Amendment

Protocol Number: 14C0021-D **Reference Number:** 365270

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Protocol Title: Randomized Control Trial of Adrenalectomy versus Observation for Subclinical Hypercortisolism

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PI is the Accountable Investigator

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* Signature signifies that investigators on this protocol have been informed that the collection and use of personally identifiable information at the NIH are maintained in a system of record governed under provisions of the Privacy Act of 1974. The information provided is mandatory for employees of the NIH to perform their assigned duties as related to the administration and reporting of intramural research protocols and used solely for those purposes. Questions may be addressed to the Protrak System Owner.

** I have reviewed this research project and considered the NIH Policy for Inclusion of Women and Minorities in Clinical Research. Taking into account the overall impact that the project could have on the research field involved, I feel the current plans adequately includes both sex/gender, minorities, children, and special populations, as appropriate. The current enrollment is in line with the planned enrollment report for inclusion of individuals on the basis of their sex/gender, race, and ethnicity and is appropriate and of scientific and technical merit.

IRB Meeting Date: Expedited

DEC Clearance Date: NA

Protocol Version Date: 12/19/2016

Abbreviated Title: Subclinical Hypercortisolism

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Investigators roles:

A. *Obtain information by intervening or interacting with living individuals for research purposes*
B. *Obtaining identifiable private information about living individuals*

C. Obtaining the voluntary informed consent of individuals to be subjects

D. Makes decisions about subject eligibility

E. Studying, interpreting, or analyzing identifiable private information or data/specimens for research purposes

F. Studying, interpreting, or analyzing de-identified data or specimens for research purposes

G. *Some/all research activities performed outside NIH*

Investigational Agents: None

Précis

Background:

- Adrenal incidentalomas are common and found in approximately 4-7% of the population.
- About 0.6 to 25% of patients with an adrenal incidentaloma are found to have subclinical hypercortisolism: 2.3% develop subclinical hypercortisolism during follow up and 0.6% develop clinical hypercortisolism during follow up.
- Subclinical hypercortisolism is defined as biochemical excess of cortisol without signs and symptoms of overt hypercortisolism but may be associated with metabolic complications or disease progression and malignancy.
- Overt signs and symptoms of hypercortisolism include facial plethora, easy bruising, violaceous straiae, and proximal muscle weakness.
- Several studies suggest that subclinical hypercortisolism may lead to long term consequences such as diabetes, hypertension, hypercholesterolemia, obesity, and osteoporosis.
- Thus, patients with subclinical hypercortisolism may benefit from operative intervention to halt or reverse metabolic complications associated with the disease and the risk of malignant progression.
- The optimal management of patients with subclinical hypercortisolism and adrenal incidentalomas is controversial and no large randomized trial has been conducted.
- We hypothesize that operative treatment would reduce the risk of long term complications of subclinical hypercortisolism and malignant progression, and propose a prospective randomized trial comparing nonoperative and operative management of subclinical hypercortisolism in patients with an adrenal neoplasm.

Objectives:

Primary Endpoints:

- To determine whether unilateral adrenalectomy in patients diagnosed with subclinical hypercortisolism and adrenal neoplasm results in normalization and/or improvement of hypertension as assessed by reduction in pharmacotherapy and/or normalization of blood pressure (systolic pressure <=140 and diastolic pressure <=90), diabetes as assessed by reduction or elimination of pharmacotherapy and/or improvement in A_1C to <6.5%, osteoporosis by increase in bone formation markers indicative of increased bone formation, hypercholesterolemia as assessed by a reduction or elimination of pharmacotherapy and/or reduction in LDL levels to risk-stratified goal levels as defined by ATP III, and/or overweight or obesity as assessed by a 10 percent reduction in weight at 6 months.

Eligibility:

- An individual with an adrenal neoplasm less than 5 cm in size with biochemically confirmed evidence of hypercortisolism (2 out of 3: dexamethasone suppression test (DST) >3 mcgl/dL, elevated urine free cortisol, and/or morning ACTH <2.2 pmol/l) without overt clinical signs and symptoms.
- Age greater than or equal to 18 years.
- Adults must be able to understand and sign the informed consent document.

- Patients must have laboratory and physical examination parameters within acceptable limits based on standard clinical practice.

Design:

- Prospective randomized study comparing adrenalectomy versus observation.
- Patients assigned to the operative arm will undergo adrenalectomy and then followed postoperatively for normalization and/or improvement of metabolic complications associated with hypercortisolism and histologic examination of the resected tumor.
- Patients assigned to the non-operative arm will be monitored for possible complications associated with hypercortisolism for six months, at which point they will cross-over to the operative intervention arm.
- Patients with bilateral adrenal neoplasms will have the larger adrenal neoplasm used as the primary lesion responsible for subclinical hypercortisolism.
- Demographic, clinical, laboratory and pathologic data will be collected for each patient participant. Data will be securely stored in a computerized database.
- Patients will have biochemical testing to determine if their adrenal neoplasm is functioning or nonfunctioning.
- Projected accrual will be 15 to 20 patients per year for a total of 5 years. Thus, we anticipate accruing 62 patients on this protocol.

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1. INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective

- To determine whether unilateral adrenalectomy in patients diagnosed with subclinical hypercortisolism and an adrenal neoplasm results in normalization and/or improvement of hypertension as assessed by reduction in pharmacotherapy and/or normalization of blood pressure (systolic pressure <=140 and diastolic pressure <=90), diabetes as assessed by reduction or elimination of pharmacotherapy and/or improvement in A_1C to <6.5%, osteoporosis by increase in bone formation markers indicative of increased bone formation, hypercholesterolemia as assessed by a reduction or elimination of pharmacotherapy and/or reduction in LDL levels to risk-stratified goal levels as defined by ATP III, and/or overweight or obesity as assessed by a10 percent reduction in weight at 6 months.

1.1.2 Secondary Objectives:

- To determine the risk of primary adrenal malignancy in patients with subclinical hypercortisolism and adrenal mass less than 5 cm.
- To determine whether FDG PET/CT scan is diagnostic of subclinical hypercortisolism.
- To determine the optimal diagnostic test for subclinical hypercortisolism.
- To determine whether patients show an improvement in quality of life after adrenalectomy compared to medical therapy.
- To determine whether patients have an increased risk of deep venous thrombosis with subclinical hypercortisolism, regardless of treatment.
- To determine whether dermal thickness is diagnostic of subclinical hypercortisolism.
- To determine whether ultrasound of the skin is diagnostic and is able to show resolution of subclinical hypercortisolism after adrenalectomy.

1.2 BACKGROUND AND RATIONALE

The advent of widespread use of computed tomography has resulted in an increase in detection of incidentally discovered adrenal masses termed adrenal incidentalomas (**1**). These adrenal incidentalomas have an estimated prevalence of 4-7% in the adult population (**2, 3**). The prevalence of these masses increases with age: the prevalence is 0.2% in young patients compared to 6.9% in subjects older than 70 years of age (**4**). The majority of these masses, 65 to 90%, are nonfunctioning adenomas (hormonally inactive). However, the remaining masses are hormonally active and may secrete excess cortisol, aldosterone, androgens, or catecholamines (**4**). Excess cortisol secretion may manifest as Cushing's syndrome, which is clinically identifiable with specific physical findings such as facial plethora, easy bruising, violaceous straiae, and proximal muscle weakness (**5**). A subset of patients, however, will have biochemical evidence of excess cortisol without these overt clinical signs and/or symptoms. It is estimated approximately 0.6 to 30% of patients with an adrenal incidentaloma and biochemical evidence of abnormal cortisol secretion will manifest in this manner. These patients are diagnosed with subclinical hypercortisolism **(2, 3, 6)**. An estimated prevalence of subclinical hypercortisolism, therefore, in the adult population is between 0.2 and 2.0% (**3**). The excess cortisol secretion may

lead to metabolic consequences that can adversely affect patients, which may be ameliorated by an adrenalectomy. This study is designed to provide answers to the optimal therapeutic management of patients with an adrenal neoplasm and subclinical hypercortisolism.

One of the major implications of the relative high prevalence of adrenal incidentalomas is the risk of malignancy that these incidentally discovered masses confer regardless of hormonal status. As the US population continues to age, *a priori* the prevalence will continue to increase. One of the most reliable factors that separate benign from malignant masses is size. In one of the largest retrospective studies of incidentally discovered masses, Mantero et. al. demonstrated that size is reliable in predicting malignancy. The retrospective multicenter study evaluated 1,004 patients with adrenal incidentalomas over a 15 year period. Of these 1,004 patients, 380 patients underwent adrenalectomy. Benign adenomas were significantly smaller than carcinomas (median 3.5 cm versus 7.5 cm, $p<0.001$), and that a cut-off at 4.0 cm had the highest sensitivity (93%) in differentiating benign from malignant tumors. Although at this size cut-off there was poor specificity (42%) and poor positive predictive value (16%), the negative predictive value was 98%. The implication of this study is any adrenal incidentaloma over 4 cm warrants strong consideration towards operative intervention regardless of hormonal status, as the authors recommend. However, if the 5 cm mass size is used as a cut-off, the sensitivity decreases to 81%, but the specificity increases to 63% (**7**). Due to the increase in specificity and risk of malignancy, we therefore will use 5 cm as our upper limit size threshold for this randomized control trial comparing adrenalectomy to observation as there are no prospective studies which have adequately ascertained risk of malignancy for adrenal incidentalomas. Although hypercortisolism status was not associated with the risk of malignancy, these masses can be functionally active resulting in adverse metabolic consequences. Patients with subclinical hypercortisolism have similar metabolic consequences as Cushing's syndrome such as diabetes, hypertension, dyslipidemia, and osteoporosis, and therefore may also benefit from treatment **(8-15**). The natural history of subclinical hypercortisolism and the prevalence of these metabolic complications, and the unknown risk of malignancy provides a basis and rationale for potential surgical intervention.

The natural history of subclinical hypercortisolism is associated with progression and consequences of metabolic diseases (**3**). Studies have shown that cortisol excess may lead to or contribute to long term consequences such as hypertension, diabetes, dyslipidemia, obesity, and osteoporosis **(1, 14, 16**). In these patients, hypertension has a prevalence of 33% to 89% **(8-15, 17**), diabetes and/or impaired glucose metabolism has a prevalence of 15 to 66% **(8-15, 17, 18**), dyslipidemia has a prevalence of 23 to 77% (8**, 10-12, 14, 17-18**), overweight and/or obesity has a prevalence of 19 to 75% (**8, 10-12, 14**), and osteoporosis has a prevalence of 30% (**10**).

Because of the high prevalence of cardiovascular disease in subclinical hypercortisolism in patients with a unilateral adrenal neoplasm some investigators have compared patients with subclinical hypercortisolism with a unilateral adenoma to patients with a nonfunctioning unilateral adrenal neoplasm to assess the consequences and contribution of increased cortisol secretion. A recent large cross-sectional study by Di Dalmazi, et. al., showed patients with subclinical hypercortisolism to have a higher prevalence of type 2 diabetes, coronary heart disease, osteoporosis, and fractures when compared to patients with nonfunctioning adrenal neoplasms. Over a ten year period, 348 eligible patients with an adrenal incidentaloma were included and divided into four groups consisting of patients with nonfunctional adenomas

(n=203), characterized by a cortisol response less than 1.8 µg/dL after the 1 mg dexamethasone suppression test (DST) or as subclinical hypercortisolism (n=19), characterized by a cortisol response to DST of > 5 µg/dL. The remaining patients had an intermediate response to the DST and either urinary free cortisol and/or plasma ACTH that were abnormal (n=71), or normal (n=55). Compared to non-functioning adenomas, those with subclinical hypercortisolism had an increased prevalence of type 2 diabetes (42.1% vs. 15.2%, p<0.01), coronary heart disease (26.3% vs. 2.9%, p<0.01), and osteoporosis (47.3% vs. 14.8%, p<0.01). Although hypertension was highly prevalent in the subclinical hypercortisolism group compared to the nonfunctioning adenoma group (94.7% vs. 73.4%), this was not statistically significant (p=0.173). There was a significant association between coronary heart disease (odds ratio (OR), 6.104; 95% CI, 1.41-26.49, p=0.016), type 2 diabetes (OR, 3.443; 95% CI, 1.181-10.038, p=0.024), osteoporosis (OR, 5.940; 95% CI, 1.793-19.677, p=0.004), and osteoporotic fractures (OR, 6.530; 95% CI, 1.292-32.994, p=0.023) when comparing the subclinical hypercortisolism and nonfunctioning adenoma groups. The data from this study indicates that there is an increased prevalence and association of adverse metabolic and cardiovascular disease in patients with subclinical hypercortisolism (**19**).

Although Di Dalmazi, et. al. did not find an increased prevalence of hypertension amongst patients with subclinical hypercortisolism compared to nonfunctioning adenomas (**19**), a recent study by Oki, et. al. clearly demonstrated a higher prevalence of hypertension. The study included 80 patients with adrenal neoplasms and were divided into three groups: nonfunctioning adenomas (n=53), subclinical hypercortisolism (n=13, mildly elevated cortisol following a 1-mg dexamethasone suppression test without any other hypothalamic-pituitary-adrenal (HPA) axis abnormality), and subclinical Cushing's syndrome (n=14, elevated cortisol following a 1-mg dexamethasone suppression test with at least one other HPA axis abnormality). The prevalence of hypertension was clearly increased in the subclinical hypercortisolism (78.6%) and subclinical Cushing's syndrome (84.6%) groups compared to the nonfunctioning group (39.6%) (p=0.002). The investigators assessed the odds of hypertension for subclinical hypercortisolism compared to nonfunctioning adenomas and found an 11.7-fold increased risk (CI 1.9-72.7, p=0.009). Similarly, the odds of hypertension for subclinical Cushing's syndrome compared to nonfunctioning adenomas showed a 9.5-fold increased risk (CI 1.9-48.3, p=0.007). Although the authors did not discuss treatment, *a priori* one would hypothesize adrenalectomy as potentially beneficial in these patients (**13**).

