Cinnamon Trial-lIfestyle iNtervention Plus Water-soluble Cinnamon Extract On loweriNg Blood Glucose in Pre-diabetics

NCT01301521

January 24, 2018

PROTOCOL FOR CLINICAL INVESTIGATION – NON-EXEMPT HUMAN
(Wilford Hall Ambulatory Surgical Center – WHASC)
PROTOCOL SUMMARY

1. Title:

Cinnamon Trial—assessment of the effe**C**t of l**I**festyle i**N**tervention plus water-soluble ci**N**n**AM**on extract **O**n loweri**N**g blood glucose in pre-diabetics: A randomized, double-blind, multicenter, placebo controlled **TRIAL**.
FWH20110035H

2.0. Principal Investigator (PI): Nellis AFB PI:

Name	Paul Crawford, MD
Rank/Corps or Civilian Rating	Col
Date of IRB Approved CITI Training	12/28/17
Branch of Service	USAF
AD Mil/DoD Civilian/Ctr/Non-DoD Civ	AD Mil
Department & Base	Graduate Medical Education, Nellis AFB
Phone & Pager #	(702) 653-3298
E-Mail Address & AKO/DKO E-Mail Address	paul.f.crawford.mil@mail.mil

3.0. Research Plan:

3.1. Purpose:

The purpose of this study is to assess whether water-soluble cinnamon extract plus aggressive lifestyle intervention is effective in lowering blood glucose in pre-diabetic patients when compared to aggressive lifestyle therapy plus placebo.

3.2. Hypotheses, Research Questions or Objectives:

Does water-soluble cinnamon extract have an effect on fasting glucose, hemoglobin A1c, lipid panel, and waist circumference in pre-diabetic patients who are already undergoing aggressive lifestyle therapy?

This study has the following goals:

1. Determine the length of time to diagnosis of diabetes using any of the ADA criteria.
2. Determine:
    a) Fasting glucose,
    b) Hemoglobin A1c,
    c) LDL, cholesterol, and
    d) Waist circumference (in inches).

4. Brief Summary of the study:

We are studying whether water-soluble cinnamon extract (Cinnulin PF) plus standard of care aggressive lifestyle therapy is effective in lowering blood glucose when compared to placebo plus standard of care aggressive life style therapy. Eligible subjects will be recruited from any form and any stage of "standard" lifestyle intervention for pre-diabetes at an individual base. "Standard" lifestyle intervention for pre-diabetes could include Group Lifestyle Balance (GLB), nutrition classes, Better Body/Better Life, or anything an investigator certifies as standard practice at that base. Subjects will take either 1 gram (2-500 milligram (mg) capsules) of water-soluble cinnamon extract (Cinnulin PF) or 2 placebo pills (gelatin capsule filled with wheat bran) once a day for 1 year plus 1 additional year of follow-up. This is a randomized, double-blind, multicenter, placebo-controlled study which will enroll subjects at the Mike O'Callaghan Military Medical Center at Nellis AFB (Nellis AFB). All subjects will be Nellis AFB DoD beneficiaries. Informed Consent and HIPAA Authorization will be obtained. After randomization, subjects will receive either 1 gram (2-500 mg capsules) of water-soluble cinnamon extract or placebo from the pharmacy--thus investigators and subjects will be blinded as to if they are taking Cinnulin PF or 2 placebo pills. Subjects will be permitted to have usual medical care for other co-morbid, preventive, and acute conditions. Analysis will be performed using intention-to-treat principles for missing data (the carry-forward method to impute missing data will be used). Subjects will bring in any remaining water-soluble cinnamon extract or placebo to determine adherence rates to the study protocol.

5. Subjects:

Subjects will be recruited from any form and any stage of "standard" lifestyle intervention for pre-diabetes at an individual base. "Standard" lifestyle intervention for pre-diabetes could include Group Lifestyle Balance (GLB), nutrition classes, Better Body/Better Life, or anything an investigator certifies as standard practice at that base. No special populations (i.e. children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons) will be eligible for this study.

6. Inclusion/exclusion criteria:

Inclusion:

- Patients will be Nellis AFBDoD beneficiaries, ages 18-65 years.
- Diagnosis of pre-diabetes (defined as a fasting plasma glucose (FPG) 100-125mg/dl, Hemoglobin A1c 5.7-6.4%, or a 2-hour oral glucose tolerance test (OGTT) 140-199).

