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### Effect of Peritoneal Dialysis on Weight Change in Pediatric Patients

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**EFFECT OF PERITONEAL DIALYSIS ON WEIGHT CHANGE  
IN PEDIATRIC PATIENTS**

A Thesis Presented to  
The Faculty of the School of Medicine  
Yale University

In Candidacy for the Degree of  
Master of Medical Science

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**Abstract:**

Obesity is associated with lower transplantation rate and higher mortality in pediatric end stage renal disease patients. Glucose-based peritoneal dialysis is the preferred method of dialysis for these patients, a therapy that can cause systemic glucose absorption. It is unknown whether this absorption leads to weight change in pediatric patients. We propose to examine whether Peritoneal Dialysis is associated with weight change in pediatric End Stage Renal Disease patients. We will prospectively observe a cohort of children aged 2-17 who are starting peritoneal dialysis. We will measure weight change after one year of dialysis, and compare these measurements to historical control groups. With this proposed study, we hope to gain insight into whether peritoneal dialysis contributes to obesity, leading to decreased eligibility for kidney transplantation. This knowledge will allow modification of renal replacement therapy and ultimately lead to improved outcomes in pediatric peritoneal dialysis patients.

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## **Chapter 1- Introduction**

### **Background: Childhood Obesity**

Childhood obesity is a growing problem faced by our nation that poses significant adverse health effects. For children aged 2-19, overweight is defined as body mass index (BMI) greater than or equal to the 85<sup>th</sup> (but less than the 95<sup>th</sup>) percentile BMI matched for age and sex of the child.<sup>1</sup> Childhood obesity is defined as BMI greater than or equal to that of the 95<sup>th</sup> percentile for age and sex.<sup>1</sup> In the United States, 31% of children aged 2-19 years old are overweight or obese.<sup>2</sup> According to the Centers for Disease Control (CDC), the prevalence of both childhood and adolescent obesity has been on the rise over the past 30 years, in this time period rising from 7% to 18% in children aged 6-11 and rising from 5 to over 20% in adolescents aged 12-19.<sup>3</sup> Childhood obesity can contribute to the development of metabolic syndrome, type II diabetes mellitus, hypertension, and other adverse future health outcomes if the child continues to be obese in adulthood.<sup>4</sup> Prospective investigation of pediatric patients has shown that 77% of overweight children remain obese in adulthood.<sup>5</sup>

### **Obesity in Pediatric End Stage Renal Disease**

In addition to the general pediatric population, the prevalence of obesity is also rising in pediatric End Stage Renal Disease (ESRD) patients undergoing Renal Replacement Therapy (RRT).<sup>6</sup> A 2015 study demonstrates that obesity is rising in prevalence in pediatric RRT patients, while the prevalence of children being underweight is decreasing.<sup>6</sup> This study performed a retrospective analysis of children initiating RRT between the years of 1995 to 2011 in the United States, and found that the prevalence of

obesity in this population has risen from 14% to 18% over this time period.<sup>6</sup> The researchers also found that the prevalence of being underweight in this population has decreased from 12% to 9% over the 16 years of data that were analyzed retrospectively.<sup>6</sup>

A 2005 retrospective analysis by Hanevold et al. found an increase in obesity among pediatric ESRD patients.<sup>7</sup> The researchers defined obesity as BMI above 95<sup>th</sup> percentile according to the child's age and gender, and obtained their data from the North American Pediatric Renal Transplant Cooperative Study database.<sup>7</sup> Specifically, before 1995 the prevalence of obesity in pediatric ESRD patients was measured at 8%.<sup>7</sup> After 1995, the prevalence increased to 12.4%.<sup>7</sup> This study suggests that in the pediatric ESRD population, obesity is increasing in prevalence.

A 2013 descriptive study by Bonthuis et al. examined the prevalence of various BMI ranges in pediatric patients undergoing RRT in Europe.<sup>8</sup> The researchers found that the prevalence of overweight in all pediatric RRT patients was 20.8%, and the prevalence of obesity was 12.5%.<sup>8</sup> Of note, the prevalence of underweight pediatric RRT patients was found to be 3.5%.<sup>8</sup>

### **Adverse Effects of Obesity in Pediatric ESRD Patients**

In addition to the risks associated with obesity, children with ESRD face additional risk of adverse health outcomes due to their renal disease. Research has shown that pediatric ESRD patients have a 30 times higher mortality rate than children without ESRD.<sup>9</sup> Risk factors for death include use of dialysis, which increases the risk of death to four times higher than the risk of death of those treated with renal transplantation.<sup>9</sup>

Obese and overweight children with ESRD face additional hardships to the direct physiological and medical consequences of their renal disease and obesity. Many



transplant programs use specific BMI ranges as a criteria to be considered for transplant, meaning that in order to be listed for transplant, a patient's BMI must fall within the range defined by the individual transplant program they are using. If a patient's BMI rises above the acceptable range, they will be temporarily withheld from consideration for a transplant until their BMI decreases to within the acceptable range. Although the exact requirements differ by transplant program (and are often based on current literature regarding safety of transplant procedure at extremes of BMI), an example of a BMI cutoff is 35 kg/square meters.<sup>10</sup>

Retrospective analysis in 2015 found that increased BMI/obesity in children with ESRD is associated with lower transplantation rate and higher risk of death.<sup>6</sup> This study found that obese children on RRT have a 1.17 times higher risk of death than children with normal BMI.<sup>6</sup> Obesity was also found to be a barrier to living donor transplant in children, demonstrated by a decreased odds ratio of living donor transplant in obese children compared with non-obese children.<sup>6</sup> This finding is an example of how obesity can act as a barrier to improved outcome, as living donor transplant has been shown to precipitate better outcomes with greater transplant graft (the transplanted organ) survival and greater patient survival.<sup>10</sup> A 2013 study found that higher BMI at the time of transplantation is associated with poorer outcomes compared lower BMI.<sup>10</sup> This study found transplant recipient BMI greater than or equal to 30 associated with higher risk of delayed graft function.<sup>10</sup> It was also found that recipient BMI greater than or equal to 35 is associated with higher risk of biopsy-proven acute rejection (cellular rejection of the transplanted kidney), death-censored graft failure (failure of graft resulting in return to dialysis or pre-emptive transplant), and all-cause graft failure (failure of graft from death,

return to dialysis, or pre-emptive transplant) after renal transplantation.<sup>10</sup> Additionally, a 2002 study by Mitsnefes et al. found that pediatric ESRD patients who were obese before renal transplant were more likely to have a lower glomerular filtration rate (GFR), which is a measure of how quickly blood is filtered through the kidney and indicates how well the kidney is functioning, one year after transplant.<sup>11</sup> It is clear that obesity is a barrier to optimal outcome in pediatric ESRD patients, especially considering the fact that the goal of most children with ESRD is renal transplantation.

The aforementioned study by Hanevold et al. investigated transplant outcomes in obese versus nonobese children aged 2-17, and found that obese children aged 6-12 had a higher risk of death after transplant when compared to nonobese children aged 6-12.<sup>7</sup> Within the high risk (of mortality) group of children, death was more likely to be attributed to cardiopulmonary causes.<sup>7</sup> Additionally, the study found that in the obese group of children, graft loss from thrombosis was higher (19%) than in the nonobese group (10%).<sup>7</sup> These data indicates that the presence obesity in children at the time of kidney transplant poses significant risk.

In addition to barriers faced at time of transplant and after transplant, the presence of obesity in pediatric ESRD patients confers risk and worse outcomes in other ways. A 2000 study by Wong et al. found a higher risk of death at the extremes of BMI (both low and high) in pediatric ESRD patients.<sup>12</sup> These results indicate that in pediatric ESRD patients, being overweight or obese is related to worse outcome, including mortality.<sup>12</sup>

A 2007 literature review found that in adults, increased BMI (in particular, increased fat mass) is associated with worse PD outcomes.<sup>13</sup> Researchers found that increased inflammation, increased incidence of peritonitis (inflammation of a patient's

peritoneal membrane that can have an infectious etiology), and faster decline in RRF may contribute to worse outcomes.<sup>13</sup>

A 2012 study by Hoogeveen et al. compared the effect of obesity on mortality between dialysis patients over 65 years of age and dialysis patients under 65 years of age.<sup>14</sup> They found that obesity was associated with a higher mortality rate in the younger cohort compared to the older cohort.<sup>14</sup> Specifically in the younger cohort, age-standardized mortality was found to be 1.7 times higher in obese patients than those with normal BMI.<sup>14</sup> In the older aged cohort, there was a smaller difference in mortality between obese dialysis patients and those with a normal BMI.<sup>14</sup> This study shows that obesity may pose additional risk to younger dialysis patients, therefore there is a need to investigate the relationship between PD and weight gain in the pediatric population.

A 2015 study that prospectively followed adult PD patients, assessing their BMI at baseline and at one year after the start of PD, showed that obesity is associated with higher cardiovascular mortality.<sup>15</sup> Specifically, the researchers associated a unit of BMI elevation with a 9% higher risk of cardiovascular mortality.<sup>15</sup> Retrospective analysis demonstrates obesity to be associated with lower GFR after renal transplantation in pediatric patients, compared with normal weight pediatric patients' GFR after renal transplantation.<sup>11</sup> In addition, multiple studies show that metabolic syndrome (a group of risk factors that increase a person's risk for heart disease, diabetes, and stroke) leads to increased cardiovascular mortality after renal transplantation.<sup>16</sup> The development of metabolic syndrome in post-transplant patients is contributed to by obesity, and it goes without saying that being obese at the time of transplantation is a risk factor for this complication.<sup>16</sup>

Other research has shown obesity to be associated with worse PD outcomes. A 2008 study found higher BMI to be associated with lower peritoneal urea Kt/v (which is a measure of dialysis adequacy) in PD patients.<sup>17</sup> A 2003 study in Australia and New Zealand found obesity to be associated with death and technique failure in PD patients.<sup>18</sup> This study demonstrated that greatest survival in PD patients was associated with a BMI of 20 kg/m<sup>2</sup>.<sup>18</sup> Above and below a BMI of 20kg/m<sup>2</sup>, survival rates declined.<sup>18</sup> Research also shows that higher BMI in PD patients is associated with increased risk of peritonitis, with higher BMI patients having a shorter time to peritonitis and a higher occurrence of peritonitis compared controls.<sup>19</sup>

A 2015 study found that adult PD patients who gain weight while on PD had a faster residual renal function (RRF) decline.<sup>20</sup> The body weight percent increase significantly correlated with an increased rate of RRF decline and an increased hs-CRP (a biomarker of systemic inflammation) level.<sup>20</sup>

Considering the above evidence, there are numerous studies to indicate that overweight/obesity in both pediatric and adult PD patients increases risk for adverse outcomes. This said, adding to the body of knowledge pertaining to whether or not PD causes weight gain in pediatric patients is necessary and vital to improving patient outcomes in this population.

### **Statement of Problem**

The preferred treatment of ESRD in pediatric patients is renal transplantation. As renal transplant is not readily available to all patients at the time of RRT initiation, pediatric patients often spend time on dialysis therapy while awaiting transplant. Peritoneal dialysis is the preferred method of dialysis in pediatric patients due to its

quality of life implications, as PD can be done in the patient's own home and promotes a more flexible lifestyle for the patient, versus hemodialysis (HD) which must be done several times per week at a dialysis center.<sup>21</sup> However, it is clear that transplantation is superior to PD in treating pediatric ESRD. Studies have shown a higher mortality rate in PD versus transplant.<sup>21</sup> Data from Australia and New Zealand found a mortality rate of 5.9 per 100 patient years in PD patients, and a mortality rate of 1.1 per 100 patient years in patients who had been treated with a transplant.<sup>9</sup>

The preferred osmotic agent in PD therapy is glucose, and has been since the start of PD use to treat ESRD.<sup>22</sup> Peritoneal dialysis solutions are available with dextrose (the D-isomer of glucose) concentrations of 1.5, 2.5 and 4.25%, with corresponding glucose content of 1360, 2250, and 3860 mg/dl.<sup>23</sup> Systemic absorption of glucose across the peritoneal membrane is a known phenomenon that can result from using glucose-based PD solution. Although absorption of glucose across the peritoneal membrane depends on various individual characteristics of the membrane, previous research shows that over a four hour PD dwell, approximately two-thirds of intra-peritoneal glucose is absorbed systemically.<sup>23</sup> A 1996 study found large variability in number of calories absorbed across the peritoneal membrane, with an average of 5.89 calories/kg.<sup>24</sup> This same study found that an average of 19% of total energy intake originated from the dialysate (the fluid used during dialysis to remove molecules from a patient's blood) with absorption across the peritoneal membrane.<sup>24</sup> Others estimate that daily systemic glucose absorption during PD ranges from 50-80%, which translates to 100 to 200g of carbohydrates or 320-640 kCal.<sup>25</sup> Although this phenomenon of systemic glucose absorption during peritoneal dialysis is variable, it is a phenomenon that has been shown to exist. Previous research

shows that this absorption is associated with dyslipidemia (abnormally elevated serum cholesterol or other lipids) and increased visceral fat accumulation in patients.<sup>25</sup>

What has been observed about the relationship of the absorption itself to actual weight gain and in turn, obesity, in the adult population has yielded contradictory results, which will be discussed in Chapter 2. Whether or not the use of glucose based PD solutions leads to weight gain in the pediatric ESRD population has not been thoroughly studied. A far greater number of studies have investigated this relationship in the adult population compared to the pediatric population. This said, the relationship of glucose-based dialysate to weight change is unknown in the pediatric population. The adverse effects of obesity in pediatric ESRD patients, which have been described in this chapter, amplify the need to study the relationship of PD and weight change in the pediatric population.