Another disease process that is affected by hypercortisolism is osteoporosis. A multicenter study in Italy addressed the prevalence of bone mineral density, fracture risk and quality of bone architecture in patients with osteopenia (control), unilateral adrenal incidentalomas with and without subclinical hypercortisolism. Two hundred and eight-seven patients with unilateral adrenal incidentalomas were evaluated for subclinical hypercortisolism, bone mineral density, and spinal fracture. Of these 287 patients, 85 were diagnosed with subclinical hypercortisolism. The study also included a control group of 194 patients without adrenal incidentalomas for comparison. A comparison of patients (n=85) with subclinical hypercortisolism, adrenal incidentaloma patients without subclinical hypercortisolism (n=202), and controls (n=194) revealed a significantly lower bone mineral density (lumbar spine -0.73 ±1.43, 0.17 ±1.33, 0.12 ±1.21, respectively, p=0.0001; femoral neck -0.37 ±1.06, 0.07 ±1.09, 0.17 ±1.02, respectively, p=0.001), higher fracture prevalence (70.6, 22.2, 21.8%, respectively, P<0.0001) and spinal deformity (calculated index by summing the grade of deformity for each vertebra, p<0.0001) in

patients with subclinical hypercortisolism. Fractures and spinal deformity were associated with subclinical hypercortisolism (odds ratio of 7.27, 95% CI 3.94-13.41, p = 0.0001) (**20**).

These aforementioned studies describe the natural history of subclinical hypercortisolism and report variable rates of metabolic disease prevalence in this population. Part of the reason for this variability is the difficulty and variable criteria used to diagnosing subclinical hypercortisolism. The most common tests to diagnosis subclinical hypercortisolism include lack of cortisol suppression after 1-mg overnight dexamethasone suppression test (DST), elevated urinary free cortisol (UFC) levels, loss of cortisol secretion circadian rhythm, altered cortisol and ACTH response to CRH stimulation, low basal ACTH, and/or low dehydroepiandronsterone sulfate (DHEAS). Of these tests, the most common test to screen and diagnose subclinical hypercortisolism is the 1-mg DST test. However, there is no consensus for the optimal cut-off value for suppression of cortisol (**3, 21-22**). The current American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons medical guidelines for the management of adrenal incidentalomas recommends a cutoff of 5 µg/dL, which is associated with a sensitivity of 58% and specificity of 100% (**21**). Other guidelines, such as the French Society of Endocrinologist recommend a lower cutoff of 1.8 µg/dL, citing the lack of consensus (**22**). Researchers have also used ^{131}I-6β-iodomethyl norcholesterol scintigraphy (IMS) to assess cortisol secretion in adrenal incidentalomas. Valli et. al. assessed the uptake of 31 patients with benign cortical neoplasms. Of the 31 patients, 19 patients had unilateral uptake and 12 patients had bilateral uptake. The patients with unilateral uptake showed lower ACTH concentrations (p=0.0005), higher midnight cortisol concentrations (p=0.02), disrupted diurnal variation of serum cortisol (p=0.02), and higher cortisol concentrations after a 1-mg dexamethasone suppression test (p=0.01). Assessing various dexamethasone suppression test cut-offs, the authors found a 2.2 µg/dL cut-off to have a sensitivity of 100% and specificity of 67% (**23**). Thus, a cut-off lower than 5 µg/dL but higher than 2.2 µg/dL may offer a compromise in terms of sensitivity and specificity.

Since there are no overt clinical signs of cortisol excess and many of the metabolic complications are concomitantly prevalent in the elderly, an interesting study by Morelli, et. al. attempted to address diagnosis of subclinical hypercortisolism by correlating between biochemical diagnostic criteria and clinical metabolic manifestations. Biochemical data from 231 patients with unilateral adrenal incidentalomas was evaluated. The different criteria consisted of various combinations of 1-mg dexamethasone suppression test with varying cut-offs, elevated urinary fractionated cortisol and low basal ACTH. The metabolic complications evaluated included hypertension, type 2 diabetes, and vertebral fractures. The study showed having 2 out of 3 positive results from a combination of a DST cut-off value of >82.8 nmol/l (~3 µg/dL), elevated urinary free cortisol, and low morning ACTH (<2.2 pmol/l) to have a sensitivity of 61.9% and a specificity of 77.1% of predicting the concomitant presence of all three metabolic complications (p=0.001) (**24**). Given the current level of clinical evidence, we will use a 1-mg dexamethasone suppression test (DST) with a cut-off of 3µg/dL for screening and either urine free cortisol or low morning ACTH (<2.2 pmol/l) as confirmatory of subclinical hypercortisolism in this study. We will also evaluate other laboratory tests in the diagnosis of subclinical hypercortisolism.

Although there is retrospective data indicating operative treatment as beneficial, the optimal therapeutic paradigm has yet to be defined with quality evidence (**1, 3**). Retrospective analyses of patients who undergo adrenalectomy has been shown to be beneficial for patients with

subclinical hypercortisolism. An earlier study with a small cohort of nine patients showed that 6 out of the 8 patients with preoperative hypertension had improvement of their blood pressure postoperatively. A reduction of pharmacotherapy due to improved glycemic control was also shown in 2 out of 3 patients with preoperative diabetes. Nearly all of the patients had a reduction in their weight postoperatively (**9**). In another retrospective analysis of patients with subclinical hypercortisolism who either opted for adrenalectomy versus observation demonstrated significant benefit in the adrenalectomy group. In the study, 20 patients underwent operative intervention and 15 patients opted for conservative management. Baseline demographics and metabolic features were similar and statistically nonsignificant between the two groups. In the operated patients, 53% of patients had an improvement in blood pressure and 50% had improved glycemic control, whereas there was no improvement in the control group ($P < .01$) (**10**). Chiodini et. al. evaluated 41 patients who were diagnosed with subclinical hypercortisolism and either underwent adrenalectomy (n=25) or refused surgery (n=16). After an 18 month follow-up, a comparison of the two groups showed the adrenalectomy group to have improvement in weight (32 vs. 12.5%, p=0.05), blood pressure (56 vs. 0%, p<0.0001), and fasting glucose levels (48 vs. 0%, p=0.001). The blood pressure (50 vs 0%, p<0.0001), fasting glucose levels (37.5 vs. 0%, p=0.001), and LDL levels (50 vs. 20%, p=0.05) worsened in patients who did not have adrenalectomy (**25**). One of the largest studies to date, a group in Italy prospectively analyzed the outcomes of 45 subclinical hypercortisolism patients over a 15-year period. The patients were divided into operative (n = 23) and nonoperative (n = 22) groups. The prevalence of metabolic complications was similar between the two groups: diabetes (34.8% vs. 27.3%), hypertension (78.3% vs. 68.2%), hypercholesterolemia (34.8% vs. 31.8%), obesity (26.1% vs. 27.3%), and osteoporosis (21.7% vs. 27.3%). The analysis of the long-term outcome of the surgical group revealed a statistically significant improvement and/or normalization in 12 out of 18 patients with hypertension (p=0.46). Although statistically not significant, diabetes normalized and/or improved in 5 out of 8 patients (p=0.619), hypercholesterolemia normalized in 3 out of 8 patients (p=0.619) and the BMI normalized in 3 out of 6 patients (p value not reported) Unfortunately, the authors did not do a data comparison between the medically managed group and the operative group (**1**).

Although these studies show resolution of metabolic complications, the studies suffer from small sample size, retrospective nature, lack of randomization, and lack of uniform medical management. A large prospective randomized study of subclinical hypercortisolism is needed to better define the optimal management of these patients and conclusively demonstrate the benefit of adrenalectomy or lack thereof. We hypothesize that operative treatment would reduce the risk of long term consequences, and propose a prospective randomized trial evaluating and comparing non-operative and operative management of subclinical hypercortisolism.

Proposed correlative studies include determination of optimal diagnostic test for subclinical hypercortisolism, improvement of patient quality of life with adrenalectomy, assessing the incidence and the risk of deep venous thrombosis, diagnostic capability of dermal thickness and subclinical hypercortisolism, the diagnostic capability of ultrasound of the skin and the ability to predict resolution of subclinical hypercortisolism, rate of malignant adrenal neoplasm or tumor growth, the ability of bone turnover markers to predict resolution of osteoporosis, and the determination of whether FDG PET/CT scan is diagnostic of subclinical hypercortisolism.

Although surgery may improve the metabolic consequences of subclinical hypercortisolism, the importance of assessing the health-related quality of life of patients cannot be underestimated. As previously described, Iacobone et. al. (**10**) retrospectively compared patients who underwent an adrenalectomy (n=20) and those who opted for conservative management (n=15). In addition to assessing the metabolic consequences between the two groups, Iacobone et. al. assessed their quality of life with the SF-36 Health Survey. The SF-36 is a validated self-administered questionnaire with 2 components: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). The two components correlate with the patient's physical and mental subjective perception of quality of life, respectively. In the operative group the SF-36 MCS score improved from a baseline score of 43.8 ± 11.8 to 54.1 ± 10.1 (p=0.003) after adrenalectomy. Similarly, the SF-36 PCS score improved from a baseline score of 50.9 ± 7.3 to 56.7 ± 7.3 (p=0.0016) after adrenalectomy. The baseline and at final follow up for patients that had opted for observation were not significantly different. A comparison of patients at final follow up who underwent adrenalectomy and patients who opted for observation showed a significant difference in quality of life scores: SF-36 MCS 54.1 ± 10.1 vs. 44.9 ± 12.4 ($p<0.05$), and SF-36 PCS 56.7 ± 7.3 vs. 50.5 ± 9.4 ($p<0.05$), respectively (**10**). However, since the patients in this study were not randomized and opted either for surgery or observation, there is an inherent selection bias. A correlative study with a randomized population would be helpful in determining the health-related quality of life score and potential improvement after adrenalectomy.

In order to better assess the quality of life impact on patients with subclinical hypercortisolism, we plan to use a validated Cushing's syndrome (CS) specific questionnaire(Appendix **A**) and correlate that questionnaire with the generic SF-36 questionnaire (Appendix **C**)). The CS specific questionnaire has been previously validated in a cohort of 125 patients with chronic exposure to hypercortisolism. The observational cross-sectional study consisted of patients with pituitary-dependent (n=107) and adrenal-dependent CS (n=18). A subset of these patients (n=26) had an elevated urine free cortisol and clinical evidence of ongoing hypercortisolism confirmed by an endocrinologist. A comparison of these patients to a subset of patients without hypercortisolism (n=60) revealed that ongoing hypercortisolism is associated with a worse score and quality of life (44 ± 22 vs. 56 ± 21, p=0.004) (**26**). This Cushing's specific questionnaire may be more specific in identifying the psychological impact of subclinical hypercortisolism and be helpful in assessing the impact of adrenalectomy.

The risk of venous thromboembolism (VTE) in patients with subclinical hypercortisolism is currently unknown and an extensive examination of the literature did not reveal any published studies. However, the risk of venous thromboembolism in patients with CS has been documented and reported to be more than 10-fold higher compared to the general population (**27**). The incidence of VTE prior to surgery in patients with CS has been documented to be between 2.5 to 3.1 per 1000 person-years. In the general population, the estimated incidence of VTE is 1 to 2 per 1000 person-years, which indicates that there is a slightly higher incidence of VTE in patients with CS. However, since the majority of patients affected by CS are women and the mean age is 40 years of age, an appropriate comparison would take these demographics into account. A demographically matched cohort reveals that the reported incidence rate is 0.27 per 1000 person-years, which shows that the incidence of VTE is much higher in patients with CS (**28**). Stuijver et. al. (**29**) published one of the largest retrospective studies examining Cushing's syndrome and VTE. The study included 473 patients with a diagnosis of CS. A subset of these

patients (n=113) were diagnosed with ACTH-independent CS. Consistent with other studies, the cohort's average age was 43.5 (range 19 to 79) and was largely female (89.4%). The incidence rate of VTE prior to treatment in this cohort was 15.2 (95% CI 6.3-36.6) (**29**). The mechanism is believed to be increased production of procoagulant factors and activation of the coagulation cascade. Although the pathophysiology of increased production is not fully understood, there have been *in vitro* studies showing the direct effect of glucocorticoids on these factors (**27**). Given the increased risk of VTE in CS and the possible role of glucocorticoids in promoting a hypercoagulable state, we propose assessing the risk of VTE in patients with subclinical hypercortisolism with preoperative and postoperative bilateral lower extremity duplex.

As documented previously, osteoporosis has a prevalence of 30% in patients with subclinical hypercortisolism (**10**) and a comparison of patients with adrenal incidentaloma and subclinical hypercortisolism reveals a significantly lower bone mineral density, higher fracture prevalence, and spinal deformity. Fractures and spinal deformity were also significantly associated with subclinical hypercortisolism (**20**). Given these findings, it is important to assess the beneficial effects of adrenalectomy for these patients.