Exclusion:

- Patients who are less than 18 yrs of age or greater than 65 years of age.
- Patients who are known to have or develop during the study any of the following upon review of their medical record:
    - Diabetes Mellitus (defined as fasting plasma glucose (FPG) ≥126mg/dl, hemoglobin A1C ≥6.5%, or a 2-hour oral glucose tolerance test (OGTT) ≥200mg/dl)
    - Stage 3 kidney disease or worse
    - Renal insufficiency defined as a glomerular filtration rate (gfr) of less than 60ml
    - Celiac disease
    - Insulinoma
    - Cushing's disease
    - Hyperthyroidism
    - Acromegaly
    - Pheochromocytoma
    - Addison's disease
    - Galactosemia
    - Glycogen storage disease
    - Hereditary fructose intolerance
- Patients taking any of the following:
    - Cinnamon as a dietary supplement
    - Daily oral steroids
    - Warfarin
    - Hypoglycemic medication
    - Weight loss medication
    - Digoxin, lithium, phenytoin, & theophylline (due to their narrow therapeutic indices)
- Patients who are pregnant or breast feeding
- Patients with a known allergy to cinnamon
- Patients with a known allergy to wheat

7. Number of Subjects: TOTAL NUMBER OF SUBJECTS (nation-wide/study-wide): 557

8. Use of an Investigational New Drug:

a. Generic Name and IND Number: Cinnulin PF (cinnamomum burmanii), IND# 114078
b. Sponsor holder of the IND Number: Paul Crawford, MD, LtCol, USAF, MC
c. Justification for use: N/A

9. Use of an Investigational Device: N/A

10. Use of a Placebo: 2 placebo pills (gelatin capsule filled with wheat bran)

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(Wilford Hall Ambulatory Surgical Center – WHASC)

1. Title:

Cinnamon Trial—assessment of the effe**C**t of l**I**festyle i**N**tervention plus water-soluble ci**N**n**AM**on extract **O**n loweri**N**g blood glucose in pre-diabetics: A randomized, double-blind, multicenter, placebo-controlled **TRIAL**.
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2.0. Principal Investigator (PI): **Nellis AFB PI:**

Name	Paul Crawford, MD
Rank/Corps or Civilian Rating	Col
Date of IRB Approved CITI Training & Date of AKO/DKO IRBNet Training	12/28/2017
Branch of Service	USAF
AD Mil/DoD Civilian/Ctr/Non-DoD Civ	AD Mil
Department & Base	Graduate Medical Education/Nellis AFB
Phone & Pager #	(702) 653-3298
E-Mail Address & AKO/DKO E-Mail Address	paul.f.crawford.mil@mail.mil

2.1. Associate Investigators (AI): See attached A2 Study Personnel Form

2.2. Research Assistants (RA) & Coordinators (RC): See attached A2 Study Personnel Form

2.3. The research relevance of this protocol focuses on:
[] Diagnosis [] Treatment [] Medical Utilization/Managed Care [x] Prevention [] Medical Readiness [] Other

2.4. Location(s):

a. Collaborating Facilities: None.

b. Air Force Sites seeking Regional IRB:

Air Force Sites	Name	Email	Phone
Nellis Air Force Base	Jill Clark, MBA/HCM, CCRP, CCRC	jill.m.clark15.ctr@mail.mil	(702) 653-3298

c. List study sponsors: Integrity Nutraceuticals, Inc. and AFMSA/SG9S

3. Research Plan:

3.1. Purpose:
The purpose of this study is to assess whether water-soluble cinnamon extract plus aggressive lifestyle intervention is effective in lowering blood glucose in pre-diabetic patients when compared to aggressive lifestyle therapy plus placebo.

3.2. Hypotheses, Research Questions or Objectives:
Does water-soluble cinnamon extract have an effect on fasting glucose, Hemoglobin A1c, lipid panel, and waist circumference in pre-diabetic patients who are already undergoing aggressive lifestyle therapy?

