LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

PROTOCOL AMENDMENT #8

LCCC 1326: Metformin with the Levonorgestrel-Releasing Intrauterine Device for the treatment of Complex Atypical Hyperplasia (CAH) and Endometrial Cancer (EC) in Non-surgical Patients

AMENDMENT INCORPORATES (check all that apply):

__X_ Editorial, administrative changes (IRB approval)
___ Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
_X_ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

This amendment addresses a change to the month 12 time point and the final study encounter. Amendment 5 changed the designation of the final study event from "visit" to "encounter" as the subject could be contacted by phone. However, activities in the final study encounter that required an office visit remained in the Time and Events Table and in the text (Section 6.5) and need to be removed. Further, the language of "Final Study Encounter" was not carried throughout the protocol.

This amendment provides editorial/administrative changes to the protocol to clarify the language surrounding the Final Study Encounter throughout the protocol and the activities associated with that encounter. The random (non-fasting) glucose originally scheduled for the Final Study Encounter has been moved to the 12-month time point in the protocol. Additionally, the Principal Investigator has been changed to Dr. Victoria Bae-Jump.

The Eligibility criteria has been changed from excluding subjects with current use of progestin therapy to excluding subjects with current use of progestin therapy that has been ongoing for > 3 months.

Editorial Changes:

1. Section 6.4.3: Added a random (non-fasting)glucose as an evaluation at month 12.

2. Section 6.5: Changed the designation of from Final Study Visit to Final Study Encounter in the title and text. Changed wording that subjects "may" rather than "will" return to the clinic. Removed the last sentence of the paragraph describing final study evaluation activities.

3. Time and Events Table. Section 6.1: Changed title of last column on the right to "Final Study Encounter." Removed History and Physical, Random (non-fasting) glucose, and

Blood and Urine collection from Final Study Encounter activities. The random (non-fasting) glucose was moved to the month 12 time point.

4. The Principal Investigator has been changed from Dr. Allison Staley to Dr. Victoria Bae-Jump.

Eligibility Change

1. Criterion 3.2.2: The criterion has been changed from excluding subjects with current use of progestin therapy to excluding subjects with current use of progestin therapy that has been ongoing for > 3 months.

The attached version dated May 15, 2020, incorporates the above revisions.

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PROTOCOL AMENDMENT #7

LCCC 1326: Metformin with the Levonorgestrel-Releasing Intrauterine Device for the treatment of Complex Atypical Hyperplasia (CAH) and Endometrial Cancer (EC) in Non-surgical Patients

AMENDMENT INCORPORATES (check all that apply):

__X_ Editorial, administrative changes (IRB approval)
___ Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
__X_ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

The time measurements for the LCCC1326 trial were originally stipulated in a mix of weeks and months that could benefit from clarification. In order to ensure consistent time measurement, this amendment modifies time references as needed. Additionally, the required time limit for screening labs has been clarified to within 30 days.

This amendment also updates the exclusion criteria to remove the limit on tumor size of less than or equal to 2cm, as an aid in enrollment of additional subjects.

In addition, because UNC Lineberger recently changed its multicenter SOPs to allow for distribution of protocol amendments to all sites at the same time, this amendment modifies language in the protocol to allow that.

Additionally, the language explaining the Study Withdrawal process, as well as the language explaining the drug handling and disposal for Metformin, has been updated.

Editorial Changes:

- Time measurements have been restated where needed for clarity and to facilitate analysis. These changes have been made in Sections 1.1, 1.3.3, 3.2.7, 3.2.10, 4.1, 4.2, 4.3, 4.4, 4.8, 5.1.6, 6.1, and 6.4.2.

- In Sections 4.2 and 5.4, the timing of screening labs has been clarified to within 30 days of starting treatment.

- The Study Withdrawal language in Section 4.10 has been updated in line with current process.

- In Section 5.1.5, the language regarding drug handling and disposal has been clarified for Metformin.

- Section 8.6 has been updated to reflect a recent change in multicenter SOPs to allow for distribution of protocol amendments to all sites at the same time.

Eligibility Changes:

- Tumor size > 2cm on MRI or pelvic ultrasound has been removed from the Exclusion Criteria in Section 3.2.3.

The attached version dated March 4, 2019, incorporates the above revisions.

LINEBERGER COMPREHENSIVE CANCER CENTER
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PROTOCOL AMENDMENT #6

LCCC 1326: Metformin with the Levonorgestrel-Releasing Intrauterine Device for the treatment of Complex Atypical Hyperplasia (CAH) and Endometrial Cancer (EC) in Non-surgical Patients

AMENDMENT INCORPORATES (check all that apply):

__X_ Editorial, administrative changes (site added, IRB notification required)
___ Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

- The role of Principal Investigator has transferred from Stephanie Sullivan, MD to Allison Staley, MD.

LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

PROTOCOL AMENDMENT #5

LCCC 1326: Metformin with the Levonorgestrel-Releasing Intrauterine Device for the treatment of Complex Atypical Hyperplasia (CAH) and Endometrial Cancer (EC) in Non-surgical Patients

AMENDMENT INCORPORATES (check all that apply):

__X_ Editorial, administrative changes (site added, IRB notification required)
___ Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

- Sections 4.2 and 5.5 updated to increase the number of days between IUD placement and start of metformin treatment. Subjects may now begin treatment within 30 days of IUD placement, instead of 7 days.
- Section 4.8 updated to remove the word "visit" in describing the last study encounter for follow-up purposes. Subjects may come in for a clinic visit, or be contacted by a study team member via phone.
- A biopsy window added to the Time and Events Table to allow a +/- 2 week window for the standard of care biopsies which occur every 3 months.

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PROTOCOL AMENDMENT #4

LCCC 1326: Metformin with the Levonorgestrel-Releasing Intrauterine Device for the treatment of Complex Atypical Hyperplasia (CAH) and Endometrial Cancer (EC) in Non-surgical Patients

AMENDMENT INCORPORATES (check all that apply):

__X_ Editorial, administrative changes (site added, IRB notification required)
___ Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

The protocol has been updated to include a clarifying note for non-surgical candidates. The following language was added to the protocol:

"Patient determined to be a non-surgical candidate by the primary treating physician."

LINEBERGER COMPREHENSIVE CANCER CENTER
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PROTOCOL AMENDMENT #3

LCCC 1326: Metformin with the Levonorgestrel-Releasing Intrauterine Device for the treatment of Complex Atypical Hyperplasia (CAH) and Endometrial Cancer (EC) in Non-surgical Patients

AMENDMENT INCORPORATES (check all that apply):

__X_ Editorial, administrative changes (site added, IRB notification required)
___ Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

We submit to you two changes to our screening procedures and one change to the wording in study information

1. Currently, we require cervical cultures for gonorrhea and chlamydia prior to IUD placement for all patients enrolled on study. This is not the standard of care and was added in by an IRB reviewer when the trial was initially reviewed. Since then, this has proved to be a significant impedance to successful enrollment as cultures are frequently collected at the time of IUD placement (to avoid multiple pelvic exams) and take 3 days to return. This requires patients to return after cultures have resulted for drug when they would have usually would not have to return again for 3 months. The American College of OB/GYNs recommends that cervical cultures only be collected prior to IUD placement for women at high risk. The US preventative services task force recommends screening for STI for women age 24 and younger as these women are at highest risk for STIs. We would like to modify our protocol to only require screening for those women who are high risk at age 24 and younger. We have consulted the IRB chair and vice-chairs regarding this change and they are in agreement with our proposed change. Additionally, the vice-chairs supported not repeating testing for women who have had or been treated for gonorrhea or chlamydia in the past 3 months which we are advocating for as well.

2. At our pre-treatment visit, we require that women undergo a urine pregnancy test prior to IUD placement. This is the standard of care for any gynecologic or surgical procedure. We are currently requiring women of childbearing potential to have a negative serum pregnancy test within 7 days of starting drug. Given the high sensitivity of a urine pregnancy test as evidence by its use to rule out pregnancy prior to IUD placement, this serum pregnancy test is redundant and unnecessary. We would like to take this out of our screening protocol.

3. We have changed verbiage surrounding the D&C procedure. The D&C procedure is frequently done to make a definitive diagnosis of hyperplasia or endometrial cancer; however, many women are diagnosed only on biopsy. If the primary provider does not feel that a D&C is necessary, many women will forgo the morbidity of the procedure and have the LR-IUD placed in clinic. We have changed the study design to reflect this practice pattern.

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PROTOCOL AMENDMENT #2

LCCC 1326: Metformin with the Levonorgestrel-Releasing Intrauterine Device for the treatment of Complex Atypical Hyperplasia (CAH) and Endometrial Cancer (EC) in Non-surgical Patients

AMENDMENT INCORPORATES (check all that apply):

__X_ Editorial, administrative changes (site added, IRB notification required)
___ Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

The Principal Investigator is changing from Dr. Kemi Doll to Dr. Stephanie Sullivan. Additionally, the hip-to-waist measurement has been removed and the funding source has been updated to Golfers Against Cancer.

LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

PROTOCOL AMENDMENT #1

LCCC 1326: Metformin with the Levonorgestrel-Releasing Intrauterine Device for the treatment of Complex Atypical Hyperplasia (CAH) and Endometrial Cancer (EC) in Non-surgical Patients

AMENDMENT INCORPORATES (check all that apply):

__X_ Editorial, administrative changes (site added, IRB notification required)
___ Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

AMENDMENT RATIONALE AND SUMMARY:

This study was a single center trial being conducted at UNC. An additional site located out of state is being added to assist with meeting accrual objectives. Text has been added in the protocol to note that this is a multi-center study in the study synopsis, study schema and statistical sections. Instructions for how metformin will be purchased and supplied have been added in the drug information section of the protocol (ie, 5.1.2 Supplier/How Supplied) to account for the addition of a new study site. Section 5.1.5 Return and Retention has been added to the drug information section. Sections 4.3 and 5.1.2 have been revised to include wording for handling of metformin at an additional study site. Section 5.1.5 return/retention of drug supply was added. Section 6.1 footnote 3 was edited to account for multi-center study. Additional standard wording has been added to Section 8.0 Study Management to account for the conduct of a multi-center trial. In addition, a new statistician has been assigned to the study due to personnel changes.

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LCCC 1326: Metformin with the Levonorgestrel-Releasing Intrauterine Device for the treatment of Complex Atypical Hyperplasia (CAH) and Endometrial Cancer (EC) in Non-surgical Patients

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Sponsor: Lineberger Comprehensive Cancer Center
Funding Source: Golfers Against Cancer Grant

Version: May 15, 2020. Version 1.1

LCCC 1326: Metformin with the Levonorgestrel-Releasing Intrauterine Device for the treatment of Complex Atypical Hyperplasia (CAH) and Endometrial Cancer (EC) in Non-surgical Patients

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Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name:_____

PI Signature: _____

Date:_____

Protocol Version Date: May 15, 2020 Version 1.1

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1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

This is an open label, single-arm, multi-center study of the addition of metformin to standard levonorgestrel-releasing intrauterine device (LR-IUD) treatment of 30 evaluable non-surgical patients with either complex atypical hyperplasia (CAH; n=15) or grade 1 endometrial adenocarcinoma (EC; n=15). Women, over the age of 18 years, with biopsy-proven CAH/EC who are not candidates for surgical management, and therefore are planned to start standard of care treatment with the LR-IUD, will be given oral metformin therapy for 12 months, or until disease progression occurs (whichever occurs first), in addition to LR-IUD treatment. Serial endometrial biopsies will be performed, as per standard of care, to assess disease status. We hypothesize that the addition of metformin to standard LR-IUD treatment of CAH and grade 1 EC will result in a complete response (CR) rate at 6 months that is significantly higher than 50% in a population of non-surgical candidates. In addition, we plan to estimate CR rate at 6 months in CAH and EC separately, and in the group as a whole at 12 months. We will also document the rate of patient adherence to long-term metformin therapy.

1.2 EC and CAH

EC is the fourth most common cancer among women in the United States (1). Type I or those tumors of endometrioid histology comprise 70-80% of cases and are thought to arise from unopposed estrogen stimulation, either endogenous or exogenous. CAH is a neoplastic condition of the endometrium and is a precursor lesion to EC. If untreated, CAH progresses to invasive cancer at a rate of 30% (2). In addition, CAH and grade 1 EC represent a spectrum of neoplasia, evidenced by a 40-50% rate of concurrent EC found on hysterectomy specimen when CAH is present (3) as well as a concordance of only 40% among pathologists when deciding between CAH and grade 1 EC (4). Given this overlap, these pathological diagnoses are treated similarly clinically.

Obesity, which increases bioavailable estrogen levels by enhancing the conversion of androstenedione to estrone in peripheral adipose tissue, is a well-established risk factor for type I EC and its precursor lesion, CAH, and has been estimated to account for up to 40-90% percent of type I EC cases (5-7). Insulin resistance, of which a marker is the level of adiponectin (a protein secreted by adipose cells), characterizes obesity associated metabolic syndrome and diabetes. Low adiponectin levels, indicating insulin resistance, have been found to be significantly associated with the development of EC (8). Correspondingly, diabetes and insulin resistance have been linked to a 2-3 fold increased risk of developing CAH and EC (8-11).

The standard of care therapy for CAH and EC is surgical excision and staging. However, there is a growing subset of patients for whom surgery is not an option. Due to the obesity epidemic and increasing numbers of reproductive-age women

being diagnosed with CAH/EC, non-surgical options that can maintain fertility and avoid operative risks are essential. Patients with major medical co-morbidity and poor performance status are not operative candidates, but require curative therapy for CAH/EC. A current accepted alternative treatment option for these patients is long-term progesterone therapy in the form of the levonorgestrel-releasing IUD (LR-IUD). Gunderson and colleagues conducted a meta-analysis of 45 studies (n=391 subjects) evaluating women with CAH or EC undergoing progestin therapy (systemic therapy or LR-IUD). For the group as a whole, the CR rate (as assessed via biopsy) was 66% for CAH and 48% for EC. (12) Median time to response was 6 months. Importantly, 25% of CAH and 37% of EC patients experienced relapse after initial response (12). In the literature for CAH/EC, an assessment of response is categorized by pathologic criteria on follow-up biopsies. A complete response ("disease regression") is defined as no evidence of microscopic viable hyperplasia or cancer cells; stable disease ("disease persistence") is defined as no change in biopsy status from prior to treatment; and progressive disease is defined as newly found or increase in grade of adenocarcinoma from the pre-treatment biopsy (12, 13).

1.3 Metformin

An adjuvant therapy to progestins for CAH/EC may be metformin. Metformin is an anti-diabetic medication (biguanide class) that is widely used as the first line treatment of type II diabetes. It is an inexpensive, well-tolerated, effective medication for normalizing hyperglycemia (14), and also prevents the development of diabetes in patients with obesity and metabolic syndrome (15, 16). Increasing epidemiological evidence suggests that metformin lowers all cancer risk and reduces cancer incidence and deaths among diabetic patients (17-19). In our own retrospective analysis of metformin and EC outcomes in diabetic patients, metformin use was significantly associated with improved progression free survival (PFS;HR 0.44, 95% CI 0.28-0.70, $p<0.01$) and overall survival (OS; HR 0.35, 95% CI 0.20-0.59, $p<0.0001$) (20).

Metformin's immediate downstream target is AMP-activated protein kinase (AMPK), and its activation by metformin leads to regulation of multiple signaling pathways involved in the control of cellular proliferation, including inhibition of the mammalian target of rapamycin (mTOR) pathway. Alterations in the mTOR pathway, involving LKB1 and PTEN, have been implicated in EC carcinogenesis in up to 83% of type 1 ECs (21-23). Furthermore, our preliminary work reveals that metformin is a potent inhibitor of cell proliferation in EC cell lines, through inhibition of mTOR signaling (24).

Metformin may be effective in treating CAH and EC. In an animal mouse model of endometrial hyperplasia (EH), metformin exhibited anti-proliferative effects on the endometrium that coincided with inhibition of downstream targets of the mTOR pathway (25). Case reports have shown that metformin plus oral contraceptives, and metformin plus progesterone have been effectively used to treat CAH refractory to progesterone alone (26, 27). Metformin has also been

implicated in the reversal of progestin resistance that can develop during long-term treatment of CAH/EC with progestins (28), providing rationale for its use in combination with localized progestin therapy.

1.3.1 Published Studies of Metformin in Non-Diabetic Cancer Patients

Two clinical trials of metformin use in cancer patients have been published, neither of which specifically enrolled diabetic patients. In a pre-operative window study in operable breast cancer patients, the percentage of cells staining for Ki-67, a marker of cell proliferation, fell significantly after only 2 weeks of treatment with metformin, with parallel beneficial effects on cell signaling pathways such as the mTOR pathway (29). A completed phase I study of temsirolimus and metformin in advanced solid tumors demonstrated acceptable toxicity and promising response rates in a heavily pre-treated group of patients (30). In these trials, no significant toxicities were associated with metformin use in non-diabetic patients. Additionally, in our own preoperative window study in obese endometrial cancer patients, we did not find any significant toxicity and most of the women were non-diabetic. Taken together, these studies suggest a similar and favorable side effect profile between non-diabetics and diabetics taking metformin.

1.3.2 Preliminary and Planned Studies of Metformin in EC

Pre-operative Window Study of Metformin. Based on our preliminary *in vitro* work (24, 31), we conducted a pre-operative window study of metformin in EC patients at UNC-CH (LCCC 1102). In this study, obese women who were to undergo surgical staging for EC received short-term treatment (2-4 weeks) with metformin that continued until the day before their surgery. Metformin significantly reduced Ki-67 staining based on comparison of pre-treatment endometrial biopsies with post-treatment hysterectomy specimens (mean of 19.5% decrease, p=0.026) (32). Metformin was also well tolerated with only two grade 1 toxicities of mild abdominal pain and loose stools, which did not require discontinuation of treatment.