### **Goals and Objectives**

The goal of this study is to improve the knowledge base used to prescribe renal replacement therapy to pediatric ESRD patients by investigating the relationship between glucose-based Peritoneal Dialysis and weight change. Renal transplantation is associated with greater quality of life and survival in children with ESRD, compared to other methods of RRT<sup>21</sup>, but can be affected by obesity. The relationship between PD use in children and weight change needs to be investigated to improve outcomes in this population. We will investigate whether PD therapy causes weight change that is in excess of that predicted by normal growth expectations, and with secondary analysis investigate various baseline variables and their relationships with possible weight change during PD therapy.

The objectives of this study are:

1. Compare actual weight change during the first year of PD therapy to expected weight change using CDC growth charts in a cohort of pediatric patients on PD therapy.
2. Compare actual weight change during the first year of PD therapy to historical values of weight change during the 12 months prior to starting PD therapy in a cohort of pediatric patients on PD therapy.
3. Investigate how starting BMI, starting age, and dialysate glucose concentration affect weight change in pediatric patients undergoing PD therapy.

### **Hypothesis**

We hypothesize that glucose-based peritoneal dialysis causes excess weight gain in pediatric ESRD patients during the first 12 months of PD therapy.

### **Definitions**

End Stage Renal Disease (ESRD): The last stage of chronic kidney disease, which often requires dialysis or transplant for patient survival.

Hemodialysis (HD): Use of a synthetic, extracorporeal membrane to remove waste and excess fluid from a patient's blood.

Intra-peritoneal: Inside the peritoneal space.

Peritoneal Dialysis (PD): Administration of dialysate into a patient's peritoneal space, and use of the patient's peritoneal membrane to filter waste from their blood.

Peritoneal Space: A potential space between the parietal and visceral peritoneum, which are two membranes that surround a patient's abdomen and pelvis.

Peritoneal Dialysis Dwell: The time, prescribed by the patient's nephrologist, that the dialysate sits in a patient's peritoneal space during peritoneal dialysis.

Renal Replacement Therapy (RRT): Medical treatment of End Stage Renal Disease that replaces some functions of the kidney that are lost due to the severity of the disease includes dialysis and kidney transplantation.

Residual Renal Function (RRF): A measure of the remaining ability of the kidney to filter the blood of a patient with kidney disease.



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## **Chapter 2- Review of the Literature**

### **Introduction and Search Criteria**

We performed a systematic review of the literature using Ovid MedLine, Ovid Embase, and PubMed@Yale, as well as the bibliographies of reviewed articles. We reviewed articles published from 1985 to present that were either published in English or translated into English. The keywords used to search these databases are listed as follows: peritoneal dialysis, body fat, body weight, body composition, body mass index, change, end stage renal disease, children, and pediatric.

### **PD Use and Weight Change in Adult Patients: Part One**

The relationship between glucose-based PD and weight change has been investigated in numerous studies in the adult population. This section will provide a detailed literature review of past research that has investigated this relationship in the adult population and that suggests a positive relationship between glucose-based PD and weight change. Additionally, the review will explain characteristics of each investigation that have influenced our project, aiding in the generation of our hypothesis and the design of our study methodology. Table 1 summarizes key findings in this section of the literature review, in the order in which they appear in the section's text.

A 1999 cross-sectional study by Park et al. found the percentage of ideal body weight in its study population to be higher in PD patients than HD patients.<sup>1</sup> This study raises the question of whether or not systemic glucose absorption or some other aspect of PD therapy causes PD patients to have more body weight than HD patients. However, as

the study is cross sectional, it does not establish causality between PD and weight change in its population.

A 2001 study performed in Japan observed a cohort of 35 adult patients undergoing PD therapy, and performed multifrequency bio impedance analysis (to measure various body composition parameters) both at the start of the investigation and after one year of observation.<sup>2</sup> The study found that 9 patients' body weights increased by more than 3kg.<sup>2</sup> The study concluded that in those patients whose body weight increased over the year, it was predominantly due to an increase in body fat.<sup>2</sup>

A 2001 retrospective chart review by Jolly et al. found that 8 of 114 PD patients gained greater than 10kg during two years of PD.<sup>3</sup> These 8 patients gained an average of 13.1kg over this time period.<sup>3</sup> A longitudinal observational study in 2000 showed an increase in total body fat mass and truncal fat mass over the course of PD therapy.<sup>4</sup> A 2008 retrospective study examined 195 incident adult PD patients (patients starting PD therapy for the first time) for Metabolic Syndrome and its components.<sup>5</sup> The study found that BMI correlated with both duration of PD therapy and dialysate glucose.<sup>5</sup>

A 1997 study by Heimbürger found that over the first 12 months of PD, a cohort of 16 PD patients experienced a significant increase in body fat.<sup>6</sup> The exact measurements of percentage of body fat were 19 with a standard deviation of 1.5 kg at the start of PD and 25.1 with SD of 2.2 kg after 12 months of PD therapy.<sup>6</sup> Not only did these findings help us to generate our hypothesis, but also aided in the formulation of our study's 12 month follow-up time.

A 1992 study by Diaz-Buxo and Burgess found a statistically significant trend in weight gain during the first 17 months of peritoneal dialysis, which was followed by a

downtrend in weight change.<sup>7</sup> The researchers examined a total of 100 peritoneal dialysis patients for this study, for a total time course of 36 months.<sup>7</sup> Over the first 17 months of PD therapy, the mean weight gain of the cohort was found to be 6.41kg (about a 6.4% increase) with a SD of 8.36kg and a p value of less than 0.01.<sup>7</sup> From 17 months to the end of the study (36 months), a downtrend in weight change was observed, and a mean weight change slightly less than 5% increase from baseline was reported. Over the course of the study, there was a mean weight gain observed in PD patients with a steady uptrend in weight and a peak in weight gain at 17 months.

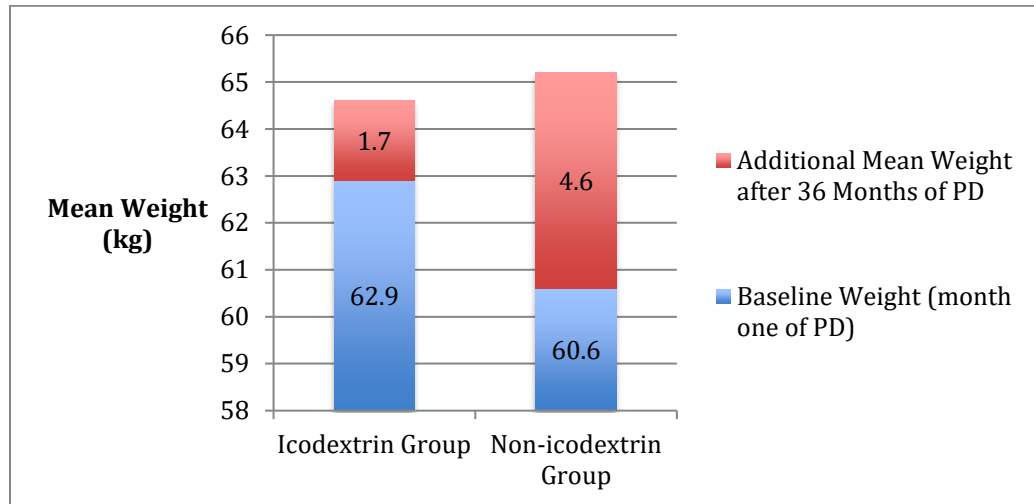
A 1998 study by Fernstrom et al. prospectively followed 12 CAPD patients, and found that body weight increased over the course of the study, from 67.1kg to 68.4kg, but that this change was not significant ( $p= 0.20$ ).<sup>8</sup> However, the researchers found a significant increase of 22.8% in intra-abdominal fat area ( $p= 0.02$ ), after a mean of 7.2 months of CAPD.<sup>8</sup> The authors also note that a statistically significant relationship between intra-peritoneal glucose absorption and body composition parameters measured in this study was not found.<sup>8</sup> The authors recognize that due to small sample size, their study may not have had adequate power to detect a significant body weight change or correlation between glucose load and body composition measurements.<sup>8</sup> Our proposed study will consider these limitations, and use an increased sample size as well as a historical comparison group, to better detect potential changes in body weight.

Some of the previous studies we reviewed compared PD patients to HD patients in the adult population. A 2011 study by Pellicano et al. examined a prospective cohort of 46 adults and found that the 17 patients of the cohort who were treated with peritoneal dialysis had a significantly increased gain in visceral fat, compared to the patients treated

with HD.<sup>9</sup> A 2001 prospective cohort consisting of new adult dialysis patients (both PD and HD) found that PD was associated with body fat increase, with no increase in lean body mass.<sup>10</sup> The researchers also found that PD patients had more moderate to severe loss of appetite, compared to HD patients.<sup>10</sup> They also found HD patients to have a healthier nutritional status compared to PD patients.<sup>10</sup> This study looked at changes in BMI over a two year time period. They found that BMI increased in both PD and HD patients, however this increase was statistically significant only in PD patients and not in HD patients.<sup>10</sup> They also found a significantly greater increase in body fat in the PD group.<sup>10</sup> These results demonstrate the need and feasibility of examining similar parameters in children, as we plan to do in our study.

A 2010 study by Cho et al. utilized a cohort of adult patients using icodextrin (a high molecular weight glucose polymer, leading to less absorption across the peritoneal membrane) as an osmotic agent in their PD therapy, and compared body composition changes to a cohort just using glucose as the PD osmotic agent. This study examined a total of 75 incident PD patients over 36 months showed that the majority (78%) of weight gain over the study period occurred during the first year of PD.<sup>11</sup> They also found that of the weight gained over the first year of PD, 88% was due to fat.<sup>11</sup> The study compared an icodextrin group (36 patients) to a non-icodextrin group (39 patients), and found a greater glucose absorption across the peritoneal membrane, as well as larger changes in body weight, fat mass, visceral fat area, and waist/hip ratio, in the non-icodextrin group.<sup>11</sup> This study concluded that use of icodextrin may lead to less weight and fat gain compared to glucose based PD.<sup>11</sup> It adds to the knowledge base about the relationship in question because it suggests a possible association of glucose-based PD and weight gain.

Icodextrin-based dialysate is not an option for comparison in our study, as it's current usage in once-daily long dwells for increased control of fluid removal during dialysis does not allow for it to replace glucose-based dialysate use in pediatric patients.<sup>12</sup>



**Figure 1. Cho et al.'s Data of Mean Weight Change after 36 months of PD<sup>11</sup>**

A 2008 study by Wu et al. exclusively utilized PD patients in its cohort and examined the metabolic and peritoneal membrane effects of PD. The study divided participants into groups based on their average dialysate glucose concentration during the first 6 months of PD therapy (low, medium, and high glucose load).<sup>13</sup> They found a higher glucose load during this period to be associated with lower serum albumin, diabetes mellitus, lower residual renal function (RRF), and a worse survival prediction.<sup>13</sup> Although the primary outcome of this study was not weight gain itself, it indicates that increased exposure to glucose increases the risk of poorer outcomes, and that understanding the relationship of peritoneal dialysis to weight gain in pediatric patients is needed.