As previously described, overt physical signs excludes the diagnosis of subclinical hypercortisolism. The classical cutaneous manifestations of Cushing's syndrome such as facial plethora, acne, purpura, cutaneous atrophy, hirsutism, vellous hypertrichosis, and wide purplish striae over the abdomen, flanks, and upper arms are not identified (**32**). Although not clinically identifiable, the cutaneous effects of glucocorticoids may be detectable by measuring the epidermal and dermal thickness of skin. A study by Lehmann et. al. demonstrated that topical application of clobetasol propionate to the forearms of 3 volunteers for 6 weeks resulted in a 59% decrease in viable epidermal thickness, and flattening of the dermal-epidermal junction (**33**). Whether the mildly elevated levels of cortisol found in subclinical hypercortisolism lead to histological changes has not been explored. We propose to obtain a skin biopsy from the site of the incision and determine whether there have been histological changes associated with the mildly elevated cortisol levels and to see whether this correlates with the diagnosis of subclinical hypercortisolism. The skin biopsy would not lead to new incisions and/or scars and would not affect the healing of the wound.

Weight gain and obesity is very common in patients with subclinical hypercortisolism. As previously stated, overweight and/or obesity has a prevalence of 19 to 75% in patients with subclinical hypercortisolism **(8, 10, 12-14**). Commonly in CS, patients have central obesity with fat deposition in the abdomen, mediastinum, face and neck (**32**). This type of fat distribution has been tested noninvasively by ultrasound. Schou et. al. (**34**) assessed the changes in fat distribution noninvasively by ultrasound in asthmatic children who were given a short course of prednisolone. Twenty children participated in a double-blinded, randomized, placebo-controlled crossover trial. One group of children (n=10) received 5 mg of prednisolone daily (active arm) for one week, while the other group of children (n=10) received placebo for one week. At days 1 and 7, ultrasound measurements of the cutis and subcutis were done at three locations: the abdomen, the volar arm, and the thigh. The total thickness of the cutis and subcutis in the thigh significantly decreased in treatment group versus the placebo group (-0.28 ± 0.15 vs. 0.07 ± 0.14 mm, p=0.04). The volar arm and the abdomen locations did not show a significant change between the treatment and placebo group. There was a significant change in the treatment group when comparing the total thickness of the cutis and subcutis of the abdomen versus the thigh

(0.23 ± 0.16 vs. -0.28 ± 0.15 mm, p=0.03) and the total thickness of the cutis and subcutis of the abdomen versus the forearm (0.23 ± 0.16 vs. -0.15 ± 0.09 mm, p=0.05). These findings would be consistent with the glucocorticoid induced effects in central and peripheral fat distribution (**34**). This noninvasive test could potentially be utilized in patients with subclinical hypercortisolism as a diagnostic tool and to identify the resolution of subclinical hypercortisolism postoperatively. We will correlate the changes in subcutaneous fat distribution in patients who undergo adrenalectomy.

Another new and important diagnostic tool in the arsenal of the clinician is FDG PET/CT scan. A thorough review of the literature identified only one published case report of a patient with subclinical hypercortisolism who underwent an FDG PET/CT scan. The case report described a 48 year-old woman with a left adrenal incidentaloma. She underwent biochemical testing, which revealed subclinical hypercortisolism. A FDG PET/CT scan showed the left adrenal mass to have a maximum standard uptake value (SUV) of 4.8. The authors concluded that FDG-PET could potentially evaluate adrenal incidentalomas and hormonal status (**35**). At the NIH, under the protocol 11-C-0149, Evaluation of Diagnostic and Prognostic Molecular Markers in Adrenal Neoplasm, we have evaluated patients with adrenal masses with a FDG PET/CT scan. A preliminary analysis (unpublished data) shows that those patients with Cushing's syndrome have a significantly elevated (SUV) compared to patients with nonfunctional cortical tumors (p=0.0161,). A receiver operator curve (ROC) was created and showed an AUC of 0.8506 (p=0.01451). An SUV cut-off of 5.0 allowed one to differentiate between functional adrenal mass with a sensitivity of 63.6% and a specificity of 85.7% (PPV 87.5%, NPV 60%). Thus, our preliminary analysis indicates that FDG PET/CT could be used an imaging modality that may differentiate between functional and nonfunctional adrenal masses. Since the diagnosis of subclinical hypercortisolism can be very difficult, FDG PET/CT scanning may be a helpful additional diagnostic tool.

Patients with bilateral adrenal incidentalomas have recently been recognized to have a high incidence of subclinical hypercortisolism. Pasternak and colleagues noted that of 23 patients with bilateral adrenal incidentalomas, 21.7% of these patients had subclinical hypercortisolism, indicating a high prevalence in this subset of patients (**34**). Papierska and colleagues assessed patients with subclinical hypercortisolism and bilateral adrenal incidentalomas. In this study, 25 patients with bilateral adrenal tumors and subclinical hypercortisolism underwent a unilateral adrenalectomy of the larger of the two glands. In all surgical patients hypercortisolism was resolved. Fifty-eight percent of patients had clinical improvement of their diabetes, hypertension, and obesity. This study indicates that patients with bilateral adrenal incidentalomas and subclinical hypercortisolism can be treated by removing the larger of the two adrenal masses with a unilateral adrenalectomy (**35**)

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 An individual with an adrenal neoplasm less than 5 cm in size with biochemically confirmed evidence of hypercortisolism (2 out of 3: DST >3 mcg/dL, elevated urine

free cortisol, and/or morning ACTH <2.2 pmol/l) without overt clinical signs and symptoms.

2.1.1.2 Age greater than or equal to 18 years.

2.1.1.3 Adults must be able to understand and sign the informed consent document.

2.1.1.4 Patients must have laboratory and physical examination parameters within acceptable limits by standard of practice guidelines prior to surgery as assessed by preoperative anesthesia assessment.

2.1.2 Exclusion Criteria

2.1.2.1 Biochemically and/or radiologically confirmed pheochromocytoma, hyperaldosteronoma, or adrenocortical carcinoma.

2.1.2.2 Nonfunctioning adrenal neoplasm.

2.1.2.3 Pre-existing cancers and/or metastatic disease to the adrenal glands.

2.1.2.4 Pregnancy and/or lactation.

2.1.2.5 Lack of metabolic complications.

2.1.2.6 Imaging features worrisome for malignancy (heterogeneous tumor, presence of calcifications, necrosis, >10 Hounsfield units on an unenhanced CT scan, and delayed washout of contrast).

2.1.3 Recruitment Strategies

Since the NIH has an excellent medical endocrinology service with a large number of referrals and investigators across two institutes (NIDDK and NICHD), we are collaborating with our endocrine colleagues (who are also co-investigators in the protocol) to increase accrual to obtain the necessary number of patients. We will also provide information regarding our protocol at national and international meetings.

2.2 SCREENING EVALUATION

Patients will undergo the following screening evaluations which may be performed within 4 weeks of enrollment

2.2.1 Detailed History and Physical Examination

H& P will include vital signs, BMI, weight, waist circumference, ECOG status, demographic information and family history.

2.2.2 Radiology and Nuclear Medicine Tests

2.2.2.1 Adrenal protocol CT scan with and without intravenous contrast.

2.2.3 Laboratory evaluation

2.2.3.1 CBC with differential

2.2.3.2 Chemistry Panel [Sodium (Na), Potassium (K), Chloride (Cl), Total CO2 (bicarbonate), Creatinine, Glucose, Urea Nitrogen (BUN), Albumin, Calcium total, Magnesium total (Mg), Inorganic Phosphorous, Alklaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin, LD, Total Protein, Total CK, Uric Acid]

2.2.3.3 PT/PTT

2.2.4 Biochemical testing

2.2.4.1 Fasting morning upright serum renin and plasma aldosterone levels

2.2.4.2 24 hour urinary free cortisol level

2.2.4.3 Midnight serum and salivary cortisol level

2.2.4.4 Baseline serum cortisol at 08:00 and 16:00 hours

2.2.4.5 Morning plasma ACTH at 08:00

2.2.4.6 Low dose dexamethasone suppression test

1mg overnight test with a cortisol suppression threshold set at 3 µg/dL

- cortisol at 08:00 hours
- plasma dexamethasone level at 08:00 hours
  - if dexamethasone level is low, the test will be repeated with a higher dose of dexamethasone; 3mg overnight test with a cortisol suppression threshold set at 3 µg/dL
    - cortisol at 08:00 hours
    - plasma dexamethasone level at 08:00 hours

2.2.4.7 Serum fractionated plasma normetanephrine and metanephrine

2.2.4.8 24-hour urinary epinephrine, dopamine, norepinephrine, fractionated normetanephrines, fractionated metanephrines

2.3 REGISTRATION PROCEDURES

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) <ncicentralregistration-l@mail.nih.gov>. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

2.4 RANDOMIZATION (OR STRATIFICATION) PROCEDURES

Patients with subclinical hypercortisolism will be randomized to adrenalectomy or observation as defined above and followed for 6 months. At the end of 6 months, the patients who were in the observation-only arm will all be offered an adrenalectomy. Patients with subclinical hypercortisolism tend to have high prevalence of metabolic consequences, specifically hypertension, diabetes, osteoporosis, hypercholesterolemia, and/or obesity. The patients will be randomized by the CRO.

To be conservative, the primary goal of this study will be to determine if the use of adrenalectomy is associated with 35% improvement vs. 5% improvement over 6 months without surgery as defined for any one or more of the following associated metabolic complications: hypertension, diabetes, osteoporosis, hypercholesterolemia, and/or obesity. With 31 patients per arm (62 total) , there would be 80% power to detect a difference of this magnitude using a 0.05 significance level two-tailed Fisher's exact test.

The following definitions will be used to determine if a given metabolic complication shows sufficient improvement in order to be considered as a component of a successful outcome:

Hypertension: normalization and/or improvement in blood pressure as assessed by reduction in pharmacotherapy and/or normalization of blood pressure (systolic pressure <=140 and diastolic pressure <=90) from baseline.

Diabetes: normalization and/or improvement in diabetes as assessed by normalization (A1C <6.5%), and/or reduction and/or discontinuation of pharmacotherapy.

Osteoporosis: an increase in the level of bone formation markers greater than the least significant change, which is calculated by multiplying the "precision error" of the specific biomarker by 2.77 (95% confidence interval) as per the National Osteoporosis Foundation (NOF) Clinician's Guide to Prevention and Treatment of Osteoporosis 2013 (**Appendix D**).

Hypercholesterolemia: improvement in cholesterol as assessed by a reduction or elimination of pharmacotherapy and/or reduction in LDL levels to the optimal risk stratified goal as defined by ATP III guidelines (**Appendix E**).

Obesity: improvement in obesity as defined by a ten percent reduction in fasting morning weight compared to baseline.

2.5 BASELINE EVALUATION

Patients will undergo the following evaluations which may be performed within 4 weeks after enrollment, prior to randomization.

2.5.1 Detailed History and Physical Examination

H & P will include vital signs, BMI, weight, waist circumference, ECOG status, demographic information and family history.

2.5.2 Quality of Life Questionnaire (see **Appendix A**)

2.5.3 Radiology and Nuclear Medicine Tests

2.5.3.1 Adrenal protocol CT scan with and without intravenous contrast.

2.5.3.2 FDG PET/CT scan

2.5.3.3 DEXA scan with body composition.

2.5.3.4 Bilateral lower extremity duplex

2.5.3.5 Vertebral X-rays as assessed by vertebral morphometry and body composition

2.5.3.6 Ultrasound of the skin at three locations: the abdomen, volar aspect of the forearm, and the thigh (as described by Schou et. al. (34))

2.5.4 Specialty Consults as Required by Patient's Medical History and Presentation

2.5.5 Laboratory evaluation

2.5.5.1 CBC with differential

2.5.5.2 Chemistry Panel [Sodium (Na), Potassium (K), Chloride (Cl), Total CO2 (bicarbonate), Creatinine, Glucose, Urea Nitrogen (BUN), Albumin, Calcium total, Magnesium total

(Mg), Inorganic Phosphorous, Alklaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin, LD, Total Protein, Total CK, Uric Acid]

2.5.5.3 PT/PTT

2.5.6 Biochemical testing

2.5.6.1 Fasting morning upright serum renin and plasma aldosterone levels

2.5.6.2 24 hour urinary free cortisol level

2.5.6.3 Midnight serum and salivary cortisol level

2.5.6.4 Baseline serum cortisol at 08:00 and 16:00 hours

2.5.6.5 Morning plasma ACTH at 08:00

2.5.6.6 Low dose dexamethasone suppression test

1mg overnight test with a cortisol suppression threshold set at 3 µg/dL

- cortisol at 08:00 hours
- plasma dexamethasone level at 08:00 hours
  - if dexamethasone level is low, the test will be repeated with a higher dose of dexamethasone; 3mg overnight test with a cortisol suppression threshold set at 3 µg/dL
    - cortisol at 08:00 hours
    - plasma dexamethasone level at 08:00 hours

2.5.7 Other Laboratory Evaluations

2.5.7.1 Serum fractionated plasma normetanephrine and metanephrine

2.5.7.2 24-hour urinary epinephrine, dopamine, norepinephrine, fractionated normetanephrines, fractionated metanephrines

2.5.7.3 Dehydroepiandrosterone sulfate

2.5.7.4 Urinary 17 ketosteroids

2.5.7.5 Testosterone (both males and females)

2.5.7.6 24 hour urinary calcium, phosphorous, and amino acid random urine.