In addition, metformin treatment resulted in decreased expression of phosphorylated AMPK (60.3%, p=0.00001), phosphorylated Akt (44.2%, p=0.0002), phosphorylated S6 (51.2%, p=0.0002) and phosphorylated 4E-BP-1 (74.7%, p=0.001). Metformin decreased estrogen receptor (ER) expression (65.7%, p=0.0002), but had no effect on progesterone (PR) expression. Metabolomic profiling of serum indicated that treatment "responders" appeared more sensitive to metformin's effect on central carbon metabolism, particularly with respect to systemic lipolysis, which correlated with a shift in lipid and carbohydrate metabolism in their corresponding tumors.

The Gynecologic Oncology Group (GOG) has recently approved a clinical trial of metformin in EC patients, and Dr. Bae-Jump is the Principal Investigator of this study. This trial is a two arm, randomized, placebo-controlled phase II/III trial designed to assess the efficacy and safety of metformin in combination with

paclitaxel and carboplatin versus paclitaxel and carboplatin alone in women with advanced and recurrent EC. This trial is set to open for enrollment in 2013.

Metformin Transporter Proteins. One critical, unanswered question in regards to the action of metformin is the extent to which this drug accumulates in neoplastic tissues. Metformin is highly hydrophilic with a net positive charge at all physiologic pH values. Therefore, it requires cation-selective transport proteins that mediate its entry into cells. The cation-selective transporters organic cation transporter (OCT)1-3, plasma membrane monoamine transporter (PMAT) and multidrug and toxin extrusion transporters (MATE) 1-2 mediate metformin transport in the liver, intestine, and kidney(33-39) Less is known about the expression of these transporter proteins in solid tumors. Studies in our laboratory show that metformin uptake into human breast cancer cell lines are dictated by the expression levels of these cation-selective transporters (unpublished data). Therefore, it is reasonable to assume that metformin uptake into endometrial cancer cell lines and tissues must be mediated by specific cation-selective transporters.

Initial real-time polymerase chain reaction (RT-PCR) experiments to determine if cation-selective metformin transporters are expressed in endometrial cancer cell lines showed that all transporters of interest are present at varying levels (unpublished data). MATE1 and 2 were the most highly expressed transporters in endometrial cancer cell lines (Ishikawa and ECC-1) while OCT2 and 3 were the least expressed transporters. In the serous endometrial cancer cell line (SPEC-2), MATE1 and PMAT expression predominated, with much decreased expression of MATE2. We also assessed the expression of the metformin transporter proteins in fifteen human endometrial cancer specimens and adjacent benign tissues. MATE1 was found to be the predominant transporter in endometrial tumor and benign tissues; however, PMAT and OCT3 were also expressed in significant amounts. Thus, we anticipate that the highly expressed MATE1 will facilitate metformin intracellular uptake into endometrial tumors and be predictive of treatment response to this agent.

1.3.3 Metformin Associated Toxicities

The risks of metformin treatment in patients with CAH/EC are minimal. Metformin is one of the most common drugs used for the treatment of type II diabetes mellitus as well as for ovulation induction in Polycystic Ovarian Syndrome (PCOS) patients. For the purpose of this study, patients will be taking a standard clinical dose of metformin that is used commonly in the treatment of type II diabetes.

The usual dose of metformin is 850-1,000 mg twice daily. The maximum safe dose is thought to be 850 mg three times daily. To minimize gastrointestinal (GI) upset or diarrhea, it is recommended to start with a low dose and work up to the recommended dose. Thus, we plan to start with the dose of 850 mg once a day and titrate this to 850 mg twice a day, over the course of 30 days. This twice a day

regimen is also the dose that is commonly being used in clinical trials for metformin as cancer treatment (see www.clinicaltrials.gov for ongoing clinical trials of metformin for cancer treatment).

GI side effects are by far the most common adverse effects associated with metformin (30% of patients) and include abdominal bloating, diarrhea, flatulence, nausea and vomiting, weight loss and loss of appetite. Lactic acidosis is a rare (0.03 cases per 1000 patient-years, with 0.015 fatal cases per 1000 patient-years) but life threatening complication. Predisposing risk factors in patients who developed lactic acidosis included decreased liver and kidney function and age greater than 80 years old. Less well-defined risk factors include alcoholism, recent radio-contrast studies with iodinated contrast media and surgical procedures or drugs that decrease fluid intake and tissue perfusion (e.g. nifedipine, furosemide and cationic drugs). Of note, in more than 20,000 patient-years exposure to metformin in clinical trials, there have been no incidents of lactic acidosis (see http://packageinserts.bms.com/pi/pi_glucophage.pdf). Recent literature has demonstrated that metformin is safe in patients with cardiovascular disease, heart failure, chronic obstructive pulmonary disease, and even patients with mild renal impairment (40, 41). However, for precautionary measures, in this study patients will be required to stop metformin for 48 hours before and after any radio-contrast studies with iodinated contrast media.

Long-term (years) use of metformin has been associated with vitamin B-12 deficiency. Hepatotoxicity is also rare with an incidence of less than 0.1% (3 case reports in the literature). In all cases, liver enzymes returned to normal after stopping metformin. Other rare side effects include rash, headache, agitation, dizziness and tiredness.

Hypoglycemia is rare when metformin is given in therapeutic doses, but may result if caloric intake is insufficient or if strenuous exercise occurs without adequate intake of calories. The risk is slightly higher for those patients who are taking metformin in combination with the following other oral medications for diabetes, including glipizide, glyburide and sitagliptin. However, in the management of diabetes, metformin is routinely combined with these other oral agents, indicating the overall safety of this drug.

With regard to non-diabetic patients, pharmacokinetic and pharmacodynamics studies do not reveal a change in basal glucose level in non-diabetic metformin users versus placebo. In a randomized study between healthy controls and randomized first degree normoglycemic relatives of patients with non-insulin dependent diabetes, basal glucose level did not differ between the groups and was within normal parameters (42). Metformin use in healthy males under strenuous exercise conditions did not induce higher rates of lactic acidosis and plasma glucose levels were similar in healthy subjects who received metformin versus placebo (43). Metformin appears to differentially act upon the erythrocyte insulin binding receptors in obese non-insulin dependent diabetics and non-diabetics; it increased the receptor capacity dramatically in the diabetics and only

moderately in non-diabetics, suggesting that metformin has a hypoglycemic effect mainly in Type II diabetics but not in non-diabetics (44).

1.4 Study Rationale

Unfortunately, 25% of CAH and 37% of EC patients go on to relapse after treatment with hormonal therapy. Relapse of CAH/EC patients after treatment with progesterone is thought to be related to progesterone resistance. Metformin is a generic oral anti-hyperglycemic. Recent evidence suggests that metformin reduces cancer risk and cancer deaths among diabetic patients (17-19). Based on preclinical *in vitro* and *in vivo* studies, metformin demonstrates anti-proliferative effects for both endometrial hyperplasia and cancer through inhibition of the mTOR pathway. Metformin has also demonstrated reversal of progesterone-resistance in endometrial cancer cell lines. In clinical data, metformin has been associated with decreased cellular proliferation (via Ki-67 staining) in endometrial cancer specimens of patients undergoing primary surgical management. Given our promising preclinical data, we hypothesize that the addition of metformin to standard LR-IUD progestin therapy will result in a CR rate at 6 months that is significantly higher than 50%. The comparator rate of 50% is based on results reported in the meta-analysis referenced earlier, and because a response rate significantly greater than this will be considered clinically meaningful by the investigators. The rate of CR at 6 months is our primary interest as this was the median time to response in the meta-analysis (12). Due to metformin's long term and wide spread use in patients with significant comorbidity, as well as proven safety and efficacy in healthy women with PCOS and non-diabetics, it is an ideal medication to evaluate in a population of non-surgical candidates.

In addition, our proposed clinical trial of metformin in combination with the LR-IUD will complement the proposed GOG trial in that we will (1) explore the potential activity of metformin in CAH and early stage EC patients as opposed to the advanced and recurrent patient population, and (2) we will investigate the combination of metformin with hormonal as opposed to cytotoxic therapy. If these study results are positive, we plan to propose a multicenter GOG trial of this treatment regimen, to establish a new standard of care for non-surgical patients with CAH/EC.

1.5 Correlative Studies

We will explore the association of metabolic factors, expression of the metformin transporter proteins and key targets of the metformin/mTOR signaling pathway (i.e. Ki-67, AMPK, LKB1, AKT, PTEN, S6, 4E-BP1) with treatment response to metformin. Metabolic factors, including baseline body mass index (BMI), and glucose levels, will be documented and followed throughout treatment. Matched paraffin embedded tissues before and during metformin treatment will also be collected for immunohistochemical analysis of the metformin transporter proteins, Ki-67, and key components of the metformin/mTOR signaling pathway. Blood and urine will be collected at baseline and every 3 months during the study as a

means to (1) explore associations between metformin concentration levels and therapeutic outcomes, and (2) identify metabolic biomarkers of response to treatment through metabolomic profiling. Endometrial tissue will also be collected at the 6 month time point for analysis of metformin uptake into the endometrium.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

2.1.1 To compare the rate of CR at 6 months in non-surgical grade 1 EC and CAH patients receiving metformin + LR-IUD to 50%

2.2 Secondary Objectives

2.2.1 To estimate the rate of CR at 6 months separately in grade 1 EC and CAH patients receiving metformin + LR-IUD

2.2.2 To estimate the rate of CR at 12 months in non-surgical grade 1 EC and CAH patients receiving metformin + LR-IUD

2.2.3 To document patient adherence to long-term (≥3 months) metformin administration

2.2.4 To describe safety of metformin + LR-IUD treatment

2.3 Exploratory Objectives

2.3.1 To explore changes in cellular proliferation as measured by the marker, Ki-67, from baseline to 6 months

2.3.2 To explore association between the level of expression of the metformin transporter proteins and key targets of the metformin/mTOR signaling pathway and CR status at 6 months

2.3.3 To perform a comprehensive unbiased profiling of metabolites by analyzing the metabolic “fingerprints” of the biofluids (i.e. serum and urine) and “footprints” of the tumor tissue pre- and post- 6 months of metformin treatment

2.3.4 To explore association between metabolic factors and metformin concentration levels in tumor tissue/blood/urine and CR at 6 months

2.4 Endpoints

2.4.1 Primary Endpoint:

CR ("complete disease regression"), as defined by no evidence of microscopic viable hyperplasia or carcinoma on endometrial biopsy after 6 months of treatment.

2.4.2 Secondary Endpoints:

- CR, as defined above, at 6 months of treatment by CAH and EC
- CR, as defined above, at 12 months of treatment in group as a whole
- Adherence to at least 80% of scheduled doses over duration of prescribed treatment
- The type, severity and attribution of adverse events, by NCI Common Toxicity Criteria for Adverse Events (CTCAE), version (v) 4.0

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

Subjects must meet all of the inclusion criteria to participate in this study:

3.1.1 Histologically confirmed CAH or grade 1 EC

3.1.2 Females age ≥ 18 years

3.1.3 ECOG Performance Status 0 – 4

3.1.4 Non-surgical candidates due to:

- Desire for fertility preserving treatment
- Unacceptable surgical risk as defined by:
    - American Society of Anesthesiologists Physical Status (ASA) ≥ 4 and/or Perioperative Cardiac Risk > 5%(45) and/or Perioperative Respiratory Failure Risk > 5%(46)

      AND

    - Independent medicine or cardiology pre-op consultation concluding 'high' surgical risk.
- Patient determined to be a non-surgical candidate by the primary treating physician.

3.1.5 Planned treatment with the LR-IUD for CAH or grade 1 EC by primary physician

3.1.6 Women of childbearing potential (WOCBP) must have negative urine pregnancy test within 7 days of D1 of treatment

3.1.7 Understand study design, risks, and benefits and have signed informed consent

3.2 Exclusion Criteria

Any patient meeting any of the exclusion criteria at baseline will be excluded from study participation.

3.2.1 Evidence of renal dysfunction (Cr > 1.5mg/dL or Cr clearance < 60mL/m^2) or liver dysfunction (AST/ALT > 2x upper limit of normal (ULN))

3.2.2 Current use of progestin therapy (local, topical, or systemic) that has been ongoing for > 3 months

3.2.3 Myometrial invasion >50% or evidence of nodal or metastatic disease on baseline MRI (MRI only to be done for EC patients)

3.2.4 Mixed histology including clear cell, serous, undifferentiated or sarcomatous elements

3.2.5 Prior or current use of metformin within the past 3 months

3.2.6 History of hypersensitivity to metformin or history of discontinuation secondary to attributed adverse effects

3.2.7 Chronic (daily use for > 30 days) use of cimetidine (significant increase in metformin concentration and risk of lactic acidosis)

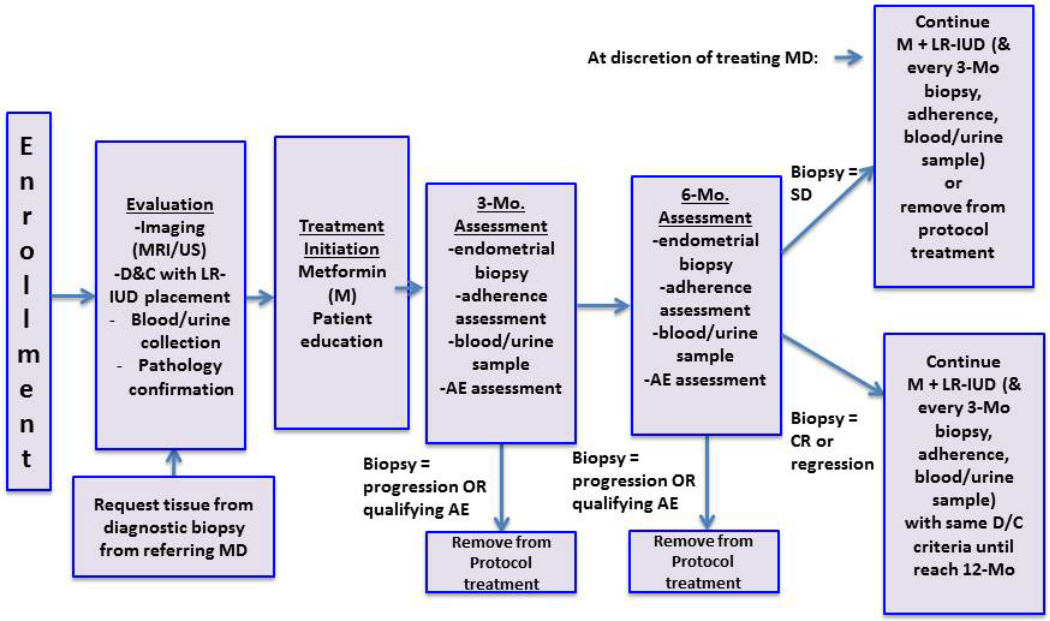
3.2.8 Iodinated contrast agents used in prior 48 hours (significant increase in metformin concentration and risk of lactic acidosis)

3.2.9 Pregnant or lactating

3.2.10 Recent (< 30 days) active, documented, cervical infection

4.0 TREATMENT PLAN

4.1 Schema



This is an open-label, single-arm, multi-center, study of the addition of metformin to the LR-IUD for treatment of non-surgical patients with CAH and grade 1 EC. While patients will be enrolled prior to dilation and curettage (D&C) and placement of the LR-IUD, both are standard of care, and will not be impacted by enrollment into the study.

Oral metformin therapy will be started within 1 week of LR-IUD placement and continued for 12 months unless disease progression occurs or the patient develops intolerability.

4.2 Dilation and Curettage (D&C)

As part of standard of care in treating CAH and EC with non-surgical progestin therapy, patients will undergo a D&C procedure for definitive diagnosis and therapeutic effect. During this procedure, the LR-IUD is placed. D&C is a safe, outpatient procedure that will be performed by a gynecologic oncology attending, fellow, or resident. In this procedure, the uterine lining tissue is removed with standard curette instruments. The main risk of this procedure is uterine perforation, which occurs at a rate of 1-2%. D&C would be performed regardless of study enrollment, and is not considered part of the current study. However, confirmation of CAH or EC will not be made, and therefore metformin will not be started, until after results of the D&C are read by the PI. This will occur within 3 days of receipt of the results and 7 days of the procedure and the patient will be informed that they can then initiate metformin. If a patient's provider does not feel

that they require a D&C procedure, the LR-IUD may be placed in clinic. The patient will undergo screening and pre-treatment testing at this time or the visit prior to the LR-IUD placement and will start the metformin within 30 days of IUD placement. Note that screening must occur within 30 days of starting treatment.

4.3 Treatment Dosage and Administration

All patients enrolled in this study will be non-surgical patients with planned LR-IUD treatment by the primary physician, per standard of care. Once the diagnosis of CAH or EC is confirmed by D&C, patients will be additionally treated with metformin as an investigational agent. Patients will be started on the standard clinical starting dose of metformin (850 mg once daily orally, titrated to twice daily over the course of one month (30 days)). This dose of 850mg twice daily will be continued for the duration of their prescribed study treatment. Patients will fill out a pill diary to record their usage. This diary will be provided to patients as a document separate from this protocol. Metformin will be obtained and dispensed by Investigational Drug Services at participating centers. The participating research sites have experience with metformin administration on clinical trials and will be well versed in managing dose escalation and side-effects. Patients will be instructed to take metformin with meals.

4.4 Toxicities and Dosing Delays/Dose Modifications

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed weekly for the first 2 weeks, then every 30 days thereafter for the development of any toxicity according to the Time and Events table (6.0). Toxicity will be assessed according to the NCI CTCAEv4. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

We anticipate that metformin related hypoglycemia and GI disturbances will be the two most common side effects. Metformin will be discontinued if the patient experiences (1) a single grade 3 or higher metformin-related GI disturbance or grade 4 or higher hypoglycemic episode, or (2) two or more grade 2 side effects considered related to metformin therapy, or (3) if the patient requires a dose less than 850mg once daily. Patients may request to stop the drug at any time.

See section 8.2 for a stopping rule related to the proportion of patients who must discontinue metformin due to toxicities for the study to be suspended.