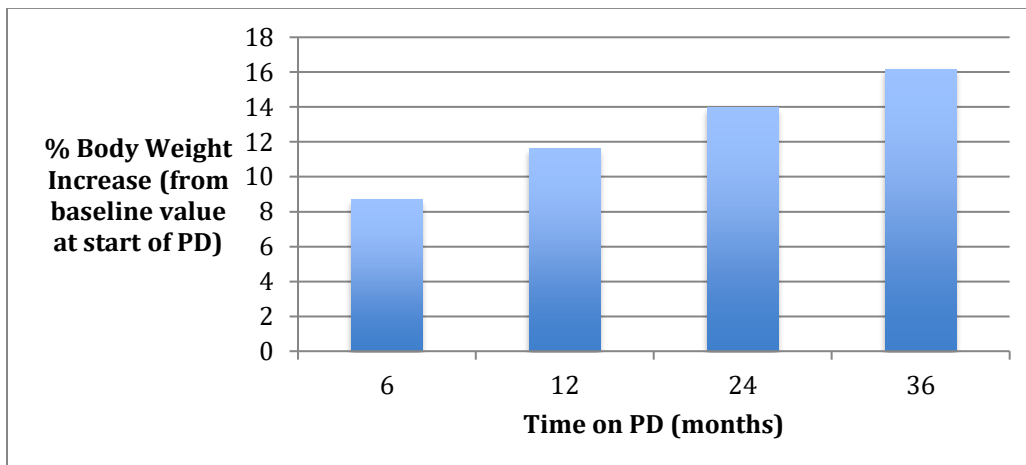
A 2012 study performed by Wu et al. examined long-term glucose exposure due to PD and its effect on patient outcomes. The study recruited 173 patients, and evaluated average glucose concentration used since the start of PD.<sup>14</sup> They concluded that higher

glucose concentration is associated with both higher risk of technique failure and higher rate of mortality.<sup>14</sup> In turn, they found lower glucose exposure associated with better technique outcome.<sup>14</sup> Additionally, a five-year retrospective cohort study published by the same researchers in 2010 indicated that high BMI and DM were associated with the use of higher dialysate glucose concentrations in PD patients during the first three years of PD.<sup>15</sup> The study calculated annual glucose weight and volume of dialysate to determine glucose load in its subjects.<sup>15</sup> The study concluded that higher BMI and DM were factors that influenced the need to use higher glucose dialysate concentrations<sup>15</sup>, which is a relationship in the opposite direction of the relationship we plan to study in pediatric patients, but demonstrates an association between the two variables.

A 2011 prospective study by Choi et al. found that in a cohort of 60 adult patients, PD was associated with weight gain during the first 6 months of the therapy.<sup>16</sup> Using body composition analysis, they determined that during this time period, subjects gained both visceral and subcutaneous fat.<sup>16</sup> Although total weight was found to increase during the entire 12 month study period, when bioelectric impedance analysis and computed tomogram were used to evaluate body composition, visceral and subcutaneous fat increased during the first 6 months but both decreased during the second 6 months. The researchers also found that low fat mass at baseline was associated with a greater increase in fat mass over the study period.<sup>16</sup> This study is similar to ours in their examination of change in body mass during PD therapy and use of different cohorts of PD patients, however we will look at a different population (children) and will include different outcomes. We will not measure different types of fat, but will be examining weight change.



A 2005 study by Jakic et al. examined a cohort of 40 adult patients receiving peritoneal dialysis, and found that although body weight gain was observed in all patients on PD therapy over the study time period of 36 months, there was no statistically significant correlation between the body weight gain and glucose absorption from the peritoneal dialysate.<sup>17</sup> The primary outcome of the study was body weight change.<sup>17</sup> Initial body weight increased by 7.9kg (or 11.62%) with a SD of 4.9kg at 12 months.<sup>17</sup> Initial body weight increased by 11kg (or 16.18%) with a SD of 5kg at the end of the 36 month study.<sup>17</sup> Even with lack of a significant correlation between weight gain and glucose absorption, these results strongly suggest the need for our study, which will examine weight change in children on PD.



**Figure 2: Jakic et al.’s Data of Body Weight Change during PD<sup>17</sup>**

A 2004 retrospective study by Pennell et al. looked at 56 adult PD patients, and compared metabolic parameters before initiation of PD to after initiating PD.<sup>18</sup> Subjects recruited were required to be on PD for at least 6 months, to allow of adequate data collection by investigators. They found that after the initiation of PD, a measurement that they defined as “excessive” weight gain occurred in 20% (11 of the total 56 patients in the study) of study patients from the initiation of PD to the end of study follow-up.<sup>18</sup> The

researchers defined “excessive” weight gain as 10-24% increase in body weight.<sup>18</sup> They also found that all lipid levels except HDL increased significantly after initiation of PD therapy.<sup>18</sup> Additionally, the occurrence of one or more of the following three factors, hyperlipidemia, hyperglycemia, and obesity, was found in 84% of the study participants.<sup>18</sup> This study shows that the initiation of peritoneal dialysis is associated with weight gain and other metabolic risk factors, and suggesting the need for our study.

A 2015 study by Kim et al. investigated weight gain and its relationship with adverse effects such as inflammation, DM, and rapid decrease in RRF over the first year of PD in adult patients. Obesity prevalence was 38.5% at the start of PD, and increased to 46.6% after one year of PD therapy.<sup>19</sup> The study found a mean 3% increase in body weight over the first year of PD.<sup>19</sup> It also found that increase in body weight was associated with an increased rate of RRF decline, and an increased risk of RRF loss.<sup>19</sup> The study concludes that in peritoneal dialysis patients who use glucose-based dialysate, weight gain is a significant risk due to dialysate glucose absorption and increase in uremic effects.<sup>19</sup>

This same 2015 study by Kim et al. found a significant association between excess body weight gain and increased glucose absorption from the dialysate.<sup>19</sup> However, the researchers were not able to establish a causal relationship between body weight change and systemic glucose absorption as their measurement of body weight did not differentiate weight due to retained volume.<sup>19</sup> This study supports a positive relationship (although not causal) between weight change and PD therapy in the adult population, further amplifying the need to study this potential relationship in the pediatric population.

**Table 1: Summary of Literature in Adult Population; Part One**

<b>Author</b>	<b>Date</b>	<b>Key Findings</b>
Park et al.	1999	Higher percent body weight in PD versus HD patients <sup>1</sup>
Kanazawa et al.	2001	Weight gain greater than 3kg in 9 of 35 patients, after one year of PD <sup>2</sup>
Jolly et al.	2001	Weight gain greater than 10kg in 8 of 114 patients after two years of PD <sup>3</sup>
Stenvinkel et al.	2000	Longitudinal observation of PD patients showed increased total fat mass and increased truncal fat mass <sup>4</sup>
Jiang et al.	2008	Increased BMI associated with increased duration of PD and increased dialysate glucose usage <sup>5</sup>
Heimbürger et al.	1997	Body fat increased significantly over 1 <sup>st</sup> 12 months of PD <sup>6</sup>
Diaz-Buxo and Burgess	1992	Statistically significant weight gain found after first 17 months of PD <sup>7</sup>
Fernstrom et al.	1998	Non-significant body weight increase in PD patients, significant increase in intra-abdominal fat area after 7.2 months PD <sup>8</sup>
Pellicano et al.		More visceral fat gain with PD therapy, compared to HD therapy <sup>9</sup>
Jager et al.	2001	Significantly greater increase in body fat in PD patients, compared to HD patients <sup>10</sup>
Cho et al.	2010	Non-icodextrin group showed greater change in body weight, fat mass, visceral fat area <sup>11</sup>
Wu et al.	2008	Higher peritoneal glucose load associated with Diabetes Mellitus, lower RRT, worse survival in PD patients <sup>13</sup>
Wu et al.	2012	Higher peritoneal glucose load associated with technique failure and increased mortality in PD patients <sup>14</sup>
Wu et al.	2010	High BMI and Diabetes Mellitus each associated with greater dialysate glucose usage <sup>15</sup>
Choi et al.	2011	PD use associated with weight gain during first 6 months therapy <sup>16</sup>
Jakic et al.	2005	Significant body weight increase after 12 months and after 36 months of PD <sup>17</sup>
Pennell et al.	2004	10-24% body weight increase in 11 of 56 patients during 6 months of PD <sup>18</sup>
Kim et al.	2015	Increase in obesity prevalence after one year PD; Significant association between body weight gain and increased glucose absorption from dialysate <sup>19</sup>

**PD Use and Weight Change in Adult Patients: Part Two**

As it is now evident, there is an existing body of research to suggest a positive association between PD and weight change in the adult population. Our proposed study will utilize similar methods to investigate the relationship between PD and weight change, which will be discussed in more detail later in this chapter as well as in Chapter 3. Our study will retain its novelty in the fact that we will be studying a pediatric population rather than an adult population. We will next discuss previous research in the adult population that does not support a positive association between PD and weight gain.

A 1992 study by Saxenhofer compared body composition changes among PD patients to adult HD patients, and found no significant differences between the two dialysis modalities in regards to muscle mass/fat distribution changes.<sup>20</sup> The researchers concluded that in their population, glucose load did not contribute to additional body composition changes (compared to HD patients).<sup>20</sup> However, this study's primary outcome differs from our primary outcome of weight change over time on PD.

A 1996 study was performed in the adult population to determine if systemic glucose absorption from PD caused adverse effects (including obesity). The results suggest that glucose absorption does not suppress appetite and does not cause obesity<sup>21</sup>. The researchers also found no difference in survival between those with higher calorie intake across the peritoneal membrane versus those with lower calorie intake across the peritoneal membrane<sup>21</sup>. This study grouped its subjects based on calorie absorption across the peritoneal membrane (two groups, one above 6cal/kg and one below 6cal/kg)<sup>21</sup>. Our study will utilize different groupings of our cohort to better detect an association.

A 1988 study compared nutritional status of HD and PD patients, including body weight, and found no difference in the nutritional status between the two groups<sup>22</sup>. The study utilized a small number of 16 PD patients, and compared this cohort to 32 HD patients. Outcomes were measured in only 54% of patients<sup>22</sup>. Our study will not utilize HD patients as a comparison, which will aid in reduction of confounders. We will also utilize a larger sample size.

A 2008 study found body fat change in 45 PD patients, over a period of one year, to be highly variable.<sup>23</sup> The study measured factors including body composition, nutritional status, and energy intake with 3-day food records.<sup>23</sup> The study did not find an association between daily glucose absorption and body fat.<sup>23</sup> However, they found that baseline BMI was the factor most associated with body fat gain.<sup>23</sup>

A 2012 study compared adult HD patients to adult PD patients and measured BMI change over a period of six years.<sup>24</sup> They found that weight gain was less likely in PD patients, compared with HD patients.<sup>24</sup> Our study will utilize different comparison groups, as well as a different population (pediatric population). Our study will also utilize a shorter follow-up time, based on previous studies that show a positive relationship between PD and weight change occurring to the largest extent in the first year of PD therapy.<sup>7,11,16,19</sup>

A 2015 study by Ho et al. did not find a significant correlation between visceral fat area and glucose load in PD patients.<sup>25</sup> However, our study will differ in that we will be exploring other independent variables such as age, in addition to glucose load, to evaluate weight change. Additionally, Ho et al.'s study specifically measured visceral fat area, while our study will measure weight change in kilograms, to detect any possible

correlation with PD therapy. Our study will also use a different population, pediatric patients.

A 2014 study by Fan and Davenport found similar results. They found that increased glucose load (as patients became anuric, and the need for a higher glucose dialysate concentration arose) was not associated with body fat gain.<sup>26</sup> Our study will be looking at a different dependent variable (weight change in kg). We will recruit patients who are just beginning dialysis, regardless of their urine output. Several studies that we reviewed that show a positive relationship between PD and weight gain show the biggest weight gain in the first 1-1.5 years.<sup>7,16,19</sup> This study may not have been designed to detect an association between body fat gain and PD, as it did not start its follow-up period at the initiation of PD, as our study will.

**Table 2: Summary of Literature in Adult Population, Part Two**

Author	Date	Key Findings
Saxenhofer et al.	1992	No significant difference in body composition between PD and HD patients <sup>20</sup>
Davies et al.	1996	No association between obesity and peritoneal glucose absorption in PD patients <sup>21</sup>
Marckmann	1998	No difference in body weight between PD and HD patients <sup>22</sup>
Vasselai et al.	2008	No association between glucose absorption and body fat <sup>23</sup>
Lievense et al.	2012	Weight gain less likely in PD, versus HD, patients after six year follow-up <sup>24</sup>
Ho et al.	2015	No significant correlation between visceral fat area and glucose load in PD patients <sup>25</sup>
Fan and Davenport	2014	No association between increased glucose load and body fat gain in PD patients <sup>26</sup>

### **PD Use and Weight Change in Pediatric Patients**

Compared to the adult population, less research has been performed in the pediatric population that explores the relationship between glucose-based PD and weight change. The following section consists of a literature review of four investigations we

reviewed that suggest an association between these two variables. Each study differs from our project in methodology and outcomes, however these studies have influenced both the generation of our hypothesis and methodology design in ways that will be discussed further in the following sections.

A 2005 retrospective analysis by Hanevold et al. examined the prevalence of obesity in pediatric ESRD patients aged 2-17, and found that obese patients had been on dialysis for a longer period of time than non-obese patients.<sup>27</sup> The main investigation of this study was transplant outcomes in obese versus non-obese children. However, this study's finding that obese patients had been on dialysis for a longer period of time helped us to generate our hypothesis, especially since it pertains to the pediatric population.

