous patient controlled analgesia
- ☐ Oral medication
- ☐ Regional therapy (local infiltration of analgesics/anesthetics)
- ☐ Nonpharmacological (acupuncture, cogmitive behavior etc)
- ☐ Don't Know

Other (please specify)

40. What pain control techniques are currently used at your institution in the immediate postoperative period (48 hours). Please check all that apply.

- ☐ Epidural
- ☐ Intrathecal medication intravenous patient controlled analgesia
- ☐ Oral medication
- ☐ Regional therapy
- ☐ Nonpharmacologic
- ☐ Don't know

Other (please specify)

41. Does a health care provider routinely discuss the amount of postoperative pain that live liver donors should expect to experience prior to surgery?

- ◯ Yes
- ◯ No
- ◯ Don't Know

42. If yes to last question, who discusses pain expectations? Please check all that apply.

- ☐ Anesthesiologist
- ☐ Acute Pain Team
- ☐ Surgeon
- ☐ Nurse
- ☐ Don't know

Other (please specify)

43. Please check all health care providers that make primary decisions about pain management following surgery.

- ☐ Attending anesthesiologist
- ☐ Acute Pain Team
- ☐ Surgery
- ☐ Don't know

Other (please specify)

44. Are there nursing protocols to adjust pain medications for live liver donors without consulting a physician?

- ○ Yes
- ○ No
- ○ Don't Know

45. Who is notified first if the live liver donor does not tolerate the pain?

- ○ Acute pain team
- ○ Surgeon
- ○ Attending anesthesiologist
- ○ Not always the same provider

Other (please specify)

Details about Pain Techniques

The following questions concern your perceptions of pain management techniques that have been used at you institution.

46. Please check all pain management techniques you currently use in the first 48 hours after surgery. Please provide your opinion regarding each technique listed. If other techniques are used, please list and provide your opinion in the text box that follows the question.

	Epidural	Intrathecal	IVPCA	Local Infiltration
Safe	☐	☐	☐	☐
Works well	☐	☐	☐	☐
Cost Effective	☐	☐	☐	☐
Uses fewer resources	☐	☐	☐	☐
No opinion	☐	☐	☐	☐

Other (please specify)

47. Please check all oral pain medications you currently use in the first 48 hours after donation and provide your opinion regarding the medication. If other agents are utilized, please specify what the agents are and provide your opinion of them.

	Oral Opioid	Gabapentin/Pregabalin	NSAID	Acetaminophen
Safe	☐	☐	☐	☐
Works well	☐	☐	☐	☐
Cost Effective	☐	☐	☐	☐
Uses fewer resources	☐	☐	☐	☐
No opinion	☐	☐	☐	☐

Other (please specify)

48. Has your institution changed pain management techniques since the start of your program?

- ◯ Yes
- ◯ No
- ◯ Don't Know

49. If yes, approximately when was the last time that your program changed techniques?

- ◯ Within the last year
- ◯ From 1 to 2 years ago
- ◯ More than 2 years ago
- ◯ Don't Know

50. If you answered Yes to question 48, how many times has your program changed pain management techniques for live liver donors since the start of your program?

- ◯ 1
- ◯ 2
- ◯ 3
- ◯ 4
- ◯ 5 or more

51. Please check all pain control techniques that your center has tried, but does not currently use in the first 48 hours after donation.

- ☐ Epidural
- ☐ Intrathecal
- ☐ IVPCA
- ☐ Local Infiltration

Other (please specify)

52. Please identify the reasons you do not use any of the techniques listed below, even if you have not tried them. If there are other techniques you feel should be included, please list them and add your reasons for not using them.

	Epidural	Intrathecal	IVPCA	Local Infiltration
Patient Complications	☐	☐	☐	☐
Does not work well	☐	☐	☐	☐
Not cost effective	☐	☐	☐	☐
Uses more resources	☐	☐	☐	☐
Personal choice	☐	☐	☐	☐
Don't know	☐	☐	☐	☐
No opinion	☐	☐	☐	☐

Other (please specify)

53. Please check all pain medications your center has tried, but does not currently use in the first 48 hours after donation.

- ◯ Oral Opioid
- ◯ Gabapentin/Pregabalin
- ◯ NSAID
- ◯ Acetaminophen

Other (please specify)

54. Please identify the reasons you do not use the listed medications to control donor pain, even if you have not used them. If there are other agents listed in question 51, please list them in the text box along with reasons for not using them.

	Oral Opioid	Gabapentin/Pregabalin	NSAID	Acetaminophen
Patient Complications	☐	☐	☐	☐
Does not work well	☐	☐	☐	☐
Not cost effective	☐	☐	☐	☐
Uses more resources	☐	☐	☐	☐
Personal choice	☐	☐	☐	☐
Don't know	☐	☐	☐	☐
No opinion	☐	☐	☐	☐

Other (please specify)

55. Please provide any additional comment you would like to make regarding management of live liver donor pain. Thank you for taking the time to complete this survey.