This study has the following goals:
1. Determine the length of time to diagnosis of diabetes using any of the ADA criteria.
2. Determine:
    a) Fasting glucose
    b) Hemoglobin A1C
    c) LDL cholesterol, and
    d) Waist circumference (in inches)

3.3. Significance:
Lowering hemoglobin A1c is correlated with reduced complications in Type 2 diabetes (e.g., retinopathy, nephropathy, neuropathy, vascular disease, and death). Water-soluble cinnamon extract is inexpensive, readily available, generally recognized as safe, and a non-pharmacological approach to management. According to the 2010 American Diabetes Association Guidelines, lifestyle intervention is the most effective way for diabetes. Historically, it has been difficult for subjects to adhere to lifestyle education programs and sustain meaningful weight loss without using significant resources, as in the Diabetes Prevention Study (NEJM, 2002).

3.4. Military Relevance:
Diabetes not only has a high morbidity and mortality amongst military beneficiaries but also is a drain on the military's medical budget. If cinnamon is found effective, it may result in long-term health care cost savings and better outcomes for our patient population. Diabetes research in the Air Force is needed to not only support its peacetime healthcare mission, but reduce Air Force health care costs, thereby freeing up funds to support other missions of the AFMS.

3.5. Background and Review of Literature:

As the worldwide incidence and prevalence of diabetes increases, the search for dietary adjuncts to treat this life-altering disease becomes far ranging. Cinnamon is purported to be a natural insulin sensitizer with adverse events of peri-oral dermatitis and stomatitis reported uncommonly with high intake.[2] There is one report of a severe exacerbation of rosacea after initiation of cinnamon for treatment of diabetes.[3] It is designated by the U.S. Food and Drug Administration as "Generally Recognized as Safe". This product was submitted to the FDA as an Investigational New Drug.

Both in vitro and in vivo animal studies have shown that cinnamon is an insulin sensitizer.[4,5] Kim et al. showed that intestinal glucosidase activity in rats was increased by cinnamon.[5] Polyphenols within cinnamon have been identified as upregulators of mouse adipocyte insulin receptors.[6] Peng and colleagues found that polyphenols from cinnamon inhibit the formation of advanced glycation end-products in bovine serum albumin.[7] Cinnamon extract (CE), high in type A polyphenols, prevents fructose feeding-induced decreases in insulin sensitivity. CE improves the postprandial overproduction of intestinal apoB48-containing lipoproteins by ameliorating intestinal insulin resistance and may be beneficial in the control of lipid metabolism.[8]

Cinnamon may improve glycemic control and insulin sensitivity.[9] To date, seven randomized trials studying cinnamon in humans with Type 2 diabetes have been published with conflicting results.[10-15] The results of these studies are mixed. Two of these studies showed a possible effect of cinnamon on fasting serum glucose, but they did not examine hemoglobin A1c levels.[10,11] One study showed no effect on plasma glucose.[12] Two studies--one each in patients with Type 1 and Type 2 diabetes--showed no effect of cinnamon on Hemoglobin A1c.[13,14] Cinnulin PF® supplementation reduced fasting blood glucose and systolic blood pressure, and increased lean body mass in a randomized trial in men and women with the metabolic syndrome.[16] A meta-analysis of these studies in divergent populations measuring different parameters showed no effect of cinnamon on hemoglobin A1c, glucose or lipids.[17] Subsequently, a RCT of 109 patients compared add-on treatment with 1 gram daily of cinnamon over a 3 month period to usual care in a population of poorly controlled Type 2 diabetics, it found that cinnamon lowered hemoglobin A1c 0.83%--similar to some prescription drugs.[15] This led to a call for more comparative effectiveness research of cinnamon versus prescription medications.[18]

There have been no trials assessing if water-soluble cinnamon extract is effective at lowering blood glucose. Guidelines recommend that new diabetics receive treatment with Metformin to help with insulin sensitization, lower blood glucose, and assist with weight loss. Water-soluble cinnamon extract appears to have many of the same mechanisms of Metformin.

Research has shown that pre-diabetics convert to diabetes at an average of 7% a year and other research performed on prevention have been multi-year trials. In order to obtain adequate power for this study, subjects will take water-soluble cinnamon extract or placebo for 1 year.