Results of a 1999 study by Schaefer et al. suggest a potential relationship between glucose-based PD therapy and weight gain in pediatric patients.<sup>28</sup> The study utilized a prospective cohort design, with a population of 51 pediatric patients on peritoneal dialysis. The cohort was followed for 18 months, and a statistically significant association between peritoneal transport and weight gain was found in the study population.<sup>28</sup> Specifically, a faster rate of peritoneal creatinine equilibration (a measure of peritoneal membrane function in PD) and increased volume of glucose-based dialysate solution during dialysis were each associated with an increase in BMI.<sup>28</sup> This study was used to generate our hypothesis. We plan to use different independent variables than Schaefer et al. used, however our outcome variable will be change in weight (comparable to the outcome variables used by Schaefer et al.). The parameters that will be measured in our study will aid in a better understanding of the relationship between glucose based PD and weight gain in pediatric patients. Also, one of our independent variables will be

expected weight change without PD therapy, which will serve as a historical control group and will allow us to more accurately explore this relationship.

A 2013 study by Bonthuis et al. investigated BMI changes in a cohort of 4474 pediatric ESRD patients from 25 different countries, who were treated between the years of 1995 and 2010.<sup>29</sup> BMI measurements were analyzed at the start of RRT (dialysis or transplant) and after 6-18 months of follow-up.<sup>29</sup> The study demonstrated that after follow-up of 6-18 months, the prevalence of patients who were overweight and obese increased.<sup>29</sup> The study also found that lower BMI at the start of RRT, older age at the start of RRT, longer time on dialysis, and starting RRT on PD (versus HD) were factors associated with a larger increase in BMI.<sup>29</sup> Our proposed study will utilize similar variables, including starting BMI and age, and will exclusively study PD patients to better understand the relationship of PD therapy with BMI change in pediatric patients.

A 2012 retrospective investigation by Watanabe et al. recruited 30 PD patients and measured various hemodynamic and anthropometric variables at the start of PD and after at least 6 months of PD therapy.<sup>30</sup> Of note, the researchers found no statistically significant difference between initial and final z-scores (a statistical representation of a measurement in relation to the mean and standard deviation of a group of measurements) for patient weight.<sup>30</sup> Although this result does not support a relationship between PD and weight change in pediatric patients, our study will utilize a historical comparison cohort to possibly more accurately detect a relationship between PD therapy and weight change.

**Table 3: Summary of Literature in Pediatric Population**

<b>Author</b>	<b>Date</b>	<b>Key Findings</b>
Schaefer et al.	1999	Increased peritoneal glucose absorption associated with increase in BMI over 18 months of PD therapy <sup>28</sup>



Hanevold et al.	2005	Obese patients on dialysis longer than non-obese patients <sup>27</sup>
Bonthuis et al.	2013	Starting RRT on PD (versus HD) associated with larger increase in BMI <sup>29</sup>
Watanabe et al.	2012	No statistically significant difference in weight after PD duration of 6 months or greater <sup>30</sup>

## **Methodology Review and Justification**

### *Study Design*

We will use a prospective cohort study design to explore the relationship between PD and weight change in children. Dialysis prescription is based upon numerous factors, including residual renal function. This said, it is both unethical and dangerous to manipulate a dialysis prescription for the purposes of a study, and we cannot utilize an experimental study design, or Randomized Control Trial (RCT). Therefore, we will use an observational study design in the form of a prospective cohort. Previous research shows that weight gain predominately occurs during the first year of dialysis initiation; therefore a prospective design with a one year follow-up period was chosen.<sup>7,11,16,19</sup>

### *Population and Setting*

We plan to recruit and examine a population aged 2 through 17 years old to investigate the relationship between PD and weight change. An investigation by Ku et al. used a population aged 2-19 for retrospective analysis of BMI and outcomes, and found that higher BMI was associated with higher risk of death and lower rate of transplant.<sup>31</sup> As this is one of the previously reviewed studies that we are using to justify the necessity of our own study, it is fitting that our population age range be similar. Additionally, a study by Hanevold et al. that contributed to the generation of our hypothesis examined the risks of obesity on renal transplant, and used a population of patients aged 2-17 years old.<sup>27</sup> Using a similar age group to that used in prior pediatric studies allows better comparison of our results to published data. Also, a lower limit of two years was decided

because CDC growth charts (which we will use to form a historical control group) pertain to children age 2-20.<sup>32</sup> An upper limit of 17 years old will improve the generalizability of our results to a pediatric ESRD population, as renal transplant listings consider patients 18 years and older as adults, leading to different transplant eligibility criteria.

We plan to conduct data collection in the outpatient dialysis clinic setting, where patients will attend regular monthly appointments while undergoing PD therapy at home. Our measurements (specifically, weight in kg) will be done routinely at each follow-up appointment whether or not a patient is enrolled in our study, which supports the feasibility of our data collection methods.

#### *Recruitment Methods*

Patients will be recruited from the Midwest Pediatric Nephrology Consortium, a collaborative group that facilitates recruitment of pediatric patients into pediatric nephrology clinical research. This consortium recruits patients from its 57 member centers from various areas in the United States into many different types of pediatric nephrology research projects, including multi-center studies. Our study will be open for recruitment patients from all member centers of the consortium, as well as the Yale Department of Pediatric Nephrology. Inclusion criteria will include age 2 through 17 years old, and access to prior health records of at least twelve months, as this will be needed to estimate expected weight change and form our study's historical control group. Exclusion criteria will consist of prior use of dialysis therapy (peritoneal dialysis or hemodialysis), to decrease possible introduction of confounding variables.

#### *Variables*

The primary outcome variable will be weight change, measured in kilograms. Kim et al.'s 2015 study investigated weight gain and its relationship with adverse effects

over the first year of PD in adult patients. The study concluded that in adult PD patients who use glucose-based dialysate, weight gain is a significant risk due to dialysate glucose absorption,<sup>19</sup> justifying the need for use of our primary outcome variable of weight change. Further justification for use of this outcome variable includes the 2005 study by Jakic et al., which was described earlier in this chapter, and which used a primary outcome of body weight change.<sup>17</sup>

The parameters that will be measured in our study will aid in a better understanding of the relationship between glucose based PD and weight change in pediatric patients. Our use of a matched control variable of expected weight change without PD therapy will aid in a greater understanding of how glucose based PD is associated with weight change. It is unethical to use a placebo group in our study, or a control group of non-PD ESRD children. We will be using a historical control group using Centers for Disease Control (CDC) growth charts to estimate expected weight change in kg at our follow-up measurement times.<sup>32</sup> Additionally, we will collect data from participants' prior health records, recording their weight in kg from 12 months prior to dialysis initiation, and use this as a self-control group that will be compared to the actual weight change in the cohort after 12 months of PD therapy. The two control groups that will each be compared to the actual weight gain during 12 months of dialysis are as follows:

1. Predicted weight gain according to CDC growth curves, from the patient's baseline weight at the initiation of dialysis
2. Weight change retrospectively reviewed and recorded from patient's prior health records, over the course of 12 months prior to initiation of dialysis

The use of a historical control group is a method that has been used in past studies in which it is unethical to use a placebo/non-treatment group due to standard of care guidelines and past research. A 2009 study examined survival benefits of treatment with alglucosidase alfa (an enzyme replacement) in children with a congenital disorder.<sup>33</sup> They used a historical control group using retrospective chart analysis because use of their intervention was the current standard of care, making the use of a placebo group unethical.<sup>33</sup> This method has also been used in studies that examine pediatric growth parameters as outcome variables, as our study will utilize. For example, a 2015 prospective randomized study used a historical control group of adolescents as a comparison to the study's intervention group receiving growth hormone therapy.<sup>34</sup> The study's control group was matched for puberty and past growth data, and the primary outcome of the study was change in height.<sup>34</sup>

Additionally, this method was used in a study investigating body composition changes over time in PD patients. A 1998 study by Johansson et al. prospectively examined 60 adult PD patients, and found that within the group, individual changes in body weight correlated significantly with individual body fat changes. The researchers compared observed values of body composition parameters (including body fat and body weight) to predicted values generated from local population studies.<sup>35</sup>

Our secondary analysis divides our cohort into groups based on:

1. Dialysate dextrose concentration used
2. Starting BMI
3. Starting age

These stratifications will help us to better understand our research question. We have chosen to group based on dialysate dextrose (a glucose isomer) content, rather than dialysate volume, to more accurately detect a relationship between peritoneal glucose load and weight change (versus dialysate presence in general).

Our review of the literature has shown a possible association between starting BMI and weight change during PD therapy. A study by Choi et al. found that subjects with a lower baseline fat mass at the start of PD demonstrate greater gain in fat mass over the first six months of PD therapy.<sup>16</sup> A 2008 study by Vasselai et al. found that baseline BMI was associated with body fat gain in PD patients.<sup>23</sup> The reviewed 2013 study by Bonthuis et al. found that, in the pediatric population, a lower starting BMI is associated with larger BMI increase during RRT.<sup>29</sup> We have chosen to use starting BMI as one of our independent variables, to assess a possible association between starting BMI and weight change during the first 12 months of PD.

Review of the literature also suggests a potential relationship between starting age and weight change during PD therapy. The pediatric cohort investigated by Bonthuis et al., in addition to the results mentioned in the above paragraph, demonstrated a larger increase in BMI (after follow-up of 6-18 months) with older age at the start of RRT.<sup>29</sup>

#### *Timing of recruitment, data collection, and follow-up*

The data collection of our study will occur over a period of 24 months. We will recruit patients on a rolling basis during the first 12 months of our study's two-year data collection period (as it will allow completion of data collection within two years time). Our follow-up time for each subject will be 12 months.

We have chosen a 12-month follow-up period because several studies that we reviewed demonstrate a positive relationship between PD and weight gain indicate the

largest amount of weight gain to occur in the first 1-1.5 years of PD therapy.<sup>7,11,16,19</sup> One of these studies examined incident PD patients over 36 months and found that the majority of weight gain over the total 36 months (78%) occurred during the first year of PD.<sup>11</sup> It was also found that 88% of the total weight gained by patients during the first year of the study was due to gain of fat mass.<sup>11</sup> After reviewing this information, it was decided that 12 months is an adequate follow-up period to detect any weight change after the start of PD.

Additionally, it has been demonstrated that trans peritoneal glucose absorption during dialysis remains relatively constant over time.<sup>36</sup> These data were collected from long term follow-up of six years.<sup>36</sup> This said, one year will be a sufficient time period to detect what percentage of the pediatric population of the study will experience a weight gain with dialysis therapy.<sup>36</sup>

Our decision to use a 12 month follow-up time is supported by the United States Renal Data System's most recent data, which state that incident (first time) dialysis patients aged 0-21 years old have a median wait time to transplant of 1.01 years from when they are listed for transplant.<sup>37</sup> This supports the notion that the majority of our study population will be able to complete the full study follow-up period of 12 months before switching RRT method to transplantation.

### *Statistical Methods*

Descriptive data that will be measured in the cohort represent characteristics that may be related to our outcome variables, and will be measured at the start of data collection and monthly for the 12-month follow-up period. These characteristics are listed in Chapter 3. Because our primary outcome utilizes historical control groups, we will use means and standard deviations to describe these characteristics of the cohort. In

our secondary analyses, in which we divide the cohort into two groups based on three covariates (starting BMI, starting age, and dialysate glucose concentration prescribed), we will utilize ANOVA to compare outcome variables. Appropriate comparison tests will be utilized at the end of data collection to compare the characteristics used to describe the sample, based on whether the data is normally or non-normally distributed.

The primary outcome of our study, mean weight change, measured monthly over the first 12 months of PD therapy, is a continuous variable. We will use a two-sided analysis to enable detection of both weight increase and weight decrease in the cohort. Therefore, we will use the paired student t-test to compare primary outcomes in patients undergoing glucose-based PD therapy with the historical control group consisting of numerical values of expected weight change in the absence of PD therapy (generated with CDC growth charts). Additionally, we will use the paired t-test to compare weight change over the course of 12 months of PD therapy to weight change generated from the cohort's prior records of weight measurements from the 12 months leading up to initiation of PD therapy.

In our secondary analysis, the outcome of mean weight change is also a continuous variable (difference between actual and expected weight change over the first 12 months of PD therapy, measured in kg). Therefore, because the cohort will be divided into two groups during our secondary analyses, we will utilize the paired t-test to compare secondary outcomes. We will then use multiple regression analysis to evaluate relationships between the groupings of our secondary analysis.

### *Sample Size*

It is now evident that the relationship between PD and weight change has been studied to a greater extent in the adult population, versus the pediatric population. This

said, the results of our literature review did not allow for an estimation of effect size of change in kg over one year of PD in pediatric patients.