2.5.7.7 25-OH Vitamin D level

2.5.7.8 Parathyroid hormone (PTH)

2.5.7.9 Thyroid stimulating hormone (TSH)

2.5.7.10 Fasting glucose, Hgb A1C

2.5.7.11 C-reactive protein (CRP)

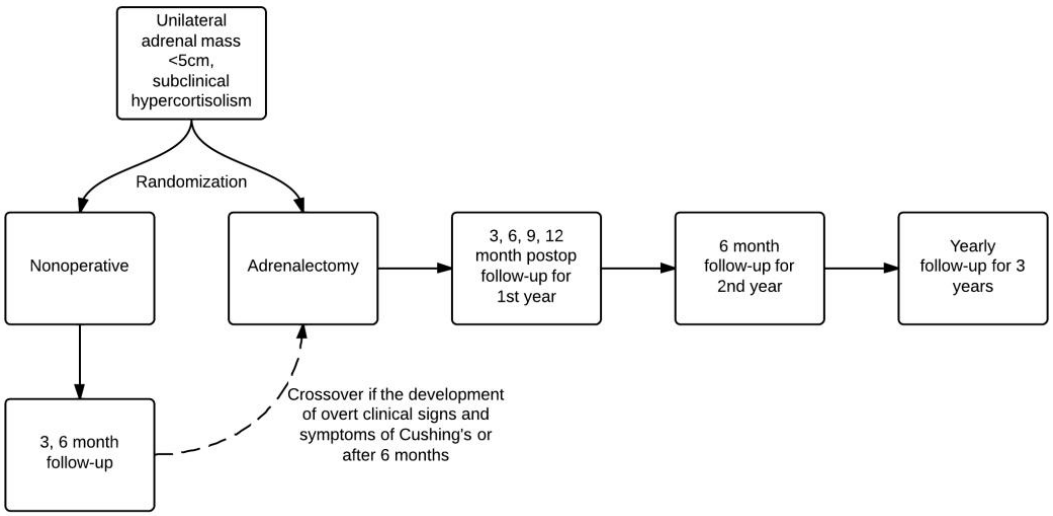
2.5.7.12 Fasting Triglyceride, total cholesterol, LDL, HDL levels

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is a prospective randomized study of individuals with an adrenal mass less than or equal to 5 cm with biochemically confirmed hypercortisolism (2 out of 3: DST >3 mmol/l, elevated urine free cortisol, and/or morning ACTH <2.2 pmol/l) without overt clinical signs and/or symptoms (facial plethora, easy bruising, violaceous straiae, and/or proximal muscle weakness) of excess cortisol. Individuals will undergo a clinical work up for an adrenal mass including laboratory and radiological studies (see below). Patients diagnosed with subclinical hypercortisolism and an adrenal mass less than 5 cm will be randomly assigned to either the non-operative or operative arm of the study. In patients found to have bilateral adrenal masses, the larger of the two masses will be treated as the adrenal lesion responsible for subclinical hypercortisolism. These patients with bilateral adrenal masses will be randomly assigned to either the non-operative or operative arm of the study. The responsible lesion will be adrenal mass that will be removed with a unilateral adrenalectomy or monitored. For patients in the non-operative or medical treatment-only arm, baseline evaluation will be undertaken, as well as follow up and re-evaluation every 3 months for 6 months, after which they will crossover to the operative arm and undergo an adrenalectomy. If a patient develops overt signs and symptoms of cortisol excess during the 6 months of observation, the tumor grows after enrollment during the 6 months of observation or 6 months have elapsed, the patient will cross over to the operative arm, and undergo an adrenalectomy. Worsening of metabolic complications will not be an indication for crossover. Patients after crossing over to the operative arm will have follow up every 3, 6, 9, and 12 months for the first year, six month follow up thereafter for the second year, and yearly follow up thereafter for three years. For a patient in the operative arm, the patient will undergo baseline evaluation, adrenalectomy, and follow up every 3, 6, 9, and 12 months for the first year, six month follow up thereafter for the second year, and yearly follow up thereafter for three years. At each follow-up visit, the patient will undergo repeat radiological and laboratory evaluation (see **Table 1**). Uniformity of medical management will be ensured by coordinating with primary care physicians, endocrinologists and the utilization of national guidelines in treating the metabolic manifestations and consequences of subclinical hypercortisolism.

Table 1



3.2 QUESTIONNAIRES

The questionnaires to be utilized include the generic SF-36 and the Cushing specific quality of life questionnaire (26). The questionnaires will assess the patient's quality of life preoperatively and postoperatively. The questionnaires will take approximately ten minutes to complete. The SF-36 form will be given first, and the Cushing's specific quality of life questionnaire will follow. The topics will address general health and wellbeing. After the questionnaires are collected and entered into a computer database, the data will be shredded.

3.3 STUDY CALENDAR

3.3.1 Operative Arm

Baseline and Follow-up Testing for Operative Arm					
Test	Baseline evaluation (MO)	3 monthly evaluation (M3)	3 monthly evaluation (M6, M9)	6 monthly evaluation (M12, M18)	12 monthly evaluation (M24, M36, M48, M60)
QoL Questionnaire	x	x		x	
CT adrenal	x				
FDG PET/CT scan	x				
DEXA	x			x	x
Duplex	x	x			
Vertebral (X-rays) morphometry and body composition	x	x	x		
Skin ultrasound	x	x	x	x	x
CBC	x	x	x	x	x
Chemistries	x	x	x	x	x
PT/PTT/INR	x				
Renin/PAC	x				
24 hour urine free cortisol	x	x			
midnight serum/salivary cortisol	x	x			
baseline serum cortisol	x	x			
DST	x	x			
plasma ACTH	x	x			
serum fractionated plasma normetanephrines and metanephrines	x				
24-hour urinary epinephrine, dopamine, norepinephrine, and fractionated normetanephrines and metanephrines	x				
DHEA	x	x	x	x	
Urinary 17 ketosteroids	x	x	x	x	x
testosterone	x	x			
24 hour urinary calcium, phosphorous,	x	x	x	x	x

Baseline and Follow-up Testing for Operative Arm					
Test	Baseline evaluation (MO)	3 monthly evaluation (M3)	3 monthly evaluation (M6, M9)	6 monthly evaluation (M12, M18)	12 monthly evaluation (M24, M36, M48, M60)
amino acid random urine					
25-OH Vitamin D Level	x	x	x	x	x
PTH	x	x			
fasting glucose	x	x	x	x	x
A_1C	x	x	x	x	x
Triglyceride, total LDL, HDL levels	x	x	x	x	x
NIH Advanced Directives Form[1]	x				

[1] As indicated in section **8.3**, all subjects will be offered the opportunity to complete an NIH advanced directives form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended, but is not required.

3.3.2 Non-Operative Arm

Baseline and Follow-up Testing for Non-Operative Arm						
Test	Baseline evaluation (MO)	Preop 3 monthly evaluation (M3, M6)	3 monthly evaluation (M9)	3 monthly evaluation (M12, M15)	6 monthly evaluation (M18, M24)	12 monthly evaluation (M30, M42, M54, M66)
QoL Questionnaire	x	x	x		x	
CT adrenal	x	x				
FDG PET/CT scan	x					
DEXA	x				x	x
Duplex	x	x	x			
Vertebral (X-rays) morphometry and body composition	x		x	x		
Skin ultrasound	x	x	x	x	x	x
CBC	x	x	x	x	x	x
Chemistries	x	x	x	x	x	x
PT/PTT/INR	x					
Renin/PAC	x					

Baseline and Follow-up Testing for Non-Operative Arm						
Test	Baseline evaluation (MO)	Preop 3 monthly evaluation (M3, M6)	3 monthly evaluation (M9)	3 monthly evaluation (M12, M15)	6 monthly evaluation (M18, M24)	12 monthly evaluation (M30, M42, M54, M66)
24 hour urine free cortisol	x	x	x			
midnight serum/salivary cortisol	x	x	x			
baseline serum cortisol	x	x	x			
DST	x	x	x			
plasma ACTH	x	x	x			
serum fractionated plasma normetanephrines and metanephrines	x	x				
24-hour urinary epinephrine, dopamine, norepinephrine, and fractionated normetanephrines and metanephrines	x	x				
DHEA	x	x	x	x	x	
Urinary 17 ketosteroids	x	x	x	x	x	x
testosterone	x	x	x			
24 hour urinary calcium, phosphorous, amino acid random urine	x	x	x	x	x	x
25-OH Vitamin D Level	x	x	x	x	x	x
PTH	x	x	x			
fasting glucose	x	x	x	x	x	x
A_1C	x	x	x	x	x	x
Triglyceride, total LDL, HDL levels	x	x	x	x	x	x

Baseline and Follow-up Testing for Non-Operative Arm						
Test	Baseline evaluation (MO)	Preop 3 monthly evaluation (M3, M6)	3 monthly evaluation (M9)	3 monthly evaluation (M12, M15)	6 monthly evaluation (M18, M24)	12 monthly evaluation (M30, M42, M54, M66)
NIH Advanced Directives Form[1]						

[1] As indicated in section 10.3, all subjects will be offered the opportunity to complete an NIH advanced directives form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended, but is not required.

3.4 SURGICAL GUIDELINES

After randomization, patients in the surgery arm will undergo an adrenalectomy as per standard of care.

3.5 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

3.5.1 Criteria for removal from protocol therapy

- Patient request to be withdrawn
- PI discretion, if the PI feels it is not in the best interest of the patient to remain on study
- Completion of protocol therapy
- Positive pregnancy test

3.5.2 Off-Study Criteria

Patients will be removed from the study if any of the following criteria are met:

- Patient requests withdrawal from the study
- Patient is consistently non-compliant with the follow-up appointments
- Completion of the protocol specified follow up period
- PI discretion
- Death

3.5.3 Off-Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off-study. An off-study form from the web site(http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) <ncicentralregistration-l@mail.nih.gov>.

4 BIOSPECIMEN COLLECTION

4.1 CORRELATIVE STUDIES FOR RESEARCH

Patients will be co-enrolled on protocol 09-C-0242. Biospecimen will be collected as specified in protocol 09-C-0242.

4.2 SAMPLE STORAGE, TRACKING AND DISPOSITION

Tissue will be snap frozen in liquid nitrogen and transported to the Endocrine Oncology Lab by calling 301-435-7891. Samples will be labeled with the date and time of acquisition, the type of tissue and patient study ID. Upon receipt in the lab, samples will be bar coded and logged in to the tissue database, LabMatrix. Tissue will be stored in -20 °C or -80 °C freezers. All freezers are monitored and are on separate emergency generator lines.

Serum and urine samples for correlative studies may also be obtained and will be stored and tracked in the same manner as tissue samples.

At the completion of the protocol, the investigator will dispose of all specimens in accordance with the environmental protection laws, regulations and guidelines of the Federal Government and the State of Maryland. {Note, all patients undergoing surgery for endocrine diseases that consent to have their tissue used for research will be enrolled on this trial and thus the trial will remain ongoing as long as identified samples are being used in the conduct of this research. It is anticipated that this protocol will remain open for at least the next 6 years}

Any loss or unintentional destruction of the samples will be reported to the IRB.

5 DATA COLLECTION AND EVALUATION

5.1 DATA COLLECTION

Data prior to and during the course of the patient's participation will be collected in order to monitor patient eligibility, and will include review of medical and family history records, completed questionnaires, non-invasive imaging and blood work. Data will be securely stored in the Labmatrix database.

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

End of study procedures: Data will be stored according to HHS, FDA, and NIH Intramural Records Retention Schedule regulations as applicable.

Loss or destruction of data: Should we become aware that a major breech in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

5.2 ROUTINE DATA COLLECTION

Following enrollment, all adverse events will be described in the source documents and be reviewed by the designated research nurse, and captured in C3D.

During the follow up period (more than 30 days following surgery), only those events that are serious, unexpected, and related to the treatment will be captured in C3D.

Exclusions to Routine Data Collection:

The following Adverse Events will be captured only in the source documents and will not be reported in C3D:

- Laboratory values that do not support the diagnosis of a reportable event
- All grade 1 events

5.3 HUMAN DATA SHARING PLANS

5.3.1 Human Data Sharing Plan

Human data generated in this research will be shared for future research as follows:

- De-identified data in an NIH-funded or approved public repository
- Identified data in BTRIS

Data will be shared through:

- An NIH-funded or approved public repository: clinicaltrials.gov
- BTRIS
- Publication and/or public presentations.

Data will be shared at the time of publication or shortly thereafter.

5.4 RESPONSE CRITERIA

For the purposes of this study, patients in the operative arm will be re-evaluated for response every 3 months from M0 to M12, every 6 months from M12 to M24, and then every 12 months thereafter through M60. Patients in the non-operative arm will be re-evaluated for response every 3 months from M0 to M18, every 6 months from M18 to M30, and then every 12 months thereafter through M66.

5.4.1 Definitions

The following definitions will be used to determine if a given metabolic complication shows sufficient improvement in order to be considered as a component of a successful outcome.

5.4.1.1 Hypertension

Normalization and/or improvement in blood pressure as assessed by reduction in pharmacotherapy and/or normalization of blood pressure (systolic pressure <=140 and diastolic pressure <=90) from baseline.

5.4.1.2 Diabetes

Normalization and/or improvement in diabetes as assessed by normalization (A1C <6.5%), and/or reduction and/or discontinuation of pharmacotherapy.

5.4.1.3 Osteoporosis

An increase in the level of bone formation markers greater than the least significant change, which is calculated by multiplying the "precision error" of the specific biomarker by 2.77 (95% confidence interval) as per the National Osteoporosis Foundation (NOF) Clinician's Guide to Prevention and Treatment of Osteoporosis 2013.

5.4.1.4 Hypercholesterolemia

Improvement in cholesterol as assessed by a reduction or elimination of pharmacotherapy and/or reduction in LDL levels to the optimal risk stratified goal as defined by ATP III guidelines.