8.6 APPENDIX F: Prospective Living Donor Pain Survey

Donor Pain Study - Patient Information and Assent

Dear Sir \ Madam,

We would be grateful if you would participate in our survey on how patients feel after surgery. The aim of the survey is to improve management of pain after live donor surgery.

The information you provide will be made anonymous once you hand in this questionnaire. This means that your name or other form of identification will be deleted from the questionnaire after you hand it in and will not be included in any records we will have.

Your answers in this questionnaire will not be shared with your medical or nursing team.

We can assure you that your team will treat you in the same way whether or not you choose to participate in our survey.

Many thanks for considering to take part in this survey.

Name of Person Administering Survey

Subject ID D

A2ALL Donor Pain Survey

PRINT FORM

Date of First Attempt Time AM PM

Sedation Score

- 0 = Fully Awake
- 1 = Light sedation, largely aware of self/surroundings. Mildly sleepy
- 2 = Moderate sedation, slightly aware of self/surrounds. Somnolent but easily aroused.
- 3 = Deeply sedated, unaware of self/surroundings.
- 4 = General anesthesia, patient is unconscious.

Type of Pain Management (check all that apply)

- Epidural
- Intrathecal
- IVPCA
- Local Infiltration
- Other

Date of Second Attempt Time AM PM Sedation Score

P1. On this scale, please indicate the **least** pain you had in the **FIRST 24 hours**.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Possible Pain

P1A. On this scale, please indicate the **least** pain you had in the **LAST 24 hours**.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Possible Pain

P2. On this scale, please indicate the **worst** pain you had in the **LAST 24 hours.**

0	1	2	3	4	5	6	7	8	9	10
No Pain										Worst Possible Pain

P3. What percentage of time in the **LAST 24 hours** were you in **severe pain**?

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
Never in severe pain										Always in severe pain

Subject ID D

P4. Choose the **one** number below that best describes how much pain **interfered or prevented you from:**

a. Doing **activities in bed** such as turning, sitting up, repositioning:

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

b. Doing **activities out of bed** such as walking, sitting in a chair, standing at the sink:

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

c. ***Falling*** **asleep:**

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

d. ***Staying*** **asleep:**

0	1	2	3	4	5	6	7	8	9	10
Does not interfere										Completely interferes

P5. Pain can affect our mood and emotions.
On this scale, please choose the **one** number that best shows how much the pain has caused you to feel:

a. Anxious

0	1	2	3	4	5	6	7	8	9	10
Not at all										Extremely

b. Depressed

0	1	2	3	4	5	6	7	8	9	10
Not at all										Extremely

c. Frightened

0	1	2	3	4	5	6	7	8	9	10
Not at all										Extremely

Subject ID D

P5. (Cont'd)
On this scale, please choose the **one** number that best shows how much pain caused you to feel:

d. Helpless

0	1	2	3	4	5	6	7	8	9	10
Not at all										Extremely

P6. Have you had any of the following side effects?
Please choose "0" if no; if yes, choose the **one** number that best shows the severity of each:

a. Nausea

0	1	2	3	4	5	6	7	8	9	10
None										Severe

b. Drowsiness

0	1	2	3	4	5	6	7	8	9	10
None										Severe

c. Itching

0	1	2	3	4	5	6	7	8	9	10
None										Severe

d. Dizziness

0	1	2	3	4	5	6	7	8	9	10
None										Severe

P7. In the last 24 hours, how complete has your pain **relief** been?
Please choose the **one** percentage that best shows how much relief you have received from all of your pain treatments combined (medicine and non-medicine treatments).

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

Subject ID D

P8. Were you **allowed to participate in decisions** about your pain treatment as much as you wanted to?

0	1	2	3	4	5	6	7	8	9	10
Not at all										Very much so

P9. Choose the **one** number that best shows how **satisfied** you are with the results of your pain treatment while in the hospital.

0	1	2	3	4	5	6	7	8	9	10
Extremely Dissatisfied										Extremely Satisfied

P10. Did you receive any **information** about your pain treatment options? ◯ Yes ◯ No

a. If yes, please choose the number that best shows **how helpful** the information was.

0	1	2	3	4	5	6	7	8	9	10
Not at all helpful										Extremely helpful

P11. Did you use any **non-medicine methods** to relieve your pain? ◯ Yes ◯ No

If yes, **check all** that apply:

- ☐ cold pack
- ☐ deep breathing
- ☐ distraction (such as watching TV, reading)
- ☐ heat
- ☐ imagery or visualization
- ☐ massage
- ☐ meditation
- ☐ listen to music
- ☐ prayer
- ☐ relaxation
- ☐ walking
- ☐ other (specify)

P12. How often did a nurse or doctor **encourage you to use** non-medication methods?

- ◯ never
- ◯ sometimes
- ◯ often

Thank you for your time and feedback!