Effect sizes from previous study designs in the adult population, which have been discussed in further detail in the first section of this chapter, were utilized. For example, Jakic et al.'s 2005 study found an effect size of 7.9kg (mean change from baseline) with a standard deviation of 4.9, after 12 months of PD therapy<sup>17</sup>.

However, we have decided to utilize the effect size found in Cho et al.'s 2010 study, as the mean change in baseline demonstrated in this study was 3.59 kg in patients undergoing the first 12 months of glucose dialysate PD<sup>11</sup>, a smaller mean change in baseline compared to Jakic et al.'s study. Because our study is using a novel population and design, we attempt to ensure the greatest chance of detecting a mean change from baseline in our own study by using the smaller effect size to calculate the required sample size. Cho et al.'s study design is very similar to our methodology in that researchers investigated weight change, in kg, of patients on glucose-based PD. They found that their sample (both the glucose dialysate group and the icodextrin dialysate group) gained an average 2.5 kg with a standard deviation of 5kg during the first 12 months of PD, which is the follow-up period of our study<sup>11</sup>. Specifically, the non-icodextrin group (glucose-based PD, the exposure being studied in our investigation) gained 3.59 kg in the first year of CAPD therapy. Our study is not utilizing an icodextrin group. We have calculated two sample sizes in the planning of our methodology, using effect sizes of 2.5kg and 3.59kg (weight change), with a standard deviation of 5kg.

*PS: Power and Sample Size Calculation version 3.1.2* software was used to calculate our study's sample size. Using an effect size of 2.5, a standard deviation of 5,



an alpha value of 0.05 and power of 80%, a sample size of 33 was calculated (**Appendix B**). Using an effect size of 3.59, with the same alpha value, power, and standard deviation, the software calculated a sample size of 17 (**Appendix B**). Ideally, we would like to recruit 33 participants per grouping, to err on the side of modesty in our study design. Because several of our study's secondary analyses will involve division of the cohort into two groups (based on the three cofactors of starting BMI, dialysate glucose concentration, and baseline age), we plan to recruit a minimum of 66 subjects into our study (double the raw sample size of 33). However, it is noted that a sample size of 17 (total of 34 when the cohort is divided into two groups) is estimated as sufficient to detect weight change (kg) from baseline, after one year of glucose-based dialysate PD therapy.

The most recent data from the United States Renal Data System indicate that in 2013, there were 367 incident cases of pediatric patients starting PD therapy. This equates to an incidence rate of 3.9 per million per year. The data also demonstrate that the point prevalence as well as incidence of pediatric patients on PD has remained relatively steady from the years 1996 to 2013. When considering the feasibility of our sample size, we extrapolate from this data that approximately 360-370 pediatric patients will initiate PD therapy in the United States each year that our study takes place.<sup>37</sup>

Another consideration we analyzed while assessing the feasibility of our sample size was the wait time of pediatric patients once they have been listed for transplant (as this is the preferred method of RRT in the pediatric ESRD population. As mentioned previously, incident dialysis patients aged 0-21 spend a median time of 1.01 years waiting for a kidney transplant (on dialysis in the meantime).<sup>37</sup> The fact that the median

time to transplant is just over one year supports the feasibility of our study to gain adequate data from a sufficient sample size over the entire study's time period.

Loss to follow up is unlikely in our study, as patients are undergoing dialysis therapy for kidney failure, and the measurements we will use in our study are routinely taken at appointments. As this study is an observational study, and the exposure will not be manipulated by our study, we don't anticipate any significant loss to follow up. We expect the predominant reasons why some patients will not be able to finish the follow-up period are changing method of dialysis (to HD), transplant, or death. A study by Tsai et al. prospectively examined a cohort of pediatric PD patients, and found a 96.55% survival rate after two years of PD therapy<sup>38</sup>. Additionally, they found that those PD patients who switched to HD at some point after initiating PD, (27.5%) remained on PD for a mean time of 3.98 years with a standard deviation of 2.14 years.<sup>38</sup> Combined with the previously discussed data that incident dialysis patients spend a median of 1.01 years waiting for a kidney transplant, we anticipate that the majority of our recruited cohort will remain on PD and therefore in our study for the full follow-up time of 12 months. However, it is likely that a percentage of patients will not be able to complete the study for the previously mentioned reasons. Recruiting a minimum sample size of 66 will allow for as much as a 48% dropout rate (32 of the 66 subjects can drop out or be lost to follow up) for our study to maintain adequate power to detect difference in outcome in our cohort, as the above mentioned calculations indicate recruitment of a total of 34 patients to detect an effect of PD therapy over 12 months.

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## **Chapter 3- Study Methods**

### **Study Design**

We will conduct a prospective, observational, analytical, multicenter study to examine the relationship of PD therapy and other baseline characteristics with the primary outcome variable of mean weight change. All recruited patients will receive glucose-based PD therapy, and will be followed for a total follow-up period of 12 months. Time zero (the start of the study) will be the time of initiation of glucose based PD therapy. All variables will be measured at initiation of PD, 6 months after starting PD, and 12 months after starting PD. The study setting will be an outpatient pediatric dialysis clinic.

### **Population and Sampling**

The study population will consist of pediatric ESRD patients aged 2-17 who are initiating PD therapy. Subjects will be recruited from the Midwest Pediatric Nephrology Consortium, a common location used to recruit patients into pediatric nephrology clinical research. We will use a non-random, convenience, consecutive sampling method. Inclusion criteria will include age 2 through 17 years old, and access to prior health records of at least twelve months prior to recruitment into the study. These records will be used to form one of our historical control groups. Exclusion criteria will consist of prior use of dialysis therapy (peritoneal dialysis or hemodialysis).

### **Variable Measures**

Baseline characteristics will be measured at the start of the study as well as monthly (when applicable) in all subjects, and then further divided by grouping for the

secondary analysis. The characteristics that will be described at the start of the study include:

1. Age
2. Gender
3. Race
4. Primary diagnosis leading to ESRD
5. Urine output
6. Prescription of erythropoietin (yes or no)
7. Prescription of growth hormone (yes or no)
8. Peritoneal Equilibration Test (PET) results
9. Daily volume of PD therapy
10. Laboratory values obtained from blood sample (serum albumin, lipid profile, and normalized protein catabolic rate)
11. Appetite (categorized into poor, average, good)
12. Physical activity level (categorized into light, moderate, and strenuous)
13. Socioeconomic status (categorized into poverty, low income, middle class, and upper class)

The characteristics that will then be measured monthly (may change throughout the 12 month follow-up period) include:

1. Daily urine output
2. Prescription of erythropoietin
3. Prescription of growth hormone
4. Daily volume PD dialysate

5. Appetite
6. Physical activity level

As stated above, the dependent variable and primary outcome of our study is mean weight change after 12 months of glucose based PD therapy. Our study will measure various independent variables to analyze their relationship with the primary outcome, mean weight change, a continuous variable. The first independent variable we will measure is the use of glucose based PD therapy. We will analyze this relationship using the expected weight change (at 12 months after the start of PD) in each recruited patient. This expected weight change will be calculated using the CDC's pediatric weight-for-age growth curves (**Appendix A**), and will serve as the outcome for the control (non-exposed) group. The measured weight change over the course of 12 months of PD therapy will serve as the outcome for the experimental (exposed) group. Additionally, to further explore our research question, participants' prior health records dating 12 months prior to initiation of dialysis will be used as a second control group. We will gather the historical 12-month weight change immediately prior to dialysis and compare this to monthly weight change during the first 12 months of dialysis. Therefore, for our primary analysis, patients will serve as their own controls.

Our secondary analysis will investigate the relationship of three cofactors; dialysate dextrose concentration, starting BMI, and starting age; to weight change over the course of 12 months on glucose based PD therapy. In this secondary analysis the outcome of weight change will be measured as the difference between observed (actual) weight change and expected weight change. Expected weight change will be determined by CDC growth curves (**Appendix A**), which will be the same measurements used to



generate the historical control group of the primary analysis. This will decrease the risk of our results being confounded by factors such as differing rates of growth based on developmental stage of the child, as well as lessen the risk of our results being due to normal growth of the child. The equation used to calculate the secondary outcome of weight change is as follows, and will be calculated monthly for each participant:

**(Observed weight change during PD therapy, in kg) – (expected weight change from baseline for corresponding point in time, using CDC growth chart, in kg)**

For our analysis of exposure to dialysate glucose, we will divide our cohort of pediatric PD patients into two groups according to dextrose concentration of the prescribed dialysate:

1. Less than 2.5% dextrose concentration
2. Greater than 2.5% dextrose concentration

We will then measure actual and expected weight change and use the above equation to obtain our outcome measurements. We will then compare the outcome variable measured monthly for the 12-month follow-up period between the two dextrose groups. If a participant changes dialysis dextrose prescription during the study, we will keep them in the dextrose group in which they started dialysis therapy.

We will also group the cohort by initial BMI to detect if this independent variable has any relationship with weight change. We will group patients as follows:

1. Below 25 kg/square meters
2. Greater than or equal to 25 kg/square meters

We will then measure actual and expected weight change, and use the above equation to arrive at our secondary outcome measurements. Next, we will compare outcome variables between the two groups.

We will also group patients based on age to examine whether this independent variable is associated with weight change. We will group patients using the age ranges as follows:

1. 2-11 years old
2. 12-17 years old

Next, we will compare outcome measurements (obtained from above equation) between the two groups.

### **Statistical Analysis**

We will describe baseline characteristics of the cohort of our primary outcome with means and standard deviations. At the end of data collection, we will compare baseline characteristics among the secondary outcome groupings using appropriate comparison tests depending on how the characteristics are distributed (normally or non-normally distributed).

We will use a two-tailed analysis to compare all outcome measurements (both primary and secondary), with a significance level (p-value) of less than or equal to 0.05. To compare outcomes in our primary analysis, which involves comparison of weight change from two groups (PD therapy and the historical control group of no PD therapy), we will utilize the paired student t-test. Additionally, patient records of weight change over the 12 months prior to PD initiation will serve as a second control group, allowing

comparison of weight change 12 months prior to dialysis and for the first 12 months of dialysis, using the paired t-test.

In our secondary analyses (division of the cohort into two groups by glucose prescription, age, and initial BMI range), we will utilize the paired t-test testing to compare outcome (weight change) between the corresponding groups, as these divisions of the cohort will result in two groups that will be compared in regards to the outcome of excess weight change.

We will also utilize multivariate regression analysis in our secondary analysis to test relationships between monthly measurements of weight change and other measured characteristics for each group of our secondary analysis.

### **Sample Size Calculation**

The sample size is calculated using PS: Power and Sample Size Calculation version 3.1.2. Our study will be powered to 0.8, paired, with an alpha level of 0.05. An estimated effect size of 2.5 mean change from baseline weight (in kg), with a standard deviation of 5, was used to calculate a sample size of 33. Several of our secondary analyses will divide the cohort into two groups, and we will recruit at least two times this number which equates 66 patients in total (**Appendix B**).

### **Recruitment**

Participants will be recruited through Yale New Haven Hospital's Pediatric Nephrology department, as well as all member centers of the Midwest Pediatric Nephrology Consortium using a nonrandom, convenience, and consecutive sampling method. All incident cases of PD aged 2-17 who are initiating glucose dialysate PD therapy at participating centers during the first 12 months of our investigation will be

asked to participate in the study. Patients who have been on a previous method of dialysis (including both peritoneal dialysis and hemodialysis) in the past will be excluded from participation. Patients will be informed of what measurements will be taken for the purposes of this study, and will sign a the appropriate consent forms in order to participate, which are described later in this chapter.

### **Confidentiality and Safety**

The study will be approved by Yale Human Investigation Committee (HIC). Employees of the study will complete HIPPA training and adhere by HIPAA regulations to ensure the confidentiality of our recruited patients. Identifying information will be removed from any public release of data gained from the study. Parents/legal guardians of minors (children under 18) will sign informed consent and HIPAA authorization (Parental Compound Authorization) before their child will be enrolled in this study. Children 7-17 years old will also sign an assent form specific to their age group (one for 7-12 years old, one for 12-17 years old), per the Yale University Human Investigation Committee Pediatric Protocol.<sup>1</sup> **Appendices C-E include copies these of consent/assent forms.**

Patient's names will be replaced with a numerical code when storing their information and measurements for the purposes of this study. Each participating dialysis center/medical center will keep any paper documents/information pertaining to the study in a locked cabinet. All information reviewed and used in this study will be treated as protected health information. Any electronic information will be viewed and stored on an encrypted device according to HIPPA regulations.

To ensure the safety of all study participants, follow-up will take place in an outpatient dialysis clinic, and patients' nephrologists will manage their dialysis prescription and efficacy.

### **Data Collection and Follow up**

Data will be collected at patients' initial dialysis appointment, and monthly at follow-up appointments for 12 months after starting dialysis. Weight will be routinely measured at all appointments, and will be extracted from the patient's chart. Data collection forms will be stored in the locked cabinet designated for our study (**Appendix F**).