3.5.1. Bibliography:

1. Nahas R, Moher M. Complementary and alternative medicine for the treatment of type 2 diabetes. Can Fam Physician. 2009 Jun; 55(6):591-6.
2. Dugoua J, Seely D, Perri D, et al. From type 2 diabetes to antioxidant activity: A systematic review of the safety and efficacy of common and cassia cinnamon bark. Can J Physiol Pharmacol 2007;85:837-847
3. Campbell TM, Neems R, Moore J. Severe exacerbation of rosacea induced by cinnamon supplements. J Drugs Dermatol. 2008 Jun; 7(6):586-7.
4. Talpur N. Echard B. Ingram C. et al. Effects of a novel formulation of essential oils on glucose–insulin metabolism in diabetic and hypertensive rats: a pilot study. Diab Obes Metab, 2005. 7:193–199.
5. Kim SH, Hyun SH, Choung SY. Anti-diabetic effect of cinnamon extract on blood glucose in db/db mice. J Ethnopharmacol 2006; 104:119–123.
6. Cao H, Polansky MM, Anderson RA. Cinnamon extract and polyphenols affect the expression of tristetraprolin, insulin receptor, and glucose transporter 4 in mouse 3T3-L1 adipocytes. Arch Biochem Biophys 2007; 459:214–222.
7. Peng X, Cheng K, Ma J, et al. Cinnamon bark proanthocyadins as reactive carbonyl scavengers to prevent the formation of advanced glycation products. J Agric Food Chem 2008; 56:1907–1911.
8. Qin B, Polansky MM, Sato Y, Adeli K, Anderson RA. Cinnamon extract inhibits the postprandial overproduction of apolipoprotein B48-containing lipoproteins in fructose-fed animals. J Nutr Biochem. 2009 Nov; 20(11):901-8. Epub 2008 Nov 6.
9. Solomon TP, Blannin AK. Changes in glucose tolerance and insulin sensitivity following 2 weeks of daily cinnamon ingestion in healthy humans. Eur J Appl Physiol. 2009 Apr; 105(6):969-76. Epub 2009 Jan 22.
10. Khan A. Khattak KN. Safdar M. Anderson RA. Ali Khan MM. Cinnamon Improves Glucose and Lipids of People With Type 2 Diabetes. Diabetes Care. 2003. 26:3215-3218.
11. Vanschoonbeek K. BJW Thomassen, JM Senden, WKWH Wodzig. LJC. van Loon. Cinnamon Supplementation Does Not Improve Glycemic Control in Postmenopausal Type 2 Diabetes Patients. J. Nutr. 2006. 136: 977–980.
12. Mang B. Wolters M. Schmitt B. Et al. Effects of a cinnamon extract on plasma glucose, HBA, and serum lipids in diabetes mellitus type 2. Eur J Clin Invest. 2006. 36:340-344.

13. Altschuler JA, Casella SJ, MacKenzie TA, Curtis KM. The effect of cinnamon on A1C among adolescents with type 1 diabetes. Diabetes Care. 2007 Apr; 30(4):813-6.
14. Blevins SM, Leyva MJ, Brown J, Wright J, Scofield RH, Aston CE. Effect of cinnamon on glucose and lipid levels in non insulin-dependent type 2 diabetes. Diabetes Care. 2007 Sep; 30(9):2236-7. Epub 2007 Jun 11.
15. Ziegenfuss TN, Hofheins JE, Mendel RW, Landis J, Anderson RA. Effects of a water-soluble cinnamon extract on body composition and features of the metabolic syndrome in pre-diabetic men and women. J Int Soc Sports Nutr. 2006 Dec 28; 3:45-53.
16. Baker WL, Gutierrez-Williams G, White CM, Kluger J, Coleman CI. Effect of cinnamon on glucose control and lipid parameters. Diabetes Care. 2008; 31(1):41-43.
17. Crawford P. Effectiveness of cinnamon for lowering hemoglobin A1C in patients with type 2 diabetes: A randomized, controlled trial. J Am Board Fam Med. 2009; 22(5):507-512.
18. Fairman KA, Curtiss FR. Call for comparative effectiveness research: lowering A1C with sitagliptin, saxagliptin, or cinnamon. J Manag Care Pharm. 2009 Oct; 15(8):696-700.
19. The DPP Research Group. *N Engl J Med*. 2002; 346:393-403.
20. UPMC DPSC website https://diabetesprevention.upmc.com/diabetesPrevention_ProfessionalServices.htm accessed 19 April 2010.

3.6. Research Design and Methods:
We will recruit male and female subjects between the ages of 18-65 years old with a diagnosis of pre-diabetes. Eligible subjects will be recruited from any form and any stage of "standard" lifestyle intervention for pre-diabetes at an individual base. "Standard" lifestyle intervention for pre-diabetes could include Group Lifestyle Balance (GLB), nutrition classes, Better Body/Better Life, or anything an investigator certifies as standard practice at that base.