5.4.1.5 Obesity

Improvement in obesity as defined by a ten percent reduction in weight compared to baseline.

5.5 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

6 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

This is an observational protocol and thus no experimental treatments or procedures are performed as a part of this protocol and therefore no adverse events are expected. In the unlikely event that an adverse event occurs that is attributable to the research, CTCAE v. 4.0 will be used for grading such events. Patients who are undergoing standard of care work up and treatment of their disease may consent to have serum and urine collected and surgical and biopsy specimens, which are obtained during standard of care procedures, stored for ongoing and future research in the Endocrine Oncology Research lab. Patients who meet the standard of care criteria for resection of their disease will undergo a major operative procedure and may receive extensive care in the ICU. The principal investigator or designee will closely monitor and document the clinical care and treatment of each patient as per standard of care at the NIH Clinical Center. As per NIH Clinical Center standards of practice, the Occurrence Reporting System will be used to report any clinical events meeting these reporting criteria.

6.1 DEFINITIONS

6.1.1 Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the research in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include

events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Serious adverse events that occur more than 30 days after the last study procedure and have an attribution of at least possibly related to the agent/intervention should be recorded and reported as per section **6.2**.

6.1.2 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

6.1.3 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

6.1.4 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

6.1.5 Disability

A substantial disruption of a person's ability to conduct normal life functions.

6.1.6 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB approved research protocol.

6.1.7 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

6.1.8 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

6.2 NCI-IRB AND NCI CLINICAL DIRECTOR REPORTING

6.2.1 NCI-IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report in the NIH Problem Form to the NCI-IRB and NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

6.2.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
   - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
   - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
   - All Grade 5 events regardless of attribution;
   - All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

6.3 DATA AND SAFETY MONITORING PLAN

6.3.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis when patients are being actively followed on the trial to discuss each patient.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

7 STATISTICAL CONSIDERATIONS

The primary objective of this study is to determine if the use of unilateral adrenalectomy is associated with normalization and/or improvement of hypertension, diabetes, osteoporosis, hypercholesterolemia, and/or obesity compared to medical treatment-only arm.

Patients with subclinical hypercortisolism will be randomized to adrenalectomy or medical treatment as defined above and followed for 6 months. At the end of 6 months, the patients who were in the medical treatment-only arm will all be offered an adrenalectomy. Patients with subclinical hypercortisolism tend to have high prevalence of metabolic consequences, specifically hypertension, diabetes, obesity and/or osteoporosis.

To be conservative, the primary goal of this study will be to determine if the use of adrenalectomy is associated with 35% who have improvement vs. 5% who improve over 6 months without surgery as defined for any one or more of the following associated complications: hypertension, diabetes, osteoporosis, hypercholesterolemia, and/or obesity. With 31 patients per arm (62 total) , there would be 80% power to detect a difference of this magnitude using a 0.05 significance level two-tailed Fisher's exact test.

For the potential 31 patients initially randomized to observation and then undergoing an adrenalectomy at 6 months, the level of MAP, systolic, and diastolic pressure at 6 months but just before surgery will be compared to these values in the potential 31 patients initially randomized to immediate adrenalectomy 6 months after surgery using a Wilcoxon rank sum test. In addition, in the patients initially randomized to observation the changes in MAP from baseline to 6 months of observation as well as the declines in systolic and diastolic pressure from 6 months of observation until 6 months after surgery will be compared with a Wilcoxon signed rank test. Other important continuous parameters such as change in weight, triglycerides, total, HDL and LDL cholesterol, A1c, fasting glucose, and bone density may also be compared within patients using Wilcoxon signed rank test.

It is expected that 15-20 eligible patients may be able to enroll on this trial per year. In order to enroll 62 evaluable patients, it is anticipated that 3-4 years would be required. In order to allow for a small number of inevaluable patients, the accrual ceiling will be set at 66 patients.

8 HUMAN SUBJECTS PROTECTIONS

8.1 RATIONALE FOR SUBJECT SELECTION

Subjects from both gender groups and all racial/ethnic groups are eligible for this study if they meet the eligibility criteria. Efforts will be made to extend accrual to a representative population.

8.2 PARTICIPATION OF CHILDREN

Because adrenal neoplasms are exceedingly rare in children and when present are more likely to be malignant, children will not be enrolled in this study.

8.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT

Adults unable to give consent are excluded from enrolling in the protocol. However re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (section **8.4**), all subjects will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MEC Policy 87-4 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

8.4 EVALUATION OF BENEFITS AND RISKS/DISCOMFORTS

Patients may experience personal benefit from the study if we find that adrenalectomy reverses the metabolic complications associated with subclinical hypercortisolism. Furthermore, there is the potential benefit of improving our ability to diagnose and predict the outcome of patients with subclinical hypercortisolism. Each individual patient would have a complication risk of <1% associated with the adrenalectomy.

Patients in the surgery group may experience personal benefit even during the follow-up period because they will be monitored for metabolic complications which may not have resolved with surgery. In these cases, we may find that the adrenalectomy did not reverse the complications and further treatment may be needed.

8.5 RISKS/BENEFITS ANALYSIS

The main risk of participation is related to the risk of complications in the adrenalectomy arm and worsening of the metabolic complications in patient in the observation arm. The risk of

adrenalectomy is less than 1% which would outweigh the potential benefit of reversal of metabolic complications. In patients in the observation arm, there may be worsening of the metabolic complications but all patients will cross over to the adrenalectomy arm after 6 months of follow up and will be medically treated as standard of care for the metabolic complications.

8.5.1 Risk of Radiation

This research study involves exposure to radiation from 1 PET/CT Scans (maximum 10 mCi per injection), 7 DEXA scans and 4 X-rays. This radiation exposure is not required for medical care and is for research purposes only. The amount of radiation received in this study is 2.7 rem which is below the guideline of 5 rem per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. More information about radiation is available in the pamphlet, An Introduction to Radiation for NIH Research Subjects.

8.6 CONSENT AND ASSENT PROCESS AND DOCUMENTATION

All patients who are being considered for this trial will undergo informed consent prior to being enrolled on the trial. The PI or associate investigator will perform the consenting process. Patients and family members when applicable will be asked to read the consent and will be encouraged to ask questions. It will be stated clearly that participation in the research study is voluntary and that participants can withdraw from the study without losing benefits they would otherwise be entitled to. Patients will be enrolled after the consent document has been signed. Separate consents will be obtained for any surgical procedures performed.

8.6.1 Telephone consent

The informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject signature will sign and date the consent.

The original informed consent document will be mailed, via the US Postal Service or FedEx, back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone.

A fully executed copy will be returned via mail for the subject’s records.

The informed consent process will be documented on a progress note by the consenting investigator and a copy of the informed consent document and note will be kept in the subject’s research record.

8.6.2 Informed consent of non-English speaking subjects

We anticipate the enrollment of Spanish speaking research participants into our study. The IRB approved full consent document will be translated into that language in accordance with the Clinical MAS Policy M77-2.

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to

obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, OSHRP SOP 12, 45 CFR 46.117 (b) (2), (If a study with an IND or IDE, also cite 21 CFR 50.27 (b) (2)). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation. Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

We request prospective IRB approval of the use of the short form process and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form.

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10 APPENDICES

10.1 APPENDIX A – CUSHING'S QUALITY OF LIFE QUESTIONNAIRE

Cushing's Quality of Life Questionnaire (modified) (26)

Instructions

The following sentences refer to what you may think or feel about your illness. Your answers will help us to know how you feel and how much your illness has interfered in your usual activities in the past 4 weeks. Below each sentence you will find several response choices. Please read each sentence carefully. After reading each sentence, check the box next to the answer that best describes what you think is happening to you. There are no rights or wrong answers. We are simply interested in what is happening to you because of your illness.

I have trouble sleeping (I wake up during the night; it takes me a long time to get to sleep, etc.)

□ Always □ Often □ Sometimes □ Rarely □ Never

I have pain that keeps me from leading a normal life

□ Always □ Often □ Sometimes □ Rarely □ Never

My wounds take a long time to heal

□ Always □ Often □ Sometimes □ Rarely □ Never

I bruise easily

□ Always □ Often □ Sometimes □ Rarely □ Never

I am more irritable, I have sudden mood swings and angry outbursts

□ Always □ Often □ Sometimes □ Rarely □ Never

I have less self-confidence, I feel more insecure

□ Always □ Often □ Sometimes □ Rarely □ Never

I'm worried about the changes in my physical appearance due to my illness

□ Always □ Often □ Sometimes □ Rarely □ Never

I feel less like going out or seeing relatives or friends

□ Always □ Often □ Sometimes □ Rarely □ Never

I have had to give up my social or leisure activities due to my illness

□ Always □ Often □ Sometimes □ Rarely □ Never

My illness affects my everyday activities such as working or studying

□ Always □ Often □ Sometimes □ Rarely □ Never

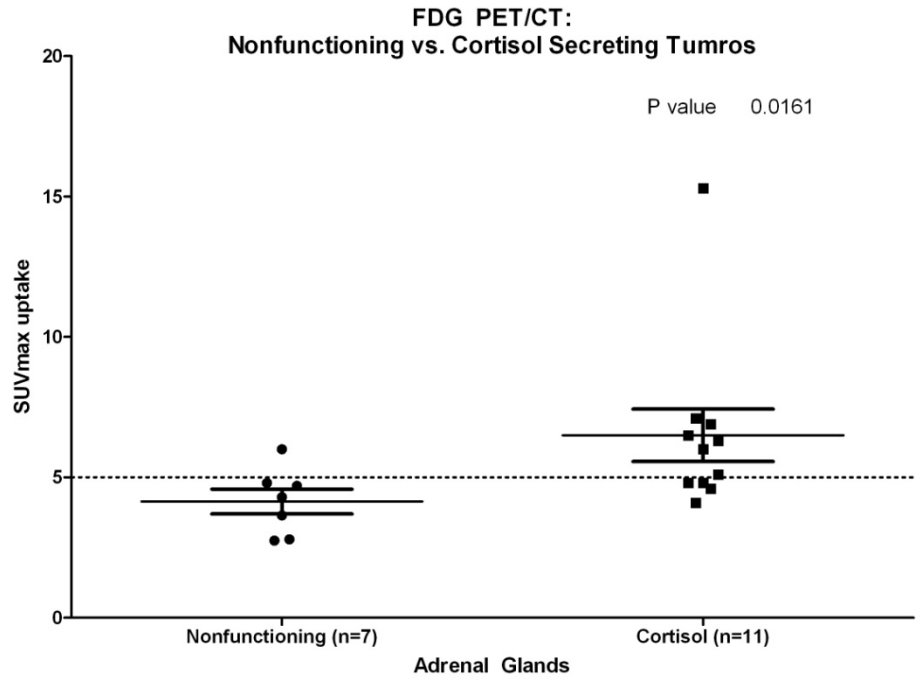
It's difficult for me to remember things

□ Always □ Often □ Sometimes □ Rarely □ Never

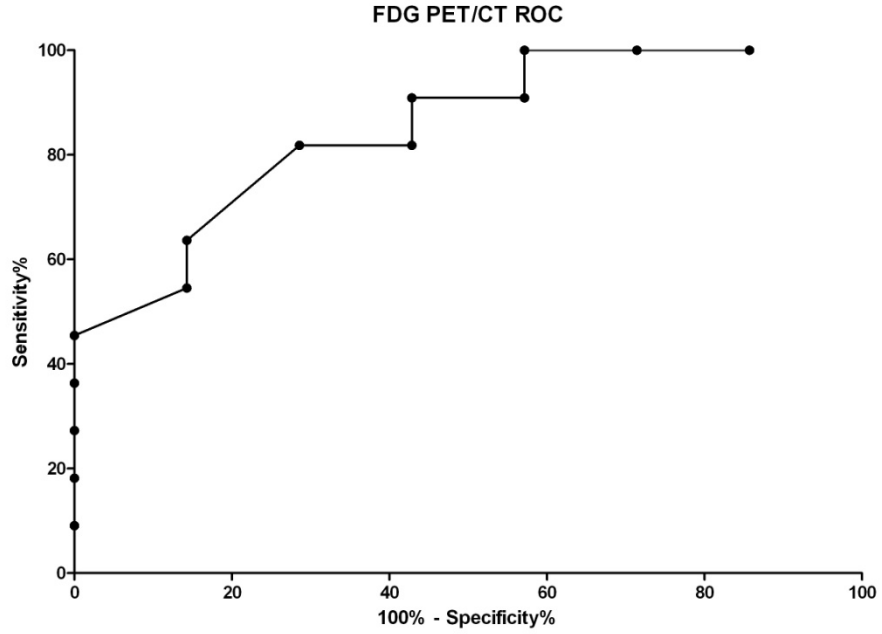
I'm worried about my health in the future

□ Always □ Often □ Sometimes □ Rarely □ Never

10.2 APPENDIX B – FDG PET/CT



FDG PET/CT scan results of patients with nonfunctioning adrenal masses versus patients with cortisol secreting adrenal masses.



Receiver operator characteristic (ROC) of FDG PET/CT scan results (AUC = 0.8506, p=0.01451).

10.3 APPENDIX C GENERIC SF-36 QUALITY OF LIFE QUESTIONNAIRE

Generic SF-36 Quality of Life Questionnaire (26)

SF36 Health Survey

INSTRUCTIONS: This set of questions asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking the answer as indicated. If you are unsure about how to answer a question please give the best answer you can.