Considering the observational nature of our study, independent variables will not be manipulated or assigned. Each patient's nephrologist will manage their dialysis prescription without any consideration that they are in the study. If a patient stops dialysis, switches dialysis method (to hemodialysis), or receives a kidney transplant during the study, they will be removed from the study as they will be unable to complete the 12-month follow-up period of data collection.

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## **Chapter 4- Conclusion**

### **Advantages and Disadvantages**

Our study aims to provide the field of pediatric nephrology with insight into the relationship between PD prescription and weight change in pediatric patients. This information will fill a gap in the literature surrounding this topic, as well as contribute to understanding of the physiologic response of pediatric patients exposed to peritoneal glucose load. PD's effect on patient weight is a relationship that if better understood, could lead to innovations in dialysis prescription to improve outcomes in pediatric patients with ESRD, as well as changes to the current standard of care. Additionally, a more concrete understanding of the effects of peritoneal glucose load in regards to weight change could stimulate further research in the pediatric population pertaining to interventions or alternatives to avoid weight change that is not explained by normal growth. With the gold standard of treating ESRD in children being renal transplantation, one that gives the child the best possible quality of life and survival, the relationship of glucose-based PD use in children and BMI is a relationship that needs to be investigated to improve treatment outcomes in this population.

Advantageous qualities of our study include use of a historical, individualized control group. This reduces confounders that would be introduced through the use of a healthy control group not on PD therapy, or a group of pediatric ESRD patients on HD therapy. This allows insight into the relationship in question without introducing confounders that would arise from interpersonal growth patterns. Additionally, the fact

that our study is prospective (versus retrospective) reduces potential selection bias, as the outcome variable is unknown at the time subjects are recruited.

We recognize and have evaluated the limitations of our study. The nature of the therapy we are studying does not allow for use of randomization or controlled assignment of study subjects to groups. Patients are prescribed PD dialysis therapy, which includes glucose content, according to their specific and individual symptoms, volume status, and serum laboratory values. Along these lines, use of a “placebo” PD group is unethical and potentially dangerous. Manipulation of dialysis prescription, including dialysate glucose content, is also unethical and dangerous. Placement of a PD catheter is a surgical procedure that is only indicated when a patient has an anticipated need for peritoneal dialysis therapy. These factors prevent the use of an experimental study design (i.e. a randomized controlled trial) to investigate the relationship in question. This said, the most accurate and ethical design is an observational, analytical prospective cohort study.

The use of an observational study (versus an experimental study) introduces selection biases that would be avoided with random allocation of subjects to study arms. This also reduces the internal validity of our study. However, for the above reasons, this bias was deemed unavoidable in light of the goals of our study.

Recruiting from a consortium introduces potential response bias, in that this method of recruitment will limit to patients who have access to consortium/want to participate in research. This may involve potential differences such as socioeconomic status or education level that would make our cohort different than the general population and therefore less generalizable to the population of pediatric ESRD patients as a whole. This could become relevant if our cohort had different eating/exercise habits than the

general population, confounding our potential association of weight change and treatment with PD. However, in order for our study to remain feasible and able to be completed in a reasonable timeline, this method will be utilized.

Lastly, our exclusion criteria limit our study population to pediatric patients who have not been on a method of dialysis in the past. This reduces the external validity of our study, as some of the pediatric ESRD population initiating PD has been on a method of dialysis in the past. According to the most recent data from the United States Renal Data System, a total of 1277 children were listed for renal transplant in the year 2013, 447 of which had already been transplanted in the past and were being listed for a repeat transplant.<sup>1</sup> This data report also states that pediatric repeat transplants range from 9-13% of total renal transplants over the years 2000-2013<sup>1</sup>. This said, a portion of children on RRT is waiting for a repeat transplant, and have likely been on a method of dialysis in the past. ESRD is a disease that must be treated with RRT for the remainder of a patient's life, often resulting in the use of different RRT methods as well as switching between methods based on the patient's medical status.

### **Clinical and Public Health Significance**

Further understanding of the relationship between PD and weight change in the pediatric ESRD patient can contribute to improved clinical outcomes in these patients. If PD's effect on patient weight is better understood, dialysis prescription can be altered to improve outcomes in pediatric ESRD patients. Additionally, improved understanding of the effects of peritoneal glucose load on weight change could stimulate further research into interventions or alternatives for use in dialyzed children, to avoid weight gain that is not explained by normal growth.



Alternatives to dextrose-based solutions are currently being investigated for use in PD therapy. Current research focuses on icodextrin solution use (a glucose polymer), and amino-acid solution use in peritoneal dialysis.<sup>2</sup> Although at this time, icodextrin is only used for long-dwell peritoneal dialysis, and amino acid dialysate is not yet approved in this country, these options could change in availability and usage in the future. Further understanding of the relationship of peritoneal glucose load and weight change in pediatric patients could significantly contribute to decisions regarding possible glucose alternative use in the pediatric population.

Alternative biochemical PD solutions are currently being studied, including use of icodextrin, a glucose polymer, and use of amino acids as osmotic agents in the dialysate. Pharmacologically active agents, and bimodal long-dwell solutions are other alternatives currently being investigated in the field.<sup>2</sup>

A 2010 study by Cho et al. comparing use of glucose based PD versus icodextrin based PD showed that the use of icodextrin resulted in less body weight and fat mass changes.<sup>3</sup> This said, possibilities exist to improve dialysis prescription in pediatric patients by using alternative osmotic agents, but a better understanding of the effects of glucose as the osmotic agent is necessary to allow for improvements in dialysis prescription contents that are more biocompatible with pediatric patients and allow for better outcomes when treating these patients' ESRD.

Amino acid dialysate is an alternative to dextrose that is being investigated. Research shows that the use of amino acid based dialysate has resulted in lower serum glucose levels compared to glucose based dialysate solutions.<sup>4</sup> It has not yet been approved for use in the U.S., but it could be available as an alternative to glucose use as

the osmotic agent in the future. A study performed in Toronto found that in pediatric PD patients, amino acid usage as the dialysate osmotic agent was similar in effectiveness to glucose based dialysate usage.<sup>5</sup> Measures of effectiveness included creatinine clearance, ultrafiltration, and absence of adverse effects.<sup>5</sup>

Other things that can be done to reduce glucose exposure in PD patients involve improving ultrafiltration (removal of excess fluid across the peritoneal membrane during dialysis) efficiency and lessening the amount of glucose used to achieve peritoneal UF.<sup>6</sup> This can be done with fluid intake restriction and/or dietary sodium restriction. Hemodialysis is another option of RRT that can be used in the pediatric population. Alternatives to glucose based PD do exist in the pediatric population. This said, understanding the relationship of glucose based PD to weight change and obesity in pediatric ESRD patients, which will arm providers with better abilities to prescribe RRT, is vital to optimal outcome.

The results of our study also have the potential for public health benefits, some of which pertain to a possible decreased time to renal transplantation. As explained in Chapter 1, obesity can act as a barrier to renal transplantation or delay renal transplantation. Expanding the knowledge base and tools available to prevent weight gain and obesity in dialyzed children could potentially lead to sooner renal transplantation in these children. Not only could this improve the quality of life and clinical outcome of the child, but it could reduce the cost of treating the patient's ESRD. Research shows that renal transplantation is more cost-effective than dialysis therapy.<sup>7</sup> The most recent data from the United States Renal Data System indicate that the per

patient per year cost of PD therapy is \$69,919, while the per patient per year cost of renal transplantation is 29,920.<sup>8</sup>

Other potential public health benefits involve the cost and other consequences of obesity in the United States. Although data gained from this study pertain to the pediatric ESRD population, pediatric obesity has long term effects, including future blood pressure and cardiovascular disease outcomes.<sup>9</sup> The American Medical Association estimates obesity contributing to United States mortality rate with 112,000 deaths per year.<sup>9</sup> The AMA characterizes these deaths as preventable.<sup>9</sup> Additionally, obesity has a large economic burden, with the most recent data from the American Medical Association equating the cost of obesity (in 2008) over the duration of one year's time to 147 billion dollars.<sup>9</sup> This said, information that could potentially alleviate the burden of obesity in the pediatric population may, in turn, improve the country's public health outcomes. This is information we hope to gain from our study.

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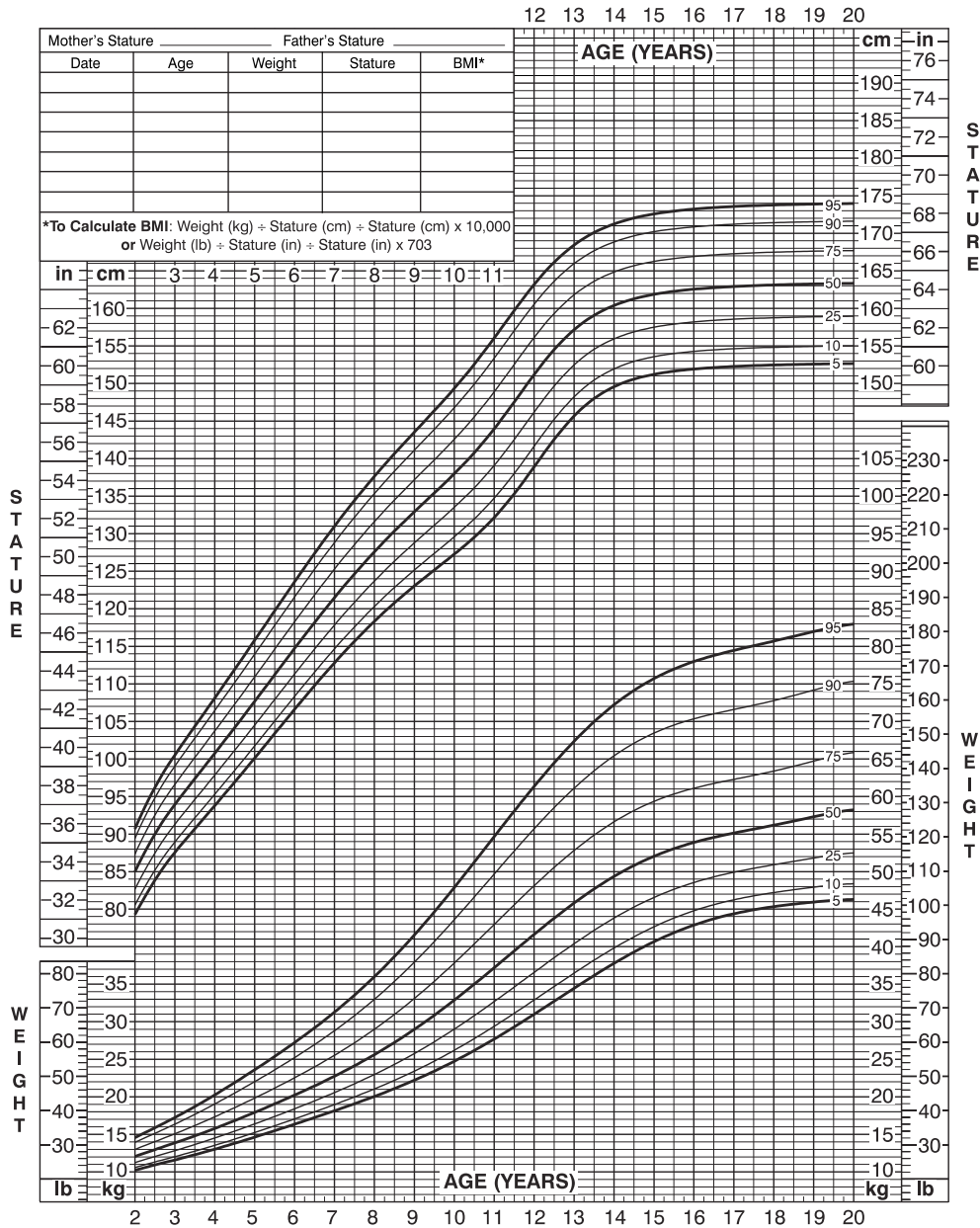
# Appendix A: CDC Growth Charts