Metformin Toxicity Dose Reductions	
Event	**Action**
Hypoglycemia	
Grade 1-2	Patient education, avoidance of fasting states
Grade 3	Decrease to metformin 850mg once daily
Grade 4	Discontinue metformin, follow-up per protocol

GI Distress	
Grade 1-2	Patient education, avoidance of fasting states
Grade 3	Discontinue metformin, follow-up per protocol

4.4.1 Management of Hypoglycemia

Hypoglycemia is a rare side effect of metformin in both diabetic and non-diabetic patients. All patients, however, will be warned of the potential signs and symptoms (i.e. hunger, headache, confusion, irritability, drowsiness, weakness, dizziness, tremors, sweating, fast heartbeat, seizure or fainting). If these symptoms were to occur, patients would be counseled to consume one of these quick-fix foods right away to raise their blood glucose.

- 3 or 4 glucose tablets
- 1 serving of glucose gel—the amount equal to 15 grams of carbohydrate
- 1/2 cup, or 4 ounces, of any fruit juice
- 1/2 cup, or 4 ounces, of a regular—not diet—soft drink
- 1 cup, or 8 ounces, of milk
- 5 or 6 pieces of hard candy
- 1 tablespoon of sugar or honey

After this, patients would be instructed to contact the gynecologic oncology clinic or study coordinator for further recommendations. If patients already have a glucose meter, patients would be counseled to check their glucose level immediately. If the level is below 70 mg/dL, one of the above quick-fix foods would be consumed right away to raise their blood glucose. Patients will be instructed to recheck their blood glucose in 15 minutes to make sure it is 70 mg/dL or above. If it is still too low, another serving of a quick-fix food should be eaten. These steps should be repeated until the blood glucose level is 70 mg/dL or above. As stated previously, hypoglycemia is less likely in non-diabetic patients. If this were to occur, they will be managed in the same manner as detailed above.

4.5 Concomitant Medications/Treatments

Patients are excluded if they are currently taking cimetidine. No other medications are absolutely contraindicated while on metformin therapy.

4.6 Other Modalities or Procedures

4.6.1 Endometrial Biopsies

Patients will undergo follow-up endometrial biopsies every 3 months to assess histology and grade and to determine disease persistence, response, or progression, as per standard of care. Metformin therapy will continue without change in dosing on biopsy days. At the 6 month time point only, an additional pass will be made with the endometrial pipelle, in order to collect tissue for the correlative studies.

These patients will already be familiar with the procedure of endometrial biopsy since most will have undergone this procedure when they were diagnosed. Endometrial biopsies will be performed either by a gynecologic oncology attending, gynecology attending, gynecology resident or gynecologic oncology clinical fellow. Patients will be offered acetaminophen or non-steroidal anti-inflammatory drugs (i.e. ibuprofen) if needed for uterine cramping. Patients will be given appropriate instruction on fever and bleeding precautions during the surgical procedure consent process.

An endometrial suction curette (e.g., Pipelle®) will be used to sample the endometrial lining for each follow up biopsy. These disposable devices are constructed of flexible polypropylene with an outer sheath measuring approximately 3 mm in diameter with a 2.4 mm distal side port, through which the endometrial sample is obtained. The flexibility of this type of curette allows the cannula to conform to the contour of the uterus and minimizes cramping. The accuracy of endometrial biopsy to detect endometrial disease, especially the sensitivity of detecting endometrial cancer is 83% to 96% (47-50).

The most common risks to the patient for this procedure are cramping and a vaso-vagal response. Other much rarer risks included uterine bleeding (usually due to previously undiagnosed coagulopathies), uterine perforation (0.1 – 1.3%), pelvic infection and bacteremia (<1%). Besides these risks, there are no known additional risks to patients undergoing multiple endometrial biopsies. These procedures would be performed regardless of study enrollment.

4.7 Duration of Metformin Therapy

The planned duration of metformin therapy is 12 months. Metformin treatment will be discontinued early in the following scenarios:

- Progression of disease, as defined by CAH progression to invasive adenocarcinoma or grade 1 EC progression to grade 2 or 3 EC, at any of the standard of care biopsies at 3, 6, and 9 months. In any of these cases, metformin will be discontinued within 3 days of results of the biopsy.
- Unacceptable toxicity as defined by a single grade 3 or higher GI disturbance attributed to metformin, a single grade 4 or higher hypoglycemia episode, 2 or more grade 2 toxicities attributed to metformin, or requirement for a dose below 850 mg once daily.

Response to therapy will be assessed at 3-month intervals. As per standard of care, endometrial biopsies will be performed every 3 months (+/- 2 weeks) to assess histology and grade to determine response. This will be the basis of whether therapy should continue. If the 3 month biopsy demonstrates disease progression, the patient will be removed from protocol directed treatment and followed-up per protocol, and treatment decisions will be at the discretion of the treating physician. Otherwise, therapy will continue through 6 months. If the 6-month or 9-month biopsy demonstrates complete response (complete disease regression) or partial response (partial disease regression), metformin will be continued until 12 months of total therapy is given. If the 6-month or 9-month biopsy demonstrates stable disease, continuation of metformin on study will be at the discretion of the treating physician. Please see the schema (section 4.1) for clarity.

In addition, treatment will be stopped in the setting of:

- Inter-current illness that prevents further administration of treatment
- Pregnancy
- Patient decides to withdraw from study treatment, **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

4.8 Duration of Follow Up

Patients will be followed until their final study encounter (this may be a clinic visit, or phone call), which will occur within 30 days of their final endometrial biopsy while on metformin. Metformin is to be stopped the day of the 12-month endometrial biopsy, or the day on which the results of prior biopsies are known, if they indicate disease progression. In the case of ongoing adverse events/serious adverse event, patients will be followed to resolution of the event.

4.9 Removal of Patients from Protocol Therapy

Patients will be removed from protocol therapy when any of the criteria listed in section 4.7 apply. The Principal Investigator will be notified, and the reason for study removal and the date the patient was removed will be documented in the electronic Case Report Form (e-CRF).

In case a patient decides to prematurely discontinue protocol therapy ("refuses treatment"), the patient should be asked if she may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.

Excessive patient withdrawals from protocol therapy or from the study can render the study un-interpretable; therefore, unnecessary withdrawal of patients should be avoided.

4.10 Study Withdrawal

If a subject decides to withdraw from the study (and not just from protocol therapy) an effort should be made to complete and report study assessments as thoroughly as possible. At the time of withdrawal, the Investigator should attempt to establish as completely as possible the reason for the study withdrawal.

- The subject should be asked if they are willing to allow for the abstraction of relevant information from their medical record in order to meet the long term follow up (e.g., survival) objectives outlined in the protocol.
- A complete final evaluation at the time of the subject's study withdrawal should be obtained with an explanation of why the subject is withdrawing from the study.
- If the subject is noncompliant and does not return for an end of study follow up assessment, this should be documented in the eCRF.
- If the reason for removal of a subject from the study is an adverse event, the principal specific event will be recorded on the eCRF.

Excessive subject withdrawals from protocol therapy or from the study can render the study un-interpretable; therefore, unnecessary withdrawal of subjects should be avoided.

5.0 DRUG INFORMATION

5.1 Commercial Drug Description and Management -Metformin

5.1.1 Mechanism of Action/Indications

Metformin is an antihyperglycemic agent that improves glucose tolerance in patients with type II diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type II diabetes or normal subjects (except in special circumstances, see adverse events section) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

5.1.2 Supplier/How Supplied

Metformin is generic and made by several different manufacturers. Investigational Drug Services at participating centers will be responsible for the purchase and distribution of metformin to the patients enrolled in this study. Patients will be provided metformin free of charge for this trial.

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

5.1.3 Dosage and Administration

For type II diabetes mellitus, the initial recommended dosage of metformin is 500 mg twice daily or 850 mg once daily given with meals, and then titrated to twice daily dosing. For this study, patient will take 850 mg once daily, and this dose will be titrated to twice daily dosing. Metformin should be taken with meals.

5.1.4 Storage and Stability

Metformin should be stored between 20 and 25 degrees Celsius (68 and 77°F) with excursions permitted between 15 and 30°C (59 and 86°F). Metformin is dispensed in a light-resistant container.

5.1.5 Handling and Disposal

The investigator or designee is responsible for keeping accurate records of the clinical supplies received for this trial, the amount dispensed to and returned by the subjects, and the amount remaining at the conclusion of the trial.

Local requirements for disposal of hazardous drugs should be followed at each participating clinical site.Please see UNC policy on hazardous drugs:
https://unchealthcare-uncmc.policystat.com/policy/4734545/latest/

Full prescribing information for Metformin is available at:
https://packageinserts.bms.com/pi/pi_glucophage_xr.pdf

5.1.6 Adverse Events Associated with Metformin

The potential risks involved in metformin treatment are minimal but include gastrointestinal side effects, lactic acidosis, hepatotoxicity and hypoglycemia. All patients will have a serum pregnancy test (if of childbearing age) and baseline creatinine and liver enzymes drawn at the time of their enrollment. These labs will be reviewed by the principal investigator, and the patient notified that she has been cleared to take metformin per the inclusion/exclusion criteria. Patients will be contacted weekly during the first 2 weeks of metformin treatment and then every 30 days by the study coordinator to ensure that these women are not experiencing any appreciable side effects.

Hypoglycemia is a rare side effect of metformin in both diabetic and non-diabetic patients. See section 4.4.1 for information on management of hypoglycemia.

Please refer to the agent's package insert for a comprehensive list of adverse events.

5.2 Commercial Drug Description and Management- Levonorgestrel-Releasing Intrauterine Device

Mechanism of Action and Indications
The LR-IUD is commercially available as the Mirena© intrauterine system. It is a sterile T-shaped polyethylene frame with a steroid reservoir containing 52 mg of levonorgestrel. It is a long-term contraceptive agent and used to treat heavy menstrual bleeding. The mechanism of action that prevent pregnancy include thickening of the cervical mucus, inhibition of sperm capacitation, and alterations of the endometrium. The alterations of the endometrium are a result of local progestin effects and include stromal pseudodecidualization, glandular atrophy, a leukocytic infiltration and a decrease in glandular and stromal mitoses. Due to these effects, the LR-IUD has been used in diseases previously treated with oral progestin therapy - heavy menstrual bleeding and hyperplasia and early endometrial adenocarcinoma.

Supplier/How Supplied
The LR-IUD is currently only commercially available in the Mirena© intrauterine system. As a standard alternative treatment for hyperplasia and early stage endometrial adenocarcinoma, it is reimbursed by insurance plans and will be supplied by the UNC pharmacy. Patients and/or their insurance companies will be billed for this product.

Formulation/Dosage and Administration
The LR-IUD contains 52 mg total of levonorgestrel and releases approximately 20 mcg/day.

Storage/Stability
Mirena© is supplied sterile and is sterilized with ethylene oxide. It is stored at 25°C with excursions permitted between 15-30°C. If the package seal is disrupted prior to use, it must be discarded. It cannot be re-sterilized.

5.3 Adverse Events Associated with Commercial Drug

The most comment adverse reactions associated with the LR-IUD is change in menstrual bleeding pattern, abdominal/pelvic pain, and the formation of headache/migraines. As part of standard therapy, patients would be counseled about these possible effects. They will be instructed to call the gynecologic oncology clinic if any concerns arise.

The majority of LR-IUD users experience resolution of such symptoms between 1 – 12 weeks after insertion. In the setting of changes in bleeding pattern, this is most commonly a decrease in heavy bleeding associated with CAH/EC and would be unlikely to require intervention. Abdominal/pelvic pain will be treated with

non-steroidal anti-inflammatory medication or acetaminophen as needed, in over the counter formulations. Headaches and/or migraines that result from the LR-IUD will be similarly treated with non-steroidal anti-inflammatory medication or acetaminophen. Persistent headaches requiring discontinuation of the LR-IUD would be addressed by the primary physician as this would impact standard of care therapy for inoperable CAH/EC.

Pregnancy. Pregnancy is rare with the LR-IUD, with a reported rate of 0.1% for ectopic pregnancy. There have been 390 live births out of 9.9 million LR-IUD users as of 2006.

Uterine Perforation. At the time of placement of the LR-IUD there is a risk of uterine perforation. Correct technique by trained personnel mitigates most of this risk. Perforation can be recognized at the time of insertion or at any time when the cervical os strings are no longer visible. Pregnancy may occur in this setting.

Expulsion. The highest rate of expulsion occurs in the first month after LR-IUD placement and can be up to 4.9%. Risk factors for expulsion include placement by untrained personnel and recent (<6 weeks) pregnancy or abortion.

Please see the package insert for a comprehensive list of adverse events.

6.0 EVALUATIONS AND ASSESSMENTS

6.1 Time and Events Table

	Screening	Pre-treatment Visit	Month (Mo) 1 Week (Wk) 1	Mo3	Mo6	Mo9	Mo12	Early Termination [2]	Final Study Encounter[2]
Inclusion/ Exclusion Criteria	X								
History[1] and Physical	X			X	X	X	X		
Informed Consent	X								
Education of potential side effects		X							
Pregnancy test (serum), if applicable	X[3]								
Random (non-fasting) glucose		X					X		
AST/ALT	X			X	X	X	X		
Serum creatinine	X			X	X	X	X		
Cervical cultures[4]	X								
MRI or Pelvic US[5]	X								
D&C, LR-IUD insertion		X							
Pregnancy test (urine)		X[3]							
Metformin Treatment[6]			Metformin treatment begins D1 of Month 1; continue as per sections 4.3-4.4						
AE Assessment			X[7]						X
Patient Diary			X	X[7]					
Request tissue	X[8]								
Endometrial Biopsy				X	X[9]	X	X		
Blood and urine collection[10]		X		X	X	X	X	X	

Footnotes to Time and Events Table

[1]Comprehensive medical history at baseline; thereafter history focused on symptoms and toxicities

[2]Patients will be followed until final study encounter, which will occur within 30 days of their final endometrial biopsy while on metformin. Metformin is to be stopped the day of the 12-month endometrial biopsy, or the day on which the results of prior biopsies are known, if they indicate disease progression. In the case of ongoing adverse events/serious adverse event, patients will be followed to resolution of the event. If early termination of the study occurs (i.e., prior to 12 months), the patient will be asked to have serum and urine collected, and the patient followed-up until any treatment related adverse events have resolved or returned to baseline. Their standard of care every 3 month (+/- 2 weeks) endometrial biopsy will be performed as scheduled by their physician as per routine care.

[3]Women of childbearing potential (WOCBP) must have negative urine pregnancy test within 7 days of D1 of treatment; urine pregnancy test (for WOCBP) will be conducted on the day of outpatient surgery as well, per standard of perioperative care.

[4]During the pelvic exam, which is part of the standard of care evaluation for newly diagnosed CAH/EC, cultures of gonorrhea and chlamydia will be taken to rule out cervical infection for women at high risk for sexually transmitted infections per ACOG recommendations. This includes women age 24 years or younger. Those women who have had negative gonorrhea or chlamydia testing or have been treated for gonorrhea or chlamydia within 3 months of placement do not require repeat cultures.

[5]For patients with EC only, MRI prior to the D&C is required to rule out >50% myometrial invasion or nodal metastases. Results of MRI studies of the uterus done within 30 days of enrollment will be accepted. For patients whose BMI precludes MRI testing, a pelvic ultrasound with tumor size measurements < 2 cm will be substituted.

[6]Treatment with metformin will last a minimum of 90 days and a maximum of 12 months depending on the patient's response to treatment as determined by endometrial biopsy.

[7]The first AE assessment will occur one week after starting metformin treatment; patients will be contacted weekly the first two weeks of therapy, and subsequently every 30 days by the study coordinator via phone to inquire about side effects of metformin. Adherence assessments will also be performed at the same intervals with patient reporting number of missed doses per week, based on review of their medication diary.

[8]Endometrial biopsy slides and blocks (pretreatment samples) will be obtained from referring physicians of these patients for analysis in this study

[9]At the 6 month timepoint only, an additional pass will be made with the endometrial pipelle, in order to collect tissue for the correlative studies.

[10]For measurement of metformin concentration, and for metabolomics (see section 6.7).

6.2 Screening

Women with CAH/grade 1 endometrial cancer will be recruited from the Gynecologic Oncology and Gynecology clinics at participating centers. All patients will already have had a baseline endometrial biopsy performed, to establish their diagnosis and referral to the gynecologic oncology clinic. A sample of this tissue will be requested from the referring physician. All patients will have a urine pregnancy test (if of childbearing age), gonorrhea and chlamydia cervical cultures if they are age 24 or younger, and baseline serum creatinine, glucose and liver enzymes drawn at the time of their screening visit. These labs will be reviewed by the principal investigator. Note that screening labs must occur within 30 days of starting treatment.

6.3 Pre-Treatment

Per standard course of treatment, all women undergoing IUD placement for the treatment of CAH/EC will undergo dilation and curettage (D&C) procedure to confirm histologic diagnosis and for placement of the IUD if deemed necessary by their primary provider. Urine pregnancy test (for women of childbearing age) will be conducted on the day of outpatient surgery as well, per standard of perioperative care at UNC. Final pathology results from the D&C will be reviewed by the principal investigator. The patient will be notified within 3 days of the receipt of results, confirming CAH/grade 1 EC histology, that she is cleared to start study treatment with metformin. This will occur within 30 days of LR-IUD placement. Blood and urine samples will also be collected for correlative studies (see section 6.7). If the patient does not require a D&C, she will have a urine pregnancy test prior to IUD placement as is the standard of care and will start metformin within 30 days of IUD placement.

6.4 Treatment Assessments

6.4.1 Month 1 Week 1

D1 Month 1: Patient is instructed to initiate metformin via phone call: Patient will be contacted weekly for first 2 weeks by the study coordinator via phone regarding toxicities, and adherence assessments.

6.4.2 Monthly during Metformin

Patient will be contacted every 30 days by the study coordinator via phone regarding toxicities, and adherence assessments.

6.4.3 Months 3, 6, 9 and 12

Laboratory evaluations: serum creatinine, liver function test
Endometrial biopsy (see section 6.7)
Blood and urine samples for correlative studies (see section 6.7)
Random (non-fasting) glucose (month 12)

6.5 Final Study Encounter

Metformin is to be stopped the day of the 12-month endometrial biopsy, or the day on which the results of prior biopsies are known, if they indicate disease progression. In the case of ongoing adverse events/serious adverse event, patients will be followed to resolution of the event. After completion of metformin treatment, patients may return to clinic as per scheduled with their primary provider. The final study encounter will be within 30 days of the final endometrial biopsy.

6.6 Early Termination/Study Withdrawal Visit

If early termination of the study occurs (i.e., prior to 12 months), the patient will be asked to have serum and urine collected, and their standard of care every 3 month endometrial biopsy will be performed as scheduled by their physician as per routine care. No other evaluations will be needed in the event of early termination. Subjects may withdraw voluntarily from participation in the study at any time (see section 4.10). Subjects may also withdraw voluntarily from receiving the study intervention for any reason.

If voluntary withdrawal occurs due to an adverse event, the subject will be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the subject's condition becomes stable.

6.7 Correlative Studies

Endometrial biopsies will be performed per standard clinical practices. At the first 6 month time point only, an additional pass will be made with the endometrial pipelle, in order to collect endometrial tissue for the correlative studies (i.e. measure metformin concentration and metabolomic profiling). The time at which the last dose of metformin was taken prior to endometrial biopsy will be recorded. Additionally, blood and urine samples will be collected from clinic and transported to the Tissue Procurement Facility for coding (to remove patient identifiers) and eventual distribution to the Principal Investigator. Samples will include: (1) a total of 10 cc of blood collected in a gold-top tube, (2) a total of 10 cc of blood collected in a green top heparinized tube, and (3) a minimum of 40 cc of urine collected in a non-sterile urine-specimen container. In addition, the endometrial biopsy slides and blocks (pretreatment samples) will be obtained from referring physicians of these patients for analysis in this study. These slides will also be compared to those obtained from serial endometrial biopsies, as a means to delineate the effect of metformin treatment. Tissue, blood and urine samples will be packaged and transported to the laboratory for determination of metformin concentration and metabolomic profiling.

Analysis of metformin in plasma and urine: Metformin concentrations in plasma and urine will be determined using a liquid chromatography–tandem mass spectrometry method in Dr. Dhiren Thakker's laboratory.

Analysis of metformin uptake in endometrial tissue: Metformin concentrations in endometrial tissue will be determined using liquid chromatography-mass spectrometry (LC-MS/MS), as previously described (51). This will be performed in the laboratory of Dr. Dhiren Thakker.

Ki-67: Tissue microarrays will be constructed and immunohistochemical analysis will be performed to assess for Ki-67. The percentage of Ki-67 positive cells, termed the Ki-67 index, will be calculated pre- and post-treatment. The Ki-max and Ki-min will also be quantified. Stained slides will be visually scored by experienced observers blinded to the identity of the tissue sections. Individual slides will be digitized using the Aperio ScanScope (Aperio Technologies, Vista, CA), and digital images will be analyzed using Aperio ImageScope software.

Immunohistochemical Analysis: Tissue microarrays will be constructed and immunohistochemical analysis will be performed to assess expression of the key components of the metformin/mTOR, including AMPK, LKB1, Akt, PTEN, S6K1 and 4E-BP1. Phosphorylated and non-phosphorylated forms of these proteins will be evaluated. Expression of the metformin transporter proteins will also be assessed by immunohistochemical analysis, including OCT1-3, MATE1/2 and PMAT. Stained slides will be visually scored by experienced observers blinded to the type of antibody used and to the identity of the tissue sections. Individual slides will be digitized using the Aperio ScanScope (Aperio Technologies, Vista, CA), and digital images will be analyzed using Aperio ImageScope software.

Metformin Transporter mRNA Expression in Endometrial Tissues. Total RNA will be isolated from EH paraffin-embedded tissues and subjected to RT-PCR for determination of metformin transporter mRNA expression, including OCT1-3, MATE1/2 and PMAT. The relative mRNA levels for individual transporters will be normalized to the 18s rRNA housekeeping gene.

Metabolomic Analysis: We will perform comprehensive metabolomic analysis of serum and urine to identify potential biomarkers responsive to metformin treatment using mass spectrometry. These analyses uncover the subtle differences between the spectra that correlate to the disease or treatment under study revealing metabolomic “footprints” (from tissue) and “fingerprints” (from biofluids). Thus, a comprehensive unbiased profiling of metabolites (molecule weight<1000 Dalton) will be performed, and we will analyze the metabolic “fingerprints” of the biofluids (i.e. serum and urine) of women with endometrial hyperplasia/cancer, pre- and post- 6 months of metformin treatment. Time of flight mass spectrometry (TOF-MS) coupled to chromatographic separations including gas chromatography (GC-TOF-MS, Leco Corp.) and liquid chromatography (LC-TOF-MS, Agilent Corp.) will be used for the measurement of tumor specimens and biofluids, and these analyses will be conducted according to previously developed methods by the UNC NORC/Nutrition Research Institute Metabolomics Core. Significant variables (metabolite markers) will be selected

based on a threshold of a multivariate statistical parameter, such as variable importance in the projection (VIP) value (usually VIP>1) from a typical 7-fold cross-validated orthogonal projections to latent structures discriminant analysis (OPLS-DA) model. These differential metabolites will be validated at a univariate level such as Student's t-test and Wilcoxon-Mann-Whitney test. The critical p value of the test is usually set to 0.05.

6.8 Assessment of Safety

Any patient who receives at least one dose of metformin treatment on this protocol will be evaluable for toxicity via NCI CTCAE v 4.0.

6.9 Assessment of Efficacy

All patients who receive at least 3 months of metformin therapy will be evaluable for assessment of the primary endpoint – response at 6 months.

6.10 Adherence

All patients who initiate treatment with metformin will be evaluable for missed doses/week to assess the endpoint of adherence to at least 80% of doses over the cumulative course of treatment.

7.0 ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence (e.g., an abnormal laboratory finding, symptom, or disease temporally associated with the use of a drug) in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable by the investigator to the study therapy.

7.1.2 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the drug is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Causality assessment to a study drug is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study drug exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering drug as the cause of the AE:

- Single occurrence of an uncommon event known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event not commonly associated with drug exposure, but otherwise uncommon in the population (e.g., tendon rupture); often more than once occurrence from one or multiple studies would be needed before the sponsor could determine that there is *reasonable possibility* that the drug caused the event.
- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the drug treatment group than in a concurrent or historical control group

7.1.3 Unexpected AE or SAR

An AE or SAR is considered unexpected if the specificity or severity of it is not consistent with the applicable product information (e.g., Investigator's Brochure (IB) for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious AE or SAR

An AE or SAR is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization (>24 hours) or prolongation of existing hospitalization;*
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- 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 the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

Pregnancy that occurs during the study must also be reported as an SAE.

7.2 Documentation of non-serious AEs or SARs

For non-serious AEs or SARs, documentation must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued.

Collected information should be recorded in the Case Report Forms (CRF) for that patient. Please include a description of the event, its severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug. Documentation should occur at least monthly.

7.3 SAEs or Serious SARs

7.3.1 Timing

After informed consent but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g. SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in).

For any other experience or condition that meets the definition of an SAE or a serious SAR, recording of the event must begin from day 1 of study treatment and continue through the 30 day follow-up period after treatment is discontinued.

7.3.2 Documentation and Notification

These events (SAEs or Serious SARs) must be recorded in the SAE console within Oncore™ for that patient within 24 hours of learning of its occurrence.

7.3.3 Reporting

IRB Reporting Requirements:

- UNC will submit an aggregated list of all SAEs to the UNC IRB annually at the time of study renewal according to the UNC IRB policies and procedures.
- The UNC-IRB will be notified of all SAEs that qualify as an Unanticipated Problem as per the UNC IRB Policies using the IRB's web-based reporting system (see section 9.5.3) within 7 days of the Investigator becoming aware of the problem.
- For affiliate sites using a local IRB of record, please submit adverse events per local IRB policy.

- For affiliate sites relying on the UNC-IRB, an aggregated list of all SAEs will be submitted to the UNC IRB annually at the time of study renewal according to the UNC IRB policies and procedures. In addition, any SAEs that qualify as an Unanticipated Problem will be entered into Oncore and reported to the UNC IRB by the UNCCN Project Manager using the IRB's web-based reporting system (see section 9.5.3) within 7 days of the Investigator becoming aware of the problem.

Pregnancy

Pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study should be recorded as SAEs. The patient is to be discontinued immediately from the study. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must document the outcome of the pregnancy (either normal or abnormal outcome). If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE.

7.4 Data and Safety Monitoring Plan

The Principal Investigator will provide continuous monitoring of patient safety in this trial with periodic reporting to the Data and Safety Monitoring Committee (DSMC).

Meetings/teleconferences will be held at a frequency dependent on study accrual, and in consultation with the study Biostatistician. These meetings will include the investigators as well as protocol nurses, clinical research associates, regulatory associates, data managers, biostatisticians, and any other relevant personnel the principal investigators may deem appropriate. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory issues, and data collection.

The team will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the oversight (Office of Human Research Ethics (OHRE) Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute Data and Safety Monitoring Board (DSMB).

The UNC LCCC Data and Safety Monitoring Committee (DSMC) will review the study on a regular (quarterly to annually) basis, with the frequency of review based on risk and complexity as determined by the UNC Protocol Review Committee. The UNC PI will be responsible for submitting the following

information for review: 1) safety and accrual data including the number of patients treated; 2) significant developments reported in the literature that may affect the safety of participants or the ethics of the study; 3) preliminary response data; and 4) summaries of team meetings that have occurred since the last report. Findings of the DSMC review will be disseminated by memo to the UNC PI, PRC, and the UNC IRB and DSMB.

8.0 STATISTICAL CONSIDERATIONS

8.1 Study Design

This is an open label, single-arm, multi-center study of metformin in addition to the LR-IUD for the treatment of non-surgical patients with CAH and grade 1 EC. We hypothesize that metformin + LR-IUD will result in a CR rate at 6 months that is significantly higher than 50%.

8.2 Sample Size, Stopping Rule, and Accrual

The goal accrual is 32 patients (16 CAH, 16 EC) and we expect to enroll 1-2 patients/per month. Our power calculation and analysis will be based on 30 patients, assuming early discontinuation of 2 participants prior to 3 months of treatment. We estimate 18 months to complete accrual.

The primary objective of this study is to compare the CR rate at 6 months to a rate of 50% (the 50% is based on results reported in the meta-analysis referenced earlier, and because a response rate significantly greater than this will be considered clinically meaningful by the investigators). With a combined sample size of 30 evaluable patients with either CAH or grade 1 EC, and assuming a null CR rate of 50% and an alternative of 75%, we will have 80% power to conclude that the CR rate at 6 months is significantly higher than 50% using an exact test for a single proportion with a two-sided α of 0.05. Furthermore, the exact 95% confidence interval for the CR rate at 6 months will have a maximum width of 0.374. This means that the CR rate will be estimated within at least 18.7%. CAH and grade 1 EC represent a spectrum of neoplasia, which is why the two groups are being combined for the primary objective. The CR rate at 6 months will be estimated separately in the CAH and EC groups as a secondary objective.

Sequential boundaries will be used to suspend the trial if excessive toxicity is seen that requires discontinuation of metformin. If the study reaches a stopping boundary, it may be terminated by the PI, or submitted to the DSMC with a description of the toxicities and a rationale for why the study should be continued. At the patient level, metformin will be discontinued if a patient experiences: (1) a single grade 3 or higher metformin-related GI disturbance or grade 4 or higher hypoglycemic episode, or (2) two or more grade 2 side effects considered related to metformin therapy, or (3) if the patient requires a dose less than 850mg once daily. The accrual will be halted if the number of patients discontinuing metformin for one of the reasons above is equal to or exceeds b_n out of n patients who have been followed for toxicity for 3 months. This is a Pocock type stopping

boundary that assumes that a metformin discontinuation rate of 0.25 is acceptable, but anything >25% is unacceptable. If the true toxicity rate is equal to 0.25, the probability of crossing the boundary is 0.05.

Stopping Rule

Number of Patients, *n*	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary, b_n	-	-	-	4	5	5	5	6	6	7	7	7	8	8	9	9	9	10	10	10
Number of Patients, *n*	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Boundary, b_n	11	11	11	12	12	12	13	13	14	14	14	15								

8.3 Data Analysis Plans

An exact test for a single proportion will be used to test the hypothesis that the CR rate at 6 months for the group as a whole is greater than 50%. The CR rates at 6 months for the group as a whole and for the CAH and grade 1 EC patients separately will also be estimated and reported along with exact 95% confidence intervals. Patients who progress at 3 or 6 months will be considered non-responders and will be included in these analyses. Patients who fail to complete 3 months of metformin therapy, for reasons unrelated to disease progression or activity, will not be included. The CR rate at 12 months will also be estimated and the analysis will include all patients who had at least 3 months of metformin therapy.

Patient adherence will be described by the percentage of patients able to adhere to at least 80% of planned metformin doses over the course of treatment. The adherence rate will be estimated and reported along with an exact 95% confidence interval. All patients who initiated treatment on study will be included in this analysis. Adverse events will be described by type and grade using frequency tables.

Changes in Ki-67 from baseline to 6 months will be analyzed using a paired t-test or the Wilcoxon signed-rank test as appropriate. Fisher's exact tests will be used to explore associations between expression (via IHC) of the metformin transporter proteins and key targets of the metformin/mTOR signaling pathway and CR at 6 months. Two-sample t-tests will be used to explore associations between metabolic factors and CR. Correlation coefficients and regression models will be used to explore associations between metabolic factors and metformin concentration levels in tumor tissue. Profiling of metabolites and all associated metabolomic analyses will be conducted by the UNC NORC/Nutrition Research Institute Metabolomics Core.

9.0 STUDY MANAGEMENT

9.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

9.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Protocol Office (CPO) at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation (NOTE: this is required if UNC holds the IND. Otherwise, the Investigator's signature documenting understanding of the protocol and providing commitment that this trial will be conducted according to all stipulations of the protocol is sufficient to ensure compliance)
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

9.3 Registration Procedures

All patients must be registered with the CPO at the University of North Carolina before enrollment to study. For UNC patients, prior to registration, eligibility

criteria must be confirmed with the UNC Study Coordinator. To register a patient, call the Oncology Protocol Office at 919-966-4432 Monday through Friday, 9:00AM-5:00PM.

For Affiliate patients, to register and confirm patient eligibility, please fax registration forms, informed consent, and source documents to 919-966-4300, or scan and email to the project manager (preferred).

9.4 Data Management and Monitoring/Auditing

The CPO of the UNC LCCC will serve as the coordinating center for this trial. Data will be collected through a web based clinical research platform, OnCore®. UNC personnel will coordinate and manage data for quality control assurance and integrity.

All data will be collected and entered into OnCore® by Clinical Research Associates (CRAs) from UNC LCCC and participating institutions. The investigators at each site will allow monitors to review all source documents supporting data entered into OnCore®. The UNCCN Data Coordinator can be reached at 919-843-2742 or 1-877-668-0683.

As an investigator initiated study, this trial will also be audited by the Lineberger Cancer Center audit committee every six or twelve months, depending on the participation of affiliate sites.

9.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

9.5.1 Emergency Modifications

UNC and Affiliate investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC or their respective institution's IRB/IEC approval/favorable opinion.

<u>For Institutions Relying on UNC's IRB:</u>
For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

<u>For Institutions Relying on Their Own IRB:</u>
For Affiliate investigators relying on their own institution's IRB, as soon as possible after the modification has been made, the implemented deviation or change and the reasons for it should be submitted to:

- To UNC Principal Investigator for agreement

- The Affiliate institution's IRB for review and approval. (Once IRB's response is received, this should be forwarded to the UNCCN Regulatory Associate).

9.5.2 Single Patient/Subject Exceptions

For Institutions Relying on UNC's IRB:
Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the UNC Principal Investigator and the UNC IRB.

For Institutions Relying on Their Own IRB:
Any request to enroll a single subject who does not meet all the eligibility criteria of this study requires the approval of the UNC Principal Investigator and the participating institution's IRB, per its policy. Please forward the IRB response to the UNCCN Regulatory Associate by facsimile or via email within 10 business days after the original submission.

9.5.3 Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs please follow the guidelines below:

For Institutions Relying on UNC's IRB:
Protocol Deviations: UNC or Affiliate personnel will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

For Institutions Relying on Their Own IRB:
In addition to adhering to the policies regarding protocol compliance set forth by your institution's IRB, the following is also required:

Protocol Deviations: In the event a deviation from protocol procedures is identified, record the deviation in OnCore®.

Protocol Violations: Any protocol violation that occurs must be reported to your IRB per institutional policies and reported to the UNCCN Project Manager within 5 days. UNC-CH will determine if the violation affects the safety of the patient and integrity of the data. Once your institution's IRB response is received, please forward to the UNCCN Regulatory Associate.
Unanticipated Problems:

Affiliate Sites:
Any events that meet the criteria for "Unanticipated Problems (UPs)" as defined by UNC's IRB must also be reported to the UNCCN Project Manager. The UNCCN Project Manager will report the event to the UNC IRB using the IRB's web-based reporting system. Examples of such UPs include a lost or stolen laptop computer that contains sensitive study information.

UNC
Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the Study Coordinator using the IRB's web-based reporting system.

9.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

For Institutions Relying on UNC's IRB:
The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

For Institutions Relying on Their Own IRB:
Investigators must submit the approved amendment to their institution's IRB for approval. For multi-center studies, any multicenter site must submit their informed consent revisions to the Multicenter Regulatory Associate prior to submission to their IRB.

9.7 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

9.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the eCRFs. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all eCRFs will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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