1. In general, would you say your health is: (Please tick **one** box.)
   - Excellent ☐
   - Very Good ☐
   - Good ☐
   - Fair ☐
   - Poor ☐

2. Compared to one year ago, how would you rate your health in general now? (Please tick **one** box.)
   - Much better than one year ago ☐
   - Somewhat better now than one year ago ☐
   - About the same as one year ago ☐
   - Somewhat worse now than one year ago ☐
   - Much worse now than one year ago ☐

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? **(Please circle one number on each line.)**

	Activities	Yes, Limited A Lot	Yes, Limited A Little	Not Limited At All
3(a)	**Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
3(b)	**Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
3(c)	Lifting or carrying groceries	1	2	3
3(d)	Climbing **several** flights of stairs	1	2	3
3(e)	Climbing **one** flight of stairs	1	2	3
3(f)	Bending, kneeling, or stooping	1	2	3
3(g)	Waling **more than a mile**	1	2	3
3(h)	Walking **several blocks**	1	2	3
3(i)	Walking **one block**	1	2	3
3(j)	Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	(Please circle one number on each line.)	Yes	No
4(a)	Cut down on the **amount of time** you spent on work or other activities	1	2
4(b)	Accomplished less than you would like	1	2
4(c)	Were **limited** in the **kind** of work or other activities	1	2
4(d)	Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (e.g. feeling depressed or anxious)?

	(Please circle one number on each line.)	Yes	No
5(a)	Cut down on the **amount of time** you spent on work or other activities	1	2
5(b)	Accomplished less than you would like	1	2
5(c)	Didn't do work or other activities as **carefully** as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups? (Please tick **one** box.)

- Not at all ☐
- Slightly ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

7. How much physical pain have you had during the past 4 weeks? (Please tick **one** box.)

- None ☐
- Very mild ☐
- Mild ☐
- Moderate ☐
- Severe ☐
- Very Severe ☐

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Please tick **one** box.)

- Not at all ☐
- A little bit ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

9. These questions are about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that is closest to the way you have been feeling for each item.

	(Please circle one number on each line.)	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
9(a)	Did you feel full of life?	1	2	3	4	5	6
9(b)	Have you been a very nervous person?	1	2	3	4	5	6
9(c)	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
9(d)	Have you felt calm and peaceful?	1	2	3	4	5	6
9(e)	Did you have a lot of energy?	1	2	3	4	5	6
9(f)	Have you felt downhearted and blue?	1	2	3	4	5	6
9(g)	Did you feel worn out?	1	2	3	4	5	6
9(h)	Have you been a happy person?	1	2	3	4	5	6
9(i)	Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives etc.) (Please tick **one** box.)

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

11. How TRUE or FALSE is each of the following statements for you?

	(Please circle one number on each line.)	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
11(a)	I seem to get sick a little easier than other people	1	2	3	4	5
11(b)	I am as healthy as anybody I know	1	2	3	4	5
11(c)	I expect my health to get worse	1	2	3	4	5
11(d)	My health is excellent	1	2	3	4	5

Thank You!

10.4 APPENDIX D - MONITORING EFFECTIVENESS OF TREATMENT OF OSTEOPOROSIS

Monitoring Effectiveness of Treatment of Osteoporosis (1)

Interval assessment should include clinical monitoring in addition to BMD and biochemical markers, see below.

Accurate height measurement yearly is a critical determination of osteoporosis treatment efficacy. Patients who lose 4 cm or 1 ½ inches or more in height should have a repeat vertebral imaging test to determine if new or additional vertebral fractures have occurred since the prior visit.

Serial central DXA testing is an important component of osteoporosis management. Measurements for monitoring patients should be performed in accordance with medical necessity, expected response and in consideration of local regulatory requirements. NOF recommends that repeat BMD assessments generally agree with Medicare guidelines of every two years, but recognizes that testing more frequently may be warranted in certain clinical situations.

The following techniques may be used to monitor the effectiveness of treatment:

Central DXA. Central DXA assessment of the hip or lumbar spine is the "gold standard" for serial assessment of BMD. Biological changes in bone density are small compared to the inherent error in the test itself, and interpretation of serial bone density studies depends on appreciation of the smallest change in BMD that is beyond the range of error of the test. This least significant change (LSC) varies with the specific instrument used, patient population being assessed, measurement site, technologist's skill with patient positioning and test analysis, and the confidence intervals used. Changes in the LSC of less than 3-6 percent at the hip and 2-4 percent at the lumbar spine from test to test may be due to the precision error of the testing itself. Information on how to assess precision and calculate the LSC is available at www.ISCD.org.

Biochemical markers of bone turnover. Suppression of biochemical markers of bone turnover after 3-6 months of specific antiresorptive osteoporosis therapies, and biochemical marker increases after 1-3 months of specific anabolic therapies, have been predictive of greater BMD responses and in some cases fracture risk reduction in large clinical trials. Biochemical marker changes in individuals must exceed the LSC in order to be clinically meaningful. The LSC is specific to the biomarker being utilized, which is calculated by multiplying the "precision error" of the specific biochemical marker (laboratory provided) by 2.77 (95% confidence level).

Biological variability can be reduced by obtaining samples in the early morning after an overnight fast. Serial measurements should be made at the same time of day. In order to have any clinical validity, sequential testing needs to be performed at the same laboratory.

Vertebral Imaging: Once the first vertebral imaging test has been performed to determine prevalent vertebral fractures (indications above), repeat testing should be performed to identify incident vertebral fractures if there is a change in the patient's status suggestive of new vertebral fracture, including documented height loss, undiagnosed back pain, postural change, or a possible finding of new vertebral deformity on chest x-ray.

10.5 APPENDIX E - ATP III GUIDELINES

ATP III Guidelines (1)

Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals*
Cigarette smoking
Hypertension (BP ≥140/90 mmHg or on antihypertensive medication)
Low HDL cholesterol (<40 mg/dL)†
Family history of premature CHD (CHD in male first degree relative <55 years; CHD in female first degree relative <65 years)
Age (men ≥45 years; women ≥55 years)*

* In ATP III, diabetes is regarded as a CHD risk equivalent.
† HDL cholesterol ≥60 mg/dL counts as a "negative" risk factor; its presence removes on risk factor from the total count.

LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories.

Risk Category	LDL Goal	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)	LDL Level at Which to Consider Drug Therapy
CHD or CHD Risk Equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug optional)*
2+ Risk Factors (10-year risk ≤20%)	<130 mg/dL	≥130 mg/dL	10-year risk 10-20%: ≥130 mg/dL 10-year risk <10%: ≥160 mg/dL
0-1 Risk Factor†	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

*Some authorizes recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.
† Almost all people with 0-1 risk factor have a 10-year risk <10%, thus 10-year risk assessment in people with 0-1 risk factor is not necessary.

INSTITUTE: National Cancer Institute

STUDY NUMBER: 14-C-0021 PRINCIPAL INVESTIGATOR: Dhaval Patel, M.D.

STUDY TITLE: Randomized Control Trial of Adrenalectomy versus Observation for Subclinical Hypercortisolism

Continuing Review Approved by the IRB on 06/27/16
Amendment Approved by the IRB on 01/13/17 (D) Date Posted to Web: 01/25/17

Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary**.**

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

We would like to determine whether the surgical removal of an adrenal tumor associated with high levels of cortisol results in improvement of high blood pressure, diabetes, obesity, osteoporosis, or high cholesterol.

Why are you being asked to take part in this study?

You are being asked to participate in this study because you have an adrenal tumor that is less than two inches in size and there is evidence of high cortisol levels in your blood.

How many people will take part in this study?

Up to 66 individuals will be asked to participate in this study.

Description of Research Study

What will happen if you take part in this research study?

Before you begin the study

Before you enroll in the study you will have lab tests, imaging studies, and a physical exam to be sure that it would be safe for you to have surgery and that you are eligible for the study. If you are eligible for the study, you will be randomly assigned to undergo surgery right away or to be observed for 6 months before surgery. Whether you will undergo surgery right away or 6 months later is based upon a randomization ("flip of a coin") at the time you agree to participate on the study.

During the study

Operative Arm

If you are randomized to this arm you will undergo a baseline evaluation and surgery to remove the largest tumor. You will then recover either in the ICU or on the patient care unit until you are ready to be discharged to home. The length of time if will take you to recover will depend on the type of operation needed to remove your tumor. Your surgeon will explain the procedure in detail and answer any questions you may have. You will be asked to sign a separate consent for the operation.

You will return to the NIH Clinical Center every 3, 6, 9, and 12 months for the first year following discharge. Following the first year you will be seen every 6 months for the second year and yearly after for 3 years. At each follow-up visit you will have imaging scans and blood tests.

Delayed Operative Arm

If you are randomized to this arm you will undergo a baseline evaluation and then return for follow-up every 3 months for 6 months. After this you will cross over to the operative arm and undergo surgery to remove the tumor. If you develop signs and symptoms of too much cortisol or your tumor grows prior to 6 months after enrollment you will cross over to the operative arm and receive surgery to remove your tumor sooner. You will then have follow up every 3, 6, 9, and 12 months for the first year following discharge. Following the first year you will be seen every 6 months for the second year and yearly after for 3 years. At each follow-up visit you will undergo repeat scans and blood tests.

Study Chart

Operative Arm

Baseline	• Quality of Life Questionnaire • CT Scan

	• PET/CT Scan • DEXA Scan • Duplex Scan • Vertebral X-Ray • Skin Ultrasound • Routine Blood Tests • 24 hour urine collection
Surgery	
Month 3 evaluation	• Quality of Life Questionnaire • Duplex Scan • Vertebral X-Ray • Skin Ultrasound • Routine Blood Tests • 24 hour urine collection
Months 6 and 9 evaluations	• Vertebral X-Ray • Skin Ultrasound • Routine Blood Tests • 24 hour urine collection
Months 12 and 18 evaluations	• Quality of Life Questionnaire • DEXA Scan • Skin Ultrasound • Routine Blood Tests • 24 hour urine collection
Months 24, 36, 48 & 60 evaluations	• DEXA Scan • Skin Ultrasound • Routine Blood Tests • 24 hour urine collection

Delayed Operative Arm

Baseline	• Quality of Life Questionnaire • CT Scan • PET/CT Scan • DEXA Scan • Duplex Scan • Vertebral X-Ray • Skin Ultrasound

	• Routine Blood Tests • 24 hour urine collection
Pre-op months 3 and 6	• Quality of Life Questionnaire • Duplex Scan • Vertebral X-Ray • Skin Ultrasound • Routine Blood Tests • 24 hour urine collection
Surgery	
Month 9 evaluation	• Quality of Life Questionnaire • Duplex Scan • Vertebral X-Ray • Skin Ultrasound • Routine Blood Tests • 24 hour urine collection
Months 12 and 15 evaluations	• Vertebral X-Ray • Skin Ultrasound • Routine Blood Tests • 24 hour urine collection
Months 18 and 24 evaluations	• Quality of Life Questionnaire • DEXA Scan • Skin Ultrasound • Routine Blood Tests • 24 hour urine collection
Months 30, 42, 54, 66 evaluations	• DEXA Scan • Skin Ultrasound • Routine Blood Tests • 24 hour urine collection

Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study. It is best to avoid radiation exposure to unborn children since they are more sensitive to radiation than adults. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice an effective form of birth control before starting study treatment, during study treatment. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

- abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

Risks or Discomforts of Participation

Surgery

The side effects from the surgery are the same as you would have if you received standard surgery for an adrenal tumor at a major medical center.

FDG-PET

The scan itself is painless. The primary discomfort you will feel from undergoing an FDG-PET is the time required to lay still. The PET scan (positron emission tomography) uses a small amount of a radioactive compound (F18-FDG) to see clearly the tumor(s) in your body. You should not eat for 4-6 hours before your scan (your doctor or nurse will give you specific instructions). If you don't already have an IV catheter (small plastic tube or needle) in your vein, one may be put in your vein, which may cause a small amount of discomfort or bruising.

Ultrasound of skin

This procedure is painless and requires no preparation.

DEXA Scan

The Dual Emission-X-Ray Absorptiometry (DEXA) is a test that measures the total amount of fat in your body and the density of your bones. It uses X ray beams of high and low energies that create two different images. Combinations of these images will identify fat content and bone mineral density.

Duplex Ultrasound

A Duplex ultrasound is a form of medical ultrasonography that incorporates two elements: Grayscale Ultrasound to visualize the structure or architecture of the body part. No motion or bloodflow is assessed. Color-doppler Ultrasound to visualize the flow or movement of a structure, typically used to image blood within an artery.

Vertebral (X-rays) morphometry and body composition

X-rays are common standard imaging tests used in the diagnosis and monitoring of many diseases. Although these tests have been in use for many years, their potential long term effects on the body are still being learned. The most common discomfort is the length of time a patient must lay still or flat while an X-ray or scan is being performed.

Risk of Radiation

This research study involves exposure to radiation from 10 mCi of 18 Fluorodeoxyglucose used for the PET scan as well the associated CT scan. Please note that this radiation exposure is not necessary for your medical care and is for research purposes only. The total amount of radiation you will receive from the FDG PET/CT study is 1.2 rem effective dose. The NIH Radiation Safety Committee has reviewed the use of radiation in this research study and has approved this use as involving slightly greater than minimal risk and necessary to obtain the research information desired.

Using the standard way of describing radiation dose, from participating in this research study, you will receive a total of 3.9 rem to your urinary bladder, 2.9 rem to the heart wall, and 2.0 rem to the spleen. All other organs will receive smaller amounts of radiation.

Although each organ will receive a different dose, the amount of radiation exposure you will receive from these procedures is equal to a uniform whole-body exposure of 1.2 rem. This calculated value is known as the "effective dose" and is used to relate the dose received by each organ to a single value. The amount of radiation received in this study is within the dose guideline established by the NIH Radiation Safety Committee for research subjects. The guideline is an effective dose of 5 rem (or 5,000 mrem) received per year.

For comparison, the average person in the United States receives a radiation exposure of 0.3 rem (or 300 mrem) per year from natural background sources, such as from the sun, outer space, and from radioactive materials that are found naturally in the earth's air and soil. If you would like more information about radiation and examples of exposure levels from other sources, please ask the investigator for a copy of the pamphlet called, An Introduction to Radiation for NIH Research Subjects.

While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence it may not be completely safe. There may be a very slight increase in the risk of cancer.

Please tell your doctor if you have had any radiation exposure in the past year, either from other research studies or from medical tests or care, so we can make sure that you will not receive too

much radiation. Radiation exposure includes x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

If you are pregnant you will not be permitted to participate in this research study. If you are breast feeding and the protocol involves injection of radioactive material you will not be permitted to participate. It is best to avoid radiation exposure to unborn or nursing infants since they are more sensitive to radiation than adults.

Potential Benefits of Participation

Are there benefits to taking part in this study?

Data from this study may be useful in developing new ways of treating subclinical hypercortisolism but you may not benefit directly from this.

Alternative Approaches or Treatments

Instead of being in this study, you have these options:

- Expectant management without particular care or treatment for your cancer
- Getting treatment or care for your adrenal tumor at a different facility without being in a study
- Taking part in another study that you are eligible for.
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible

Please talk to your doctor about these and other options.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.

- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Cancer Institute Institutional Review Board

A description of this clinical trial will be available on http://www.Clinicaltrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most the Web site will include a summary of the results. You can search this Web site at any time.

Stopping Therapy

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if new information shows that another treatment would be better for you
- if you become pregnant

In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have

already been distributed to other researchers or placed in the research databases can**not** be recalled and destroyed.

Use of Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your data will be used for research purposes only and will not benefit you. It is also possible that the stored data may never be used. Results of research done on your data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored data used for future research, please contact us in writing and let us know that you do not want us to use your data. Then your data will not be used for future research. However, it may not be possible to withdraw or delete data once they have been shared with other researchers.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Dhaval Patel, M.D., Building 10, Room 3-5840, Telephone: 240-760-6155 or Electron Kebebew M.D., Building 10, Room 4-5952, Telephone: 240-760-6153. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 240-760-6070

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/ Legal Representative _____ Date _____

Print Name _____

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.
(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/ Guardian _____ Date _____

Print Name _____

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian _____ Date _____ Print Name _____

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM JUNE 27, 2016 THROUGH JUNE 26, 2017.

Signature of Investigator _____ Date _____

Print Name _____

Signature of Witness _____ Date _____

Print Name _____

INSTITUTE: Instituto Nacional del Cáncer *(National Cancer Institute)*

STUDY NUMBER: 14-C-0021 PRINCIPAL INVESTIGATOR: Dhaval Patel, M.D.

STUDY TITLE: Estudio aleatorizado comparativo entre la adrenalectomía y la observación del paciente en el hipercortisolismo subclínico *(Randomized Control Trial of Adrenalectomy versus Observation for Subclinical Hypercortisolism)*

Continuing Review Approved by the IRB on 06/27/16
Amendment Approved by the IRB on 01/13/17 (D) Date Posted to Web: 01/25/17

Standard Spanish

INTRODUCCIÓN

Deseamos invitarlo a participar en un estudio de investigación en los Institutos Nacionales de Salud (*National Institutes of Health, NIH*).

En primer lugar, queremos que usted sepa que:

La participación en una investigación del NIH es totalmente voluntaria.

Usted puede decidir no participar o retirarse del estudio en cualquier momento. En cualquier caso, no perderá ninguna prestación a la que pueda tener derecho. No obstante, para recibir atención médica en el NIH usted debe participar en un estudio o estar en evaluación para participar en uno.

Es posible que no reciba ningún beneficio por su participación. Con la investigación podemos adquirir conocimientos que ayuden a otras personas en el futuro.

En segundo lugar, algunas personas pueden tener creencias personales, religiosas o éticas que limiten los tipos de tratamientos médicos o de investigación que deseen recibir (por ejemplo, transfusiones de sangre). Si usted es una de esas personas, hable al respecto con sus médicos o con el equipo de investigación del NIH antes de acceder a participar en el estudio.

El estudio se describe en las siguientes páginas. Antes de decidir participar, tómese todo el tiempo que necesite para formular preguntas y hablar del estudio con cualquier persona del NIH, o con su familia, sus amigos, su médico personal u otro profesional de la salud.

¿Por qué se está realizando este estudio?

Nos gustaría determinar si la extirpación quirúrgica de un tumor suprarrenal que se asocia con concentraciones altas de cortisol produce mejoras en la presión arterial alta, la diabetes, la obesidad, la osteoporosis o las concentraciones altas de colesterol.

¿Por qué le hemos pedido que participe en este estudio?

Le hemos pedido que participe en este estudio porque usted tiene un tumor de menos de dos pulgadas en las glándulas suprarrenales y presenta concentraciones altas de cortisol en la sangre.

¿Cuántas personas participarán en este estudio?

Les pediremos a un máximo de 66 personas que participen en este estudio.

Descripción del estudio de investigación

¿Qué pasará si usted participa en este estudio?

Antes de iniciar el estudio

Antes de que se inscriba en el estudio le haremos análisis de laboratorio, pruebas de diagnóstico por imagen y una exploración física para estar seguros de que usted puede someterse a la operación sin peligro y de que cumple los requisitos para participar en el estudio. Si los cumple, se le asignará de manera aleatoria para que se someta a la operación de inmediato o para que pase por un período de observación de 6 meses antes de la operación. La decisión de tener la operación de inmediato o 6 meses después dependerá de una asignación aleatoria (un proceso parecido a lanzar suertes con una moneda). Esta asignación se realizará en el momento en que usted acceda a participar en el estudio.

Durante el estudio

Grupo que se somete a la operación inmediatamente

Si resulta asignado de manera aleatoria a este grupo, le haremos una evaluación inicial y una operación para extirpar el tumor más grande. Luego se recuperará en la unidad de cuidados intensivos o en la unidad de hospitalización hasta que esté listo para que le den de alta y pueda regresar a casa. El tiempo que dure en recuperarse dependerá del tipo de operación que se requiera para extirpar el tumor. El cirujano le explicará la intervención en detalle y responderá a todas las preguntas que usted tenga. Se le pedirá que firme un formulario de consentimiento aparte para la operación.

Durante el primer año, regresará al Centro Clínico del NIH al cabo de 3 meses, 6 meses, 9 meses y 12 meses del alta hospitalaria. Después de que pase el primer año le examinaremos cada 6 meses durante el segundo año y luego una vez al año durante tres años más. En cada consulta de seguimiento le haremos pruebas de diagnóstico por imagen y análisis de sangre.

Grupo en el que se retrasa la operación

Si resulta asignado de manera aleatoria a este grupo, le haremos una evaluación inicial y luego tendrá que regresar a seguimiento cada 3 meses durante 6 meses. Después pasará al grupo que se somete a la operación y le extirparemos el tumor. Si presenta signos y síntomas de exceso de cortisol o si el tumor crece antes de que transcurran 6 meses de haberse inscrito en el estudio, pasará al grupo que se somete a la operación y le extirparemos el tumor más pronto. Luego se le

hará seguimiento al cabo de 3 meses, 6 meses, 9 meses y 12 meses del alta hospitalaria durante el primer año. Después de que pase el primer año le examinaremos cada 6 meses durante el segundo año y luego una vez al año durante tres años más. En cada consulta de seguimiento le repetiremos las pruebas de diagnóstico por imagen y los análisis de sangre.

Programación del estudio

Grupo que se somete a la operación inmediatamente

Evaluación inicial	• Cuestionario sobre la calidad de vida • Tomografía computarizada • • Tomografía por emisión de positrones con tomografía computarizada • Radioabsorciometría de doble energía (DEXA) • Ecografía doble • Radiografía de vértebras • Ecografía de la piel • Análisis corrientes de sangre • Recolección de orina de 24 horas
Operación	
Evaluación a los 3 meses	• Cuestionario sobre la calidad de vida • Ecografía doble • Radiografía de vértebras • Ecografía de la piel • Análisis corrientes de sangre • Recolección de orina de 24 horas

Evaluaciones al cabo de 6 meses y 9 meses	• Radiografía de vértebras • Ecografía de la piel • Análisis corrientes de sangre • Recolección de orina de 24 horas
Evaluaciones al cabo de 12 meses y 18 meses	• Cuestionario sobre la calidad de vida • Radioabsorciometría de doble energía (DEXA) • Ecografía de la piel • Análisis corrientes de sangre • Recolección de orina de 24 horas
Evaluaciones al cabo de 24 meses, 36 meses, 48 meses y 60 meses	• Radioabsorciometría de doble energía (DEXA) • Ecografía de la piel • Análisis corrientes de sangre • Recolección de orina de 24 horas

Grupo en el que se retrasa la operación

Evaluación inicial	• Cuestionario sobre la calidad de vida • Tomografía computarizada • Tomografía por emisión de positrones con tomografía computarizada • Radioabsorciometría de doble energía (DEXA) • Ecografía doble • Radiografía de vértebras • Ecografía de la piel • Análisis corrientes de sangre • Recolección de orina de 24 horas

Evaluaciones preoperatorias al cabo de 3 meses y 6 meses	• Cuestionario sobre la calidad de vida • Ecografía doble • Radiografía de vértebras • Ecografía de la piel • Análisis corrientes de sangre • Recolección de orina de 24 horas
Operación	
Evaluación a los 9 meses	• Cuestionario sobre la calidad de vida • Ecografía doble • Radiografía de vértebras • Ecografía de la piel • Análisis corrientes de sangre • Recolección de orina de 24 horas
Evaluaciones al cabo de 12 meses y 15 meses	• Radiografía de vértebras • Ecografía de la piel • Análisis corrientes de sangre • Recolección de orina de 24 horas
Evaluaciones al cabo de 18 meses y 24 meses	• Cuestionario sobre la calidad de vida • Radioabsorciometría de doble energía (DEXA) • Ecografía de la piel • Análisis corrientes de sangre • Recolección de orina de 24 horas
Evaluaciones al cabo de 30 meses, 42 meses, 54 meses y 66 meses	• Radioabsorciometría de doble energía (DEXA) • Ecografía de la piel • Análisis corrientes de sangre • Recolección de orina de 24 horas

Métodos anticonceptivos

Si usted es mujer y está embarazada o amamantando no podrá participar en el estudio. Es mejor evitar exponer el feto a radiaciones porque es más sensible a las radiaciones que el adulto. Si puede quedar embarazada o si es hombre y su pareja es una mujer que puede quedar embarazada, tendrá que usar un método anticonceptivo eficaz antes de iniciar el tratamiento del estudio y durante el tratamiento del estudio. Si cree que usted o su pareja está embarazada, debe avisarle de inmediato al médico o a la enfermera del estudio.

Entre los métodos anticonceptivos eficaces están:

- abstenerse de tener relaciones sexuales
- dispositivo intrauterino (DIU)
- métodos hormonales (anticonceptivos orales, inyecciones o implantes)
- ligadura de trompas
- vasectomía

Riesgos o molestias relacionados con la participación

Operación

Los efectos secundarios de la operación son los mismos que podría presentar si se sometiera a la operación corriente para extirpar un tumor suprarrenal en una institución médica grande.

Tomografía por emisión de positrones con desoxiglucosa marcada con flúor (FDG-TEP)

La tomografía misma es indolora. La principal molestia que sentirá al someterse a esta prueba es el tiempo que tendrá que pasar acostado e inmóvil. En la tomografía por emisión de positrones (PET, por sus siglas en inglés) se usa una cantidad pequeña de un compuesto radioactivo llamado 18-fluorodesoxiglucosa (F18-FDG) para ver con claridad los tumores que haya en el cuerpo. No debe comer por un período de entre 4 y 6 horas antes de la prueba. El médico o la enfermera le dará instrucciones específicas. Si todavía no tiene en la vena un catéter intravenoso (un tubo plástico pequeño o una aguja), es posible que le pongamos uno, lo cual puede causar una molestia leve o la aparición de moretones.

Ecografía de la piel

Esta técnica no duele ni requiere preparación.

Radioabsorciometría de doble energía (DEXA)

La radioabsorciometría de doble energía (DEXA) es una prueba que mide la cantidad total de grasa del cuerpo y la densidad de los huesos. Emplea haces de rayos X de alta y baja energía que producen dos imágenes diferentes. La combinación de estas imágenes permite determinar el contenido de grasa y la densidad mineral de los huesos.

Ecografía doble

La ecografía doble es una forma de ecografía en la que se combinan dos elementos. El primero es la ecografía en escala de grises, mediante la cual se visualiza la estructura o arquitectura de una determinada parte del cuerpo. Este tipo de ecografía no evalúa el movimiento ni el flujo sanguíneo. El segundo elemento es la ecografía Doppler color, que sirve para visualizar el flujo o movimiento de una estructura. Por lo general, se usa para obtener imágenes de la sangre que se encuentra dentro de una arteria.