2 to 20 years: Girls

NAME \_\_\_\_\_

Stature-for-age and Weight-for-age percentiles

RECORD # \_\_\_\_\_



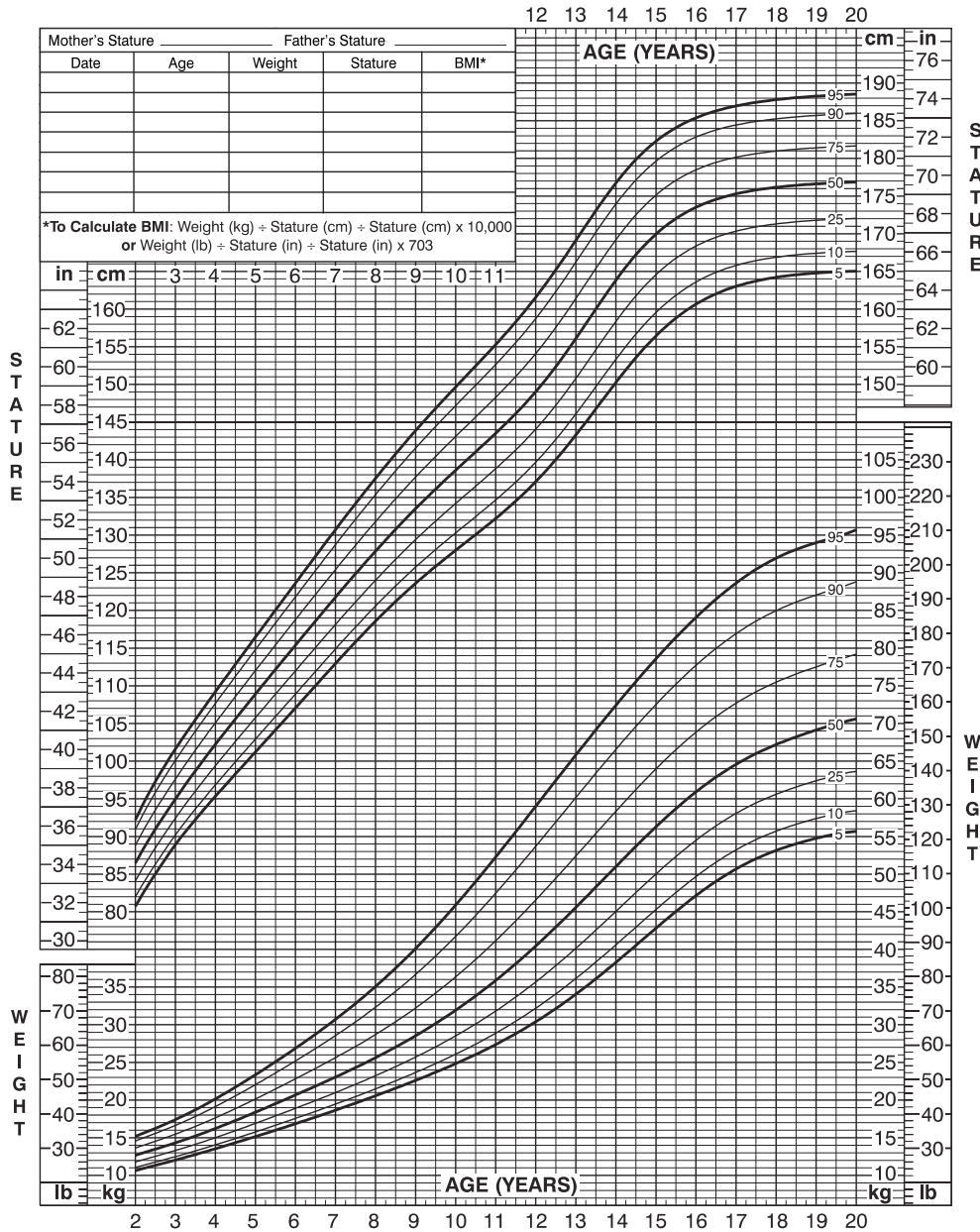
Published May 30, 2000 (modified 11/21/00).  
SOURCE: Developed by the National Center for Health Statistics in collaboration with  
the National Center for Chronic Disease Prevention and Health Promotion (2000).  
<http://www.cdc.gov/growthcharts>



**2 to 20 years: Boys**  
**Stature-for-age and Weight-for-age percentiles**

NAME \_\_\_\_\_

RECORD # \_\_\_\_\_



Published May 30, 2000 (modified 11/21/00).

SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).  
<http://www.cdc.gov/growthcharts>



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## Appendix B: Sample Size Calculations

Power and Sample Size Program: Main Window

File Edit Log Help

Survival t-test Regression 1 Regression 2 Dichotomous Mantel-Haenszel Log

[Studies that are analyzed by](#)

**Output**

[What do you want to know?](#) Sample size

[Sample Size](#) 33

---

**Design**

[Paired or independent?](#) Paired

---

**Input**

$\alpha$  .05  $\delta$  2.5  $\sigma$  5

[power](#) .8

Calculate

Graphs

---

**Description**

We are planning a study of a continuous response variable from matched pairs of study subjects. Prior data indicate that the difference in the response of matched pairs is normally distributed with standard deviation 5. If the true difference in the mean response of matched pairs is 2.5, we will need to study 33 pairs of subjects to be able to reject the null hypothesis that this response difference is zero with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05.

PS version 3.1.2

Copy to Log Exit

Logging is enabled.

Power and Sample Size Program: Main Window

File Edit Log Help

Survival t-test Regression 1 Regression 2 Dichotomous Mantel-Haenszel Log

[Studies that are analyzed by](#)

**Output**

[What do you want to know?](#) Sample size

[Sample Size](#) 17

---

**Design**

[Paired or independent?](#) Paired

---

**Input**

$\alpha$  .05  $\delta$  3.59  $\sigma$  5

*power* .8

Calculate

Graphs

---

**Description**

We are planning a study of a continuous response variable from matched pairs of study subjects. Prior data indicate that the difference in the response of matched pairs is normally distributed with standard deviation 5. If the true difference in the mean response of matched pairs is 3.59, we will need to study 17 pairs of subjects to be able to reject the null hypothesis that this response difference is zero with probability (power) 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05.

PS version 3.1.2

Copy to Log Exit

Logging is enabled.



## **Appendix C: Parental Compound Authorization Form**

### COMPOUND AUTHORIZATION AND PARENTAL PERMISSION FOR PARTICIPATION IN A RESEARCH PROJECT

**310 FR. 3a (2016-1)**

YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL

**Study Title:** Effect of Peritoneal Dialysis on Weight Change in Pediatric Patients

**Principal Investigator:** Lindsey Belliveau, PA-SII

#### Invitation to Participate and Description of Project

We are inviting your child to participate in a research study designed to look at weight change in pediatric patients in their first year of PD therapy. Your child has been asked to participate because he/she has been prescribed peritoneal dialysis to treat his/her renal disease.

In order to decide whether or not you wish your child to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This permission form gives you detailed information about the research study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, and any risks of the procedures. Once you understand the study, you will be asked if you wish your child to participate; if so, you will be asked to sign this form.

#### **Description of Procedures**

If you agree to your child participating in this study, we will record your child's weight at the start of peritoneal dialysis therapy, and every six months thereafter for a total of 12 months. At the start of the study, we will also record laboratory testing results and characteristics of your child like appetite and exercise level.

- *We will utilize your child's past medical record to obtain past measurements of growth (height and weight) to predict how much their weight will change with normal growth during the 12 months of the study, which we will compare with their actual weight change during the study.*
- *Under HIPAA the consent form and HIPAA Research Authorization form (RAF) can be combined for the same study, e.g., a single research purpose.*

#### **Risks and Inconveniences**

- *The measurements we will use in this study are things that are routinely done at dialysis checkups, regardless of study participation. The only difference is that*

*we would be recording these measurements and using them for an additional purpose, to investigate the relationship of peritoneal dialysis use and weight change.*

- There are no physical risks associated with this study. However there is the possible risk of loss of confidentiality. Every effort will be made to keep your child's information confidential; however, this cannot be guaranteed.

### **Benefits**

- *There is no likelihood that your child will benefit directly from participation in this study, but the knowledge gained from using your child's weight change and other measurements will add to the general scientific body of knowledge pertaining to peritoneal dialysis use in children. Future endeavors based upon this study may improve the use of peritoneal dialysis therapy in children.*

### **Confidentiality and Privacy**

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Examples of information that we are legally required to disclose include abuse of a child or elderly person, or certain reportable diseases. We will use a locked cabinet to store any written data obtained from this study, and only researchers directly employed by the study will have access to these data. Additionally, any electronic access of data will be done on encrypted devices by individuals employed by the study. When the results of the research are published or discussed in conferences, no information will be included that would reveal your child's identity unless your specific permission for this activity is obtained.

We understand that information about your child obtained in connection with their health is personal, and we are committed to protecting the privacy of that information. If you decide to allow your child to be in this study, the researcher will get information that identifies your child and his or her personal health information. This may include information that might directly identify your child, such as his or her name and age. This information will be de-identified at the earliest reasonable time after we receive it, meaning we will replace your child's identifying information with a code that does not directly identify him or her. The principal investigator will keep a link that identifies your child to his or her coded information, and this link will be kept secure and available only to the PI or selected members of the research team. Any information that can identify your child will remain confidential. The research team will only give this coded information to others to carry out this research study. The link to your child's personal information will be kept for five years, after which time the link will be destroyed and the data will become anonymous. The data will be kept in this anonymous form indefinitely.

*The information about your child's health that will be collected in this study includes:*

#### Research study records

- Medical and laboratory records of only those services provided in connection with this Study.
- The entire research record and any medical records held by the child's nephrologist or primary care provider used in the study
- The following information:
  - Records about phone calls made as part of this research
  - Records about your child's study visits

*Information obtained during this research regarding:*  
*Physical exams*  
*Laboratory, x-ray, and other test results*

Information about your child and your child's health which might identify your child may be used by or given to:

- *The U.S. Department of Health and Human Services (DHHS) agencies*
- Representatives from Yale University, the Yale Human Research Protection Program and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- Those providers who are participants in the Electronic Medical Record (EMR) system.
- Those individuals at Yale who are responsible for the financial oversight of research including billings and payments
- The Principal Investigator Lindsey Belliveau
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- Health care providers who provide services to your child in connection with this study
- Laboratories and other individuals and organizations that analyze your child's health information in connection with this study, according to the study plan
- Co-Investigators and other investigators
- Study Coordinator and Members of the Research Team
- Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study
- 

*By signing this form, you authorize the use and/or disclosure of the information described above for this research study. The purpose for the uses and disclosures you are authorizing is to ensure that the information relating to this research is available to all parties who may need it for research purposes.*

*All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at the Yale School of Medicine and Yale-New Haven Hospital are required to comply with HIPAA and to ensure the confidentiality of your child's*

*information. Some of the individuals or agencies listed above may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However to better protect your child's health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.*

*You have the right to review and copy your child's health information in your child's medical record in accordance with institutional medical records policies.*

This authorization to use and disclose your child's health information collected during your child's participation in this study will never expire.

#### Guidelines:

- Your child's name will be replaced with a numerical code when their data is stored for purposes of the study. However, we will not be able to code other personal information, like age and sex, because this information will be used as a part of the data of our study. However, all information recorded in this study will be stored in a locked cabinet, or on an encrypted computer/device.
- Information about your child's study participation will be entered into your child's Electronic Medical Record (EMR). Once placed in your EMR, these results are accessible to all providers who participate in the EMR system. Information within your child's EMR may also be shared with others who are appropriate to have access to your EMR (e.g. health insurance company, disability provider.)
- Authorized representatives of the Food and Drug Administration (FDA) may need to review records of individual subjects. As a result, they may see your name; but they are bound by rules of confidentiality not to reveal your identity to others.

#### In Case of Injury

If your child is injured while on study, seek treatment and contact the study doctor as soon as you are able.

Yale School of Medicine and Yale-New Haven Hospital do not provide funds for the treatment of research-related injury. If your child is injured as a result of his or her participation in this study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.

You do not give up any of your legal rights by signing this form.

## Voluntary Participation and Withdrawal

You are free to choose not to have your child participate in this study. Refusing to participate will involve no penalty or loss of benefits to which your child is otherwise entitled (such as your child's health care outside the study, the payment for your child's health care, and your child's health care benefits). However, your child will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your child's information as part of this study.

### *Withdrawing From the Study*

If your child does become a subject, he or she is free to stop and withdraw from this study at any time during its course.

To withdraw from the study, you can call a member of the research team at any time and tell them that your child no longer wants to take part. This will cancel any future use of your child's weight measurements and other data for the study.

The researchers may withdraw your child from participating in the research if necessary.

Withdrawing from the study will involve no penalty or loss of benefits to which your child is otherwise entitled. If your child chooses not to participate or if your child withdraws it will not harm your child's relationship with your own doctors or with Yale-New Haven Hospital.

### *Withdrawing Your Authorization to Use and Disclose Your Child's Health Information*

You or your child may withdraw or take away his or her permission to use and disclose his or her health information at any time. You do this by telling the study staff or by writing to the study doctor. If you withdraw your permission, your child will not be able to stay in this study.

When you withdraw your child's permission, no new health information identifying your child will be gathered after that date. Information that has already been gathered may still be used and given to others until the end of the research study, as necessary to insure the integrity of the study and/or study oversight.