To capture potentially eligible subjects, we will use one or more of the following recruitment strategies. The instructors of these "standard" lifestyle interventions will:

1. Utilize the Marquees on base. The marquee will state "Pre-Diabetic, Contact (insert contact) for Cinnamon Trial, (insert phone number)
2. Mail a recruitment letter to all participants.
3. Announce at the beginning of class that we have a research study that they may potentially be interested in and ask permission to forward their contact information along to the research staff.

Screening Visit:

- Obtain signed Informed Consent Document and HIPAA Authorization (research-driven).
- Record: Date of birth, gender, race, ethnicity, name of lifestyle intervention for pre-diabetes, current email address height (in inches), weight (in pounds), waist circumference (in inches) measurement, blood pressure, and whether subject is taking any statins, fibrate, niacin or bile acid binding agent and, if yes, the name of drug, strength and dose.
- Women of childbearing potential will have a serum pregnancy test (5-10 milliliters (mls), approximately 1-2 teaspoons of blood) (research-driven).
- Subjects will have the following research-driven blood test drawn which include:
  - Fasting comprehensive metabolic panel (liver function, renal function, plasma glucose tests) via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood will be drawn)
    **Subjects who have had a fasting comprehensive metabolic panel test within the two weeks prior to Visit 1 will not need to have this test repeated.*
  - Hemoglobin A1c via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood will be drawn)
    **Subjects who have had a Hemoglobin A1c test within the two weeks prior to Visit 1 will not need to have this test repeated.*
  - Lipid panel via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood will be drawn)
    **Subjects who have had a lipid panel within the two weeks prior to Visit 1 will not need to have this test repeated.*

Visit 1 (Day 1 within-30 days of Screening Visit*labs must be re-done if greater than 2 weeks from Screening Visit):

- Record: whether subject is taking any statins, fibrate, niacin or bile acid binding agent and, if yes, the name of drug, strength and dose.
- Subjects will complete the RAND 36 Item Health Survey.
- Subjects will be randomized by a non-investigator at the pharmacy. We will use a random-number generator and use blocking to ensure roughly equal sample sizes. Both subjects and investigators will be blinded to the study group assignments. Subjects will be randomized by the pharmacy into one of two groups (research-driven):
  - Group 1: Will take (by mouth) 2 gelatin capsules that contains 1 gram (2-500 mg capsules) water-soluble cinnamon extract (Cinnulin PF) once a day for 1 year plus 2 years of follow-up plus standard of care aggressive lifestyle therapy.
  - Group 2: Will take (by mouth) 2 placebo capsules (gelatin capsule filled with wheat bran) once a day for 1 year plus 2 years of follow-up plus standard of care aggressive lifestyle therapy.

- Subjects will be provided a pill container to assist with remembering to take their IP and a bathroom scale to weigh themselves with (if available).
- Subjects will be given a Study Medication Diary and will be instructed to bring it with them to next study visit.
- Subjects will be told to fast for at least 10 hours prior to Visit 2.

Visit 2-Month 3 (90 days after Visit 1):

- Record: Weight (in pounds), waist circumference (in inches), blood pressure, verify current email address , and whether subject is taking any statins, fibrate, niacin or bile acid binding agent and, if yes, the name of drug, strength and dose.
- Study staff will record whether subject had any side effects to report to include cardiovascular procedures and events and other morbidity data (research-driven).
- Subjects will bring in any remaining medication to determine adherence rates to the study protocol.
- Research staff will collect the subject's Study Medication Diary and issue them a new one.
- Subjects will be told to fast for at least 10 hours prior to Visit 3.
- Refill water-soluble cinnamon extract or placebo (research-driven).
- Subjects will have standard of care blood test drawn to include:
    - Fasting comprehensive metabolic panel (liver function tests, renal function, and plasma glucose test) via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood will be drawn).
      **Subjects who have had a fasting comprehensive metabolic panel test within the two weeks prior to Visit 2 will not need to have this test repeated.*
    - Hemoglobin A1c via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood will be drawn)
      **Subjects who have had a Hemoglobin A1c test within the two weeks prior to Visit 2 will not need to have this test repeated.*
    - Lipid panel via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood will be drawn)
      **Subjects who have had a lipid panel within the two weeks prior to Visit 2 will not need to have this test repeated.*

Visit 3-Month 6 (90 days after Visit 2):

- Record: Weight (in pounds), waist circumference (in inches), blood pressure, verify current email address , and whether subject is taking any statins, fibrate, niacin or bile acid binding agent and, if yes, the name of drug, strength and dose..
- Study staff will record whether subjects had any side effects to report to include cardiovascular procedures and events and other morbidity data (research-driven).
- Subjects will bring in any remaining medication to determine adherence rates to the study protocol.
- Research staff will collect the subject's Study Medication Diary and issue them a new one.
- Subjects will be told to fast for at least 10 hours prior to Visit 4.
- Refill water-soluble cinnamon extract or placebo (research-driven).
- Subjects will have research-driven blood test drawn which include:
    - Fasting comprehensive metabolic panel (liver function tests, renal function, and plasma glucose test) via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood will be drawn).
      **Subjects who have had a fasting comprehensive metabolic panel test within the two weeks prior to Visit 3 will not need to have this test repeated.*
    - Hemoglobin A1c via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood will be drawn).
      **Subjects who have had a Hemoglobin A1c test within the two weeks prior to Visit 3 will not need to have this test repeated.*
    - Lipid panel via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood will be drawn).
      **Subjects who have had a lipid panel within the two weeks prior to Visit 3 will not need to have this test repeated.*

Visit 4-Month 9 (90 days after Visit 3):

- Record weight (in pounds), waist circumference) (in inches), blood pressure, verify current email address , and whether subject is taking any statins, fibrate, niacin or bile acid binding agent and, if yes, the name of drug, strength and dose.
- Study staff will also record whether subjects had any side effects to report to include cardiovascular procedures and events and other morbidity data (research-driven).
- Subjects will bring in any remaining medication to determine adherence rates to the study protocol.
- Research staff will collect the subject's Study Medication Diary and issue them a new one.
- Subjects will be told to fast for at least 10 hours prior to Visit 5.
- Refill water-soluble cinnamon extract or placebo (research-driven).
- Subjects will have standard of care blood test drawn to include:
    - Fasting comprehensive metabolic panel (liver function tests, renal function, and plasma glucose test) via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood will be drawn).
      **Subjects who have had a fasting comprehensive metabolic panel test within the two weeks prior to Visit 4 will not need to have this test repeated.*

- Hemoglobin A1c via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood will be drawn) **Subjects who have had a Hemoglobin A1c test within the two weeks prior to Visit 4 will not need to have this test repeated.*
- Lipid panel via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood will be drawn) **Subjects who have had a lipid panel within the two weeks prior to Visit 4 will not need to have this test repeated.*

Visit 5-Month 12 (90 days after Visit 4) *_SUBJECTS STOP TAKING STUDY MEDICATIONS AT THIS VISIT_:

- Record weight (in pounds), waist circumference (in inches), blood pressure, verify current email address , and whether subject is taking any statins, fibrate, niacin or bile acid binding agent and, if yes, the name of drug, strength and dose.
- Record whether subjects had any side effects to report to include cardiovascular procedures and events and other morbidity data (research-driven).
- Subjects will complete the RAND 36 Item Health Survey.
- Subjects will bring in any remaining medication to determine adherence rates to the study protocol.
- Research staff will collect the subject's Study Medication Diary.
- Subjects will be told to fast for at least 10 hours prior to Visit 6.
- Subjects will have research-driven labs drawn which include:
  - Fasting comprehensive metabolic panel (liver function, renal function, and plasma glucose) via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood will be drawn). **Subjects who have had a fasting comprehensive metabolic panel test within the two weeks prior to Visit 5 will not need to have this test repeated.*
  - Hemoglobin A1C via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood will be drawn). **Subjects who have had a hemoglobin A1c test within the two weeks prior to Visit 5 will not need to have this test repeated.*
  - Lipid panel via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood will be drawn). **Subjects who have had a lipid panel within the two weeks prior to Visit 5 will not need to have this test repeated.*

Visit 6-Month 15 (90 days after Visit 5):

- Record weight (in pounds), waist circumference (in inches), blood pressure, verify current email address , and whether subject is taking any statins, fibrate, niacin or bile acid binding agent and, if yes, the name of drug, strength and dose.
- Record whether subjects had any side effects to report to include cardiovascular procedures and events and other morbidity data (research-driven).
- Subjects will be told to fast for at least 10 hours prior to Visit 7.
- Subjects will have standard of care blood tests drawn including:
  - Fasting comprehensive metabolic panel (liver function tests, renal function, and plasma glucose) via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood will be drawn). **Subjects who have had a fasting comprehensive metabolic panel test within the two weeks prior to Visit 6 will not need to have this test repeated.*
  - Hemoglobin A1c via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood will be drawn). **Subjects who have had a hemoglobin A1c test within the two weeks prior to Visit 6 will not need to have this test repeated.*
  - Lipid panel via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood will be drawn). **Subjects who have had a lipid panel within the two weeks prior to Visit 6 will not need to have this test repeated.*

Visit 7-Month 18- (90 days after Visit 6):

- Record weight (in pounds), waist circumference (in inches), blood pressure, verify current email address , and whether subject is taking any statins, fibrate, niacin or bile acid binding agent and, if yes, the name of drug, strength and dose.
- Record whether subjects had any side effects to report to include cardiovascular procedures and events and other morbidity data (research-driven).
- Subjects will be told to fast for at least 10 hours prior to Visit 8.
- Subjects will have a research-driven blood tests draw which includes:
  - Fasting plasma glucose via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood). **Subjects who have had a fasting glucose test within the two weeks prior to Visit 7 will not need to have this test repeated.*
  - Hemoglobin A1c via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood will be drawn). **Subjects who have had a hemoglobin A1c test within the two weeks prior to Visit 7 will not need to have this test repeated.*
  - Lipid panel via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood will be drawn).

**Subjects who have had a lipid panel within the two weeks prior to Visit 7 will not need to have this test repeated.*

Visit 8-Month 21 (90 days after Visit 7):

- Record: Weight (in pounds), waist circumference (in inches), blood pressure, verify current email address , and whether subject is taking any statins, fibrate, niacin or bile acid binding agent and, if yes, the name of drug, strength and dose.
- Study staff will also record whether subjects had any side effects to report to include cardiovascular procedures and events and other morbidity data (research-driven).
- Subjects will be told to fast for at least 10 hours prior to Visit 9.
- Subjects will have standard of care blood test drawn which include:
    - Fasting plasma glucose via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood will be drawn).
      **Subjects who have had a fasting glucose test within the two weeks prior to Visit 8 will not need to have this test repeated.*
    - Hemoglobin A1c via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood will be drawn).
      **Subjects who have had a hemoglobin A1c test within the two weeks prior to Visit 8 will not need to have this test repeated.*
    - Lipid panel via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood will be drawn).
      **Subjects who have had a lipid panel within the two weeks prior to Visit 8 will not need to have this test repeated.*

Visit 9-Month 24 (90 days after Visit 8):

- Record: Weight (in pounds), waist circumference (in inches), blood pressure, verify current email address , and whether subject is taking any statins, fibrate, niacin or bile acid binding agent and, if yes, the name of drug, strength and dose.
- Subjects will complete the RAND 36 Item Health Survey.
- Study staff will also record whether subjects had any side effects to report to include cardiovascular procedures and events and other morbidity data (research-driven).
- Subjects will have research-driven blood tests drawn which include:
    - Fasting plasma glucose via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood will be drawn).
      **Subjects who have had a fasting glucose test within the two weeks prior to Visit 9 will not need to have this test repeated.*
    - Hemoglobin A1c via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood will be drawn).
      **Subjects who have had a Hemoglobin A1c test within the two weeks prior to Visit 9 will not need to have this test repeated.*
    - Lipid panel via 1 venipuncture (5-10 mls, approximately 1-2 teaspoons of blood will be drawn).
      **Subjects who have had a lipid panel within the two weeks prior to Visit 9 will not need to have this test repeated.*

VISIT WINDOWS: Visits have a window of plus or minus 10 days. Subjects are encouraged to come in as close to the 90 day mark as possible since they are only given a 90 day supply of IP. Postponement of any follow up visits (after subject stopped taking study medication) is authorized for up to 6 weeks in case of a temporary condition that would affect glucose tolerance (i.e. moderate to