Morfometría vertebral (mediante rayos X) y composición corporal

Las radiografías son pruebas corrientes de diagnóstico por imágenes que se usan para diagnosticar y controlar muchas enfermedades. Aunque estas pruebas se han usado durante muchos años, todavía se están descubriendo los efectos que pueden causar a largo plazo en el organismo. La molestia más frecuente es la cantidad de tiempo que el paciente debe permanecer acostado e inmóvil durante la radiografía o la prueba de diagnóstico por imagen.

Riesgos causados por la radiación

Este estudio de investigación conlleva exposición a radiación a partir de 10 mCi provenientes de la 18-fluorodesoxiglucosa que se utiliza en la tomografía por emisión de positrones y a partir de la tomografía computarizada que realiza con esta prueba. Tenga en cuenta que esta exposición a radiaciones no es necesaria para su atención médica y que solo ocurre para efectos de la investigación. La cantidad total de radiación que recibirá a partir de la tomografía por emisión de positrones con FDG combinada con tomografía computarizada es una dosis eficaz de 1.2 rem. El Comité de Seguridad en Radiaciones del NIH ha examinado el uso de radiaciones en este estudio de investigación y lo ha aprobado ya que implica un riesgo ligeramente mayor que el mínimo y es necesario para la obtención de la información que se desea.

Si usamos la forma acostumbrada de describir las dosis de radiación, podemos decir que al participar en este estudio usted recibirá un total de 3.9 rem en la vejiga urinaria, 2.9 rem en la pared cardíaca y 2.0 rem en el bazo. Los demás órganos recibirán cantidades menores de radiación.

Aunque cada órgano recibirá una dosis diferente, la cantidad de radiación que usted recibirá a partir de estas técnicas equivale a una exposición corporal uniforme de 1.2 rem. Este valor calculado se conoce como "dosis eficaz" y se usa para comparar la dosis recibida por cada órgano con un valor único. La cantidad de radiación recibida en este estudio se ciñe a las normas

recomendadas en sujetos de investigación por el Comité de Seguridad en Radiaciones del NIH. La norma es de una dosis eficaz de 5 rem (5,000 mrem) al año.

Para efectos comparativos, en los Estados Unidos una persona corriente recibe una exposición a radiaciones de 0.3 rem (300 mrem) al año a partir de fuentes ambientales naturales como el sol, el espacio exterior y los materiales radiactivos naturales del aire y el suelo de nuestro planeta. Si desea obtener más información acerca de las radiaciones y quiere ver ejemplos de niveles de exposición a partir de otras fuentes, pídale al investigador una copia del folleto "Introducción al tema de las radiaciones para sujetos de investigación del NIH" (*An Introduction to Radiation for NIH Research Subjects)*.

Aunque no hay pruebas directas de que la cantidad de exposición que se reciba al participar en este estudio sea peligrosa, hay pruebas indirectas de que quizá no sea completamente inofensiva. Puede haber un aumento muy leve del riesgo de contraer cáncer.

Avísele a su médico si ha tenido alguna exposición a radiaciones en el último año, ya sea a partir de otros estudios de investigación, por pruebas médicas o por la atención médica que haya recibido, de modo que nos aseguremos de que no reciba demasiada radiación. La exposición a radiaciones comprende las radiografías que le hayan tomado, los cateterismos cardíacos, las radioscopias y las pruebas de medicina nuclear en las que le hayan inyectado sustancias radiactivas en el cuerpo.

Si está embarazada no le permitiremos participar en este estudio de investigación. Si está amamantando y el protocolo exige la inyección de materiales radiactivos, no se le permitirá participar. Es mejor no exponer a radiaciones al feto y al lactante, porque ellos son más sensibles a las radiaciones que los adultos.

Posibles beneficios derivados de la participación

¿Existen beneficios asociados con la participación en este estudio?

Los datos de este estudio pueden contribuir al descubrimiento de nuevas formas de tratar el hipercortisolismo, pero es posible que usted no se beneficie directamente de esto.

Estrategias o tratamientos alternativos

En vez de participar en este estudio, usted tiene estas alternativas:

- El tratamiento expectante sin cuidado o tratamiento en particular para su cáncer
- Recibir tratamiento o atención para su tumor suprarrenal en una instalación diferente sin estar en un estudio

- Participar en otro estudio en el que usted sea elegible
- Obtener cuidados de confort, también llamados cuidados paliativos. Este tipo de cuidado ayuda a reducir el dolor, cansancio, problemas de apetito y otros problemas causados por el cáncer. No trata el cáncer directamente. En su lugar, trata de mejorar cómo te sientes. El cuidado de la comodidad trata de mantenerte lo más activo y cómodo posible

Hable con su médico sobre estas y otras alternativas.

Derechos de los participantes en la investigación

¿Cuál es el costo de participar en este estudio?

Si decide participar en el estudio, se aplicará lo siguiente, según las normas del NIH:

- Usted recibirá el tratamiento del estudio completamente gratis. El tratamiento puede comprender una operación, medicamentos, pruebas de laboratorio, radiografías y otras pruebas de diagnóstico por imagen que se realicen en el Centro Clínico de los Institutos Nacionales de Salud o fuera de él, si en el NIH no se cuenta con ese tratamiento relacionado con el estudio y el equipo de investigación ha hecho arreglos para que se realice en otro centro.
- Hay fondos limitados para pagar el costo de algunas pruebas e intervenciones que se realicen fuera del Centro Clínico del NIH. Es posible que tenga que pagar el costo de estas pruebas e intervenciones si su compañía de seguros no lo cubre.
- El Centro Clínico del NIH no proporcionará los medicamentos que no formen parte del tratamiento del estudio ni pagará por ellos.
- Cuando usted haya finalizado su participación en el estudio, ya no se le prestará atención médica en el Centro Clínico del NIH.

¿Se mantendrá en confidencialidad su información médica?

Haremos todo lo posible por asegurarnos de que la información personal contenida en su expediente médico se mantenga en confidencialidad. Sin embargo, no podemos garantizarle privacidad completa. Las organizaciones que pueden ver o copiar sus expedientes médicos para efectos de investigación, garantía de calidad y análisis de datos comprenden:

- El Instituto Nacional del Cáncer (NCI) y otros organismos gubernamentales —como la Administración de Alimentos y Medicamentos (FDA)— que se encargan de que las investigaciones no constituyan un peligro para las personas
- El comité de ética en investigación (IRB) del Instituto Nacional del Cáncer

Tal como lo exige la ley en los Estados Unidos, una descripción de este ensayo clínico estará disponible en: http://www.Clinicaltrials.gov. Este sitio web no incluirá formación que pudiera identificarlo a usted. En el sitio solo se incluirá un resumen de los resultados del estudio. Usted puede visitar el sitio cuando lo desee.

Suspensión del tratamiento

El médico puede decidir suspender el tratamiento por las siguientes razones:

- Si cree que esto es lo que más le conviene a usted.
- Si se dispone de nueva información que muestre que otro tratamiento sería mejor para usted.
- Si se queda embarazada

Si esto sucede, se le informará la razón por la que se está suspendiendo el tratamiento.

Usted puede dejar de participar en el estudio en cualquier momento. Sin embargo, si decide dejar de participar, nos gustaría que hablara primero con el médico del estudio y con su médico personal.

Si decide en algún momento retirar su consentimiento para participar en el estudio, no recolectaremos ninguna información médica adicional acerca de usted. Si retira su consentimiento y se va del estudio, todas las muestras que se hayan obtenido de usted para el estudio y que se conserven en el NCI se pueden destruir cuando usted lo solicite. Sin embargo, las muestras y los datos obtenidos a partir de ellas que ya se hayan entregado a otros investigadores o que ya se hayan incluido en las bases de datos de investigación **no se podrán** recuperar ni destruir.

Uso de información para investigaciones futuras

Para que la ciencia avance, resulta útil que los investigadores compartan la información que obtienen al estudiar muestras humanas. Hacen esto al guardar la información en una o más bases de datos científicas, donde se almacena junto con la información de otros estudios. Un

investigador que desee analizar la información debe solicitar acceso a la base de datos y su solicitud debe ser aprobada. Los investigadores utilizan las muestras y la información almacenadas en las bases de datos científicas para que la ciencia avance y para aprender sobre la salud y las enfermedades.

Planeamos conservar algunas de las muestras y datos que se recopilen de usted con el fin de usarlos para investigaciones futuras y compartirlos con otros investigadores. No nos pondremos en contacto con usted en relación con cada uno de esos usos futuros. Estas muestras y estos datos no tendrán identificadores, tales como nombre, dirección o número de cuenta, de modo que puedan utilizarse en investigaciones futuras sobre cualquier tema y se puedan compartir ampliamente con fines de investigación. Sus muestras y datos serán utilizados únicamente con fines de investigación y su uso no lo beneficiará a usted. También es posible que las muestras y los datos guardados nunca se usen. Los resultados de las investigaciones realizadas con sus muestras y datos no estarán a disposición suya ni de su médico, pero más adelante podrían ayudar a personas que padecen cáncer u otras enfermedades.

Si no desea que sus muestras y datos guardados sean utilizados para investigaciones futuras, póngase en contacto con nosotros por escrito y háganos saber que no desea que utilicemos sus muestras ni sus datos. Así, cualquier muestra que no haya sido utilizada ni compartida será destruida y sus datos no se utilizarán en investigaciones futuras. Sin embargo, es posible que no podamos retirar o eliminar materiales o datos una vez que se hayan compartido con otros investigadores.

INFORMACIÓN PERTINENTE ADICIONAL

1. Confidencialidad. Cuando los resultados de un estudio de investigación del NIH se dan a conocer en revistas médicas o reuniones científicas, no se menciona la identidad de los participantes. En la mayoría de los casos, el NIH no divulgará ninguna información sobre su participación en una investigación a menos que usted otorgue su permiso por escrito. No obstante, si usted firma una autorización de divulgación de información, por ejemplo, a una empresa aseguradora, el NIH le proporcionará a ésta información de su expediente médico. Esta información podría influir (en forma favorable o desfavorable para usted) en la disposición de la aseguradora de venderle el seguro.

La Ley Federal de Protección de la Vida Privada *(Federal Privacy Act)* protege el carácter confidencial de sus expedientes médicos en el NIH. Sin embargo, es importante que sepa que esta ley permite la divulgación de cierta información de su expediente médico sin su autorización, por ejemplo, si lo solicitan la Administración de Alimentos y Medicamentos (FDA), los miembros del Congreso, los agentes encargados del cumplimiento de la ley o las organizaciones autorizadas para efectos de acreditación hospitalaria.

2. Normas sobre lesiones relacionadas con la investigación. El Centro Clínico le dará atención médica a corto plazo para cualquier lesión que se deba a su participación en una investigación que se realice allí. En general, ni los Institutos Nacionales de Salud, ni el Centro Clínico, ni el gobierno federal le darán atención médica a largo plazo ni indemnización económica por lesiones relacionadas con la investigación. Sin embargo, usted tiene derecho a buscar una compensación legal si cree que la lesión justifica dicha medida.

3. Pagos. El monto del pago que se ofrece a los voluntarios de investigación se rige por las normas de los Institutos Nacionales de Salud. En general, a los pacientes no se les paga por participar en estudios de investigación en los Institutos Nacionales de Salud. Se ofrecerá reembolso de gastos de viaje y de viáticos según las normas del NIH.

4. Problemas o preguntas. Si hay algún problema o usted tiene una pregunta respecto a este estudio, a sus derechos de participante en un estudio de investigación clínica o a alguna lesión relacionada con la investigación, debe comunicarse con el investigador principal, el doctor Dhaval Patel, Building (edificio) 10, Room (sala) 3-5840, teléfono: 240-760-6155 o con el doctor Electron Kebebew; Building (edificio) 10, Room (sala) 4-5952, teléfono: 240-760-6153. También puede llamar al representante de los pacientes del Centro Clínico, al teléfono (301) 496-2626. Si tiene preguntas sobre el uso de sus muestras o de sus datos en estudios futuros de investigación, puede comunicarse también con la oficina del Director Clínico, llamando al teléfono240-760-6070.

5. Documento de consentimiento. Le sugerimos que conserve una copia de este documento para consultarla posteriormente.

COMPLETE LAS CASILLAS CORRESPONDIENTES A CONTINUACIÓN:

A. Consentimiento de un paciente adulto.

He leído la explicación relacionada con este estudio y he tenido la oportunidad de comentarla y hacer preguntas. Por este medio otorgo mi consentimiento para participar en este estudio.

Firma del paciente adulto o de su representante legal _____ Fecha _____

Nombre en letra de imprenta _____

B. Permiso otorgado por el (los) padre(s) de un paciente menor de edad.

He leído la explicación relacionada con este estudio y he tenido la oportunidad de comentarla y hacer preguntas. Por este medio otorgo permiso para que mi hijo participe en este estudio.
(Anéxese el formulario de asentimiento para menores de edad, NIH 2514-2, Asentimiento de un menor de edad, si corresponde.)

Firma del (los) padre(s) o del tutor legal _____ Fecha _____

Nombre en letra de imprenta _____

C. Asentimiento verbal de un niño (si corresponde)

Se le explicó a mi hijo la información contenida en el formulario de consentimiento anterior y mi hijo accede a participar en el estudio.

Firma del (los) padre(s) o del tutor legal _____ Fecha _____ Nombre en letra de imprenta _____

EL USO DE ESTE DOCUMENTO DE CONSENTIMIENTO ESTÁ APROBADO DESDE EL 27 DE JUNIO DE 2016 HASTA EL 26 DE JUNIO DE 2017.

Firma del investigador _____ Fecha _____ Firma del testigo _____ Fecha _____

Nombre en letra de imprenta _____ Nombre en letra de imprenta _____