### Guidelines:

- *Data will have been anonymized, and your child's name will be replaced by a numerical code. Therefore, we will not be able to delete data that has already been obtained if your child withdraws from the study before the end of the study. However, if your child withdraws, we will not use their data in our analysis or any publication of the study.*

- *If there are medical needs required by the subject upon withdrawal, these should be stated. Any follow-up procedures or assessments accompanying the withdrawal should be clearly explained.*

**Questions**

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the permission form carefully – as long as you feel is necessary – before you make a decision.

**Authorization and Permission**

*I have read (or someone has read to me) this form and have decided to allow my child to participate in the project described above. Its general purposes, the particulars of my child's involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this permission form.*

By signing this form, I give permission to the researchers to use [and give out] information about my child for the purposes described in this form. By refusing to give permission, I understand that my child will not be able to be in this research.

Name of Child: \_\_\_\_\_

Parent 1 Signature: \_\_\_\_\_

Parent 2 Signature (if applicable): \_\_\_\_\_

Date: \_\_\_\_\_

Date: \_\_\_\_\_

\_\_\_\_\_  
Signature of Person Obtaining Permission

\_\_\_\_\_  
Date

*If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator: Lindsey Belliveau, 603-391-2743.*

*If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at (203) 432-5919*

*If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688*



## **Appendix D: Child (age 7-12) Assent Form**

310 FR.1

(2016-1)

Child's Assent for Being in a Research Study  
Yale-New Haven Hospital/Yale University School of Medicine

Title: Effect of Dialysis on Weight Change

### Why am I here?

We are asking you to take part in a research study because we are trying to learn more about dialysis therapy and weight change. We are inviting you to be in the study because you have been prescribed peritoneal dialysis (PD) treatment by your nephrologist (kidney doctor).

### Why are they doing this study?

They are doing this study to see if children on PD have weight change, in addition to the normal weight you gain as you grow. If PD causes this weight change, doctors may be able to help people on PD to prevent this from happening in the future.

### What will happen to me?

You will be weighed on a scale each time you have a dialysis checkup. You will also be asked about your appetite, daily activities during the study. We will also get some tests done to your blood, that are regularly done at dialysis checkups. Some of these measurements will be used in the study.

### Will the study hurt?

The study will not hurt, and there will be no risks to being in the study. The study uses measurements that are regularly done at dialysis checkups.

### What if I have any questions?



You can ask any questions that you have about the study. If you have a question later that you didn't think of now, you can call me or ask me next time.

Do my parents know about this?

This study was explained to your parents and they said that you could be in it. You can talk this over with them before you decide.

Do I have to be in the study?

You do not have to be in the study. No one will be upset if you don't want to do this. If you don't want to be in this study, you just have to tell them. You can say yes now and change your mind later. It's up to you.

Writing your name on this page means that that you agree to be in the study, and know what will happen to you. If you decide to quit the study all you have to do is tell the person in charge.

\_\_\_\_\_  
Signature of Child

\_\_\_\_\_  
Date

\_\_\_\_\_  
Signature of Researcher

\_\_\_\_\_  
Date

## **Appendix E: Adolescent (age 13-17) Assent Form**

### ADOLESCENT ASSENT FOR PARTICIPATION IN A RESEARCH PROJECT

YALE UNIVERSITY SCHOOL OF MEDICINE – YALE-NEW HAVEN HOSPITAL

#### **310 FR 3 (2016-1)**

**Study Title:** *Effect of Peritoneal Dialysis on Weight Change in Pediatric Patients*

**Principal Investigator:** *Lindsey Belliveau, PA-SII*

#### Invitation to Participate and Description of Project

You are invited to take part in a research study that will look at weight change in children on peritoneal dialysis therapy. You have been asked to take part because your doctor has prescribed peritoneal dialysis to treat your kidney disease. Between 50-100 patients will take part in this study, in hospitals and dialysis centers across the United States.

In order to decide whether or not you wish to be a part of this research study, you should know enough about its risks and benefits to make an informed decision. This assent form gives you detailed information about the study, which a member of the research team will discuss with you and your parents. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, and any risks of the procedures.

If you agree to be in this study, we will record your weight at the start of peritoneal dialysis therapy, and every six months thereafter for a total of 12 months. At the start of the study, we will also record some of your laboratory testing results and characteristics like appetite and exercise level.

#### Guidelines:

- *We will utilize your past medical record to obtain past measurements of growth (height and weight) to predict how much your weight will change with normal growth during the 12 months of the study, which we will compare with your actual weight change during the study.*
- *Under HIPAA the consent form and HIPAA Research Authorization form (RAF) can be combined for the same study, e.g., a single research purpose.*

#### Risks and Inconveniences

- *The measurements we will use in this study are things that are routinely done at dialysis checkups, regardless of study participation. The only difference is that we would be recording these measurements and using them for an additional*

*purpose, to investigate the relationship of peritoneal dialysis use and weight change.*

- There are no physical risks associated with this study. However there is the possible risk of loss of confidentiality. Every effort will be made to keep your information confidential; however, this cannot be guaranteed.

### **Benefits**

#### Guidelines:

- *There is no likelihood that you will benefit directly from participation in this study, but the knowledge gained from using your weight change and other measurements will add to the general scientific body of knowledge pertaining to peritoneal dialysis use in children. Future endeavors based upon this study may improve the use of peritoneal dialysis therapy in children.*

### **Confidentiality and Privacy**

#### Guidelines:

- We will use a numerical code to replace your name when recording data for our study. However, we will not be able to code other personal information, like age and sex, because this information will be used as a part of the data of our study. However, all information recorded in this study will be stored in a locked cabinet, or on an encrypted computer/device.
- Information about your study participation will be entered into your Electronic Medical Record (EMR). Once placed in your EMR, these results are accessible to all providers who participate in the EMR system. Information within your EMR may also be shared with others who are appropriate to have access to your EMR (e.g. health insurance company, disability provider.)
- Authorized representatives of the Food and Drug Administration (FDA) may need to review records of individual subjects. As a result, they may see your name; but they are bound by rules of confidentiality not to reveal your identity to others.

Any identifiable information that we obtain about you during this study will stay confidential and will be shared only if you agree to it. There are also situations where we would have to release your identifiable information (your name for example) according to the U.S. or State law. Examples of information that we have to report to authorities include abuse of a child, certain reportable diseases (such as being HIV positive or having Hepatitis B), or when we believe you may harm yourself or someone else. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless you allow us to do so.

*We understand that information about your health is personal, and we are committed to protecting the privacy of that information. If you decide to be in this study, the researchers will get information that identifies you and your personal health information. For example, we will collect age and sex. This information will be de-identified as soon as possible, which means that we will replace your identifying information with a code. The principal investigator (the person who is responsible for this research) will keep a link that matches you to your coded information, and this link will be kept safe and available only to a few people on this research team. The link to your personal information will be kept for five years, and then it will be destroyed and the data will become anonymous. The data will be kept in this anonymous form indefinitely. We will use a locked cabinet to store any written data obtained from this study, and only researchers directly employed by the study will have access to these data. Additionally, any electronic access of data will be done on encrypted devices by individuals employed by the study. The research team will only give coded information to others to carry out this research study.*

*The information about your health that will be collected in this study includes:*

- Research study records
- Medical and laboratory records of only those services provided in connection with this Study.
- The entire research record and any medical records obtained during the study
- The following information:
  - Records about phone calls made as part of this research
  - Records about your study visits

Information about you and your health may be used by or given to:

- *The U.S. Department of Health and Human Services (DHHS) agencies*
- *Representatives from Yale Human Research Protection Program and the Yale Human Investigation Committee (the committee that reviews, approves, and monitors research on human subjects), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.*
- *Those providers who are participants in the Electronic Medical Record (EMR) system.*
- *Those individuals at Yale who are responsible for the financial oversight of research including billings and payments*
- *The Principal Investigator Lindsey Belliveau*

Select as appropriate the following additional groups with whom the data may be shared and delete those that do not apply.

- *The U.S. Food and Drug Administration (FDA)*
- *Governmental agencies to whom certain diseases (reportable diseases) must be reported*

- *Health care providers who provide services to you in connection with this study.*
- *Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan.*
- *Co-Investigators and other investigators*
- *Study Coordinator and Members of the Research Team*
- *Data and Safety Monitoring Boards and others authorized to monitor the conduct of the Study: List any separate or local committees not in the protocol, if applicable*

By signing this form, you let us use the information in the way we described above for this research study. *This authorization to use and disclose your health information collected during your participation in this study will never expire.*

*The research staff at the Yale School of Medicine and Yale New Haven Hospital have to obey the privacy laws and make sure that your information stays confidential. Some of the people or agencies listed above may not have to obey those laws, which means that they do not have to protect the data in the same way we do. They could use or share your information in ways not mentioned in this form. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.*

### **In Case of Injury**

If you are injured while on study, seek treatment and contact the study doctor as soon as you are able.

Yale School of Medicine and Yale New Haven Hospital do not provide funds for the treatment of research-related injury. If you are injured as a result of your participation in this study, treatment will be provided. Your parents or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available.

You do not give up any of your legal rights by signing this form.

### **Voluntary Participation and Withdrawal**

You do not have to take part in this study. Refusing to participate will involve no penalty or loss of benefits to which you are otherwise entitled (such as your health care outside the study, the payment for your health care, and your health care benefits). Your health care outside the study will not change if you do not agree to participate. However, you will not be able to enroll in this research study and will not receive study procedures as a study participant if you do not allow use of your information as part of this study.

### **Withdrawing From the Study**

If you decide to take part in this study, and then change your mind, you can always stop and withdraw from this study at any time during its course. Withdrawing from the study will involve no penalty or loss of benefits to which you are otherwise entitled. It will not harm your relationship with your own doctors or with Yale New Haven Hospital.

To stop your participation in the study, you can call a member of the research team at any time and tell them that you no longer want to take part. This will cancel any future appointments.

The researchers may withdraw you from participating in the research if necessary.

### Withdrawing your Authorization to Use and Share Your Health Information

If you do not want researchers to use and disclose your health information as described in the Confidentiality section, you and your parent(s) may withdraw your permission by telling the study staff or by writing to Lindsey Belliveau at the Yale University Physician Associate Program, New Haven, CT 06520.

When you do that, no new health information identifying you will be collected after that date. Again, the investigators will be able to use the information that they already collected about you to finish the study.

If you withdraw your authorization, you will not be able to stay in this study.

### Questions

We have used some complicated terms in this form. Please feel free to ask about anything you don't understand and to think about this research and the assent form carefully – as long as you need to – before you make a decision. We encourage that you talk to your family about your decision as well. If you come up with questions after reading this form, you can call me at 603-391-2743.

**Authorization and Permission**

*I have read (or someone has read to me) this form and have decided to participate in the project described above. Its general purposes, the things I will do in the study and possible risks and inconveniences have been explained to my satisfaction. My signature also shows that I have been given a copy of this assent form.*

By signing this form, I give permission to the researchers to use [and give out] information about me for the reasons described in this form. If I decide not to give permission, I understand that I will not be able to be in this research.

Name of Subject: \_\_\_\_\_

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

\_\_\_\_\_  
Signature of Person Obtaining Assent

\_\_\_\_\_  
Date

*If you have further questions about this project or if you have a research-related problem, you may contact the Principal Investigator [Lindsey Belliveau, 603-391-2743](#). If you would like to talk with someone other than the researchers to discuss problems, concerns, and questions you may have concerning this research, or to discuss your rights as a research subject, you may contact the Yale Human Investigation Committee at (203) 785-4688. If after you have signed this form you have any questions about your privacy rights, please contact the Yale Privacy Officer at (203) 432-5919.*

**Appendix F: Data Collection Form**

**Patient Identification Number:** \_\_\_\_\_

**Descriptive Characteristics, measured once at start of study (time zero)**

Age	
Gender	
Race	
Primary diagnosis leading to ESRD	
Peritoneal Equilibration Test results	
Laboratory values	
Socioeconomic Status	

**Descriptive Characteristics of the Cohort, measured monthly**

	Time zero	1	2	3	4	5	6	7	8	9	10	11	12
Urine Output													
Prescription of erythropoietin													
Prescription of growth hormone													
Daily dialysate volume													
Appetite													
Physical Activity Level													

**Weight from prior health records**

Month prior to starting PD	Weight (kg)
1	
2	
3	
4	
5	
6	
7	
8	



9	
10	
11	
12	

**Expected weight change (from CDC growth charts)**

Months of PD use	Expected weight using CDC growth charts (kg)
Time zero (start of PD)	
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	

**Actual weight change (during PD therapy)**

Months of PD Use	Actual weight (kg)
Time zero (start of PD)	
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	

**Secondary Outcome (Weight change) Calculation**

**Weight Change= (Actual weight change) - (Expected Weight Change)**

Month	Expected Weight Change	Actual Weight Change	Weight Change
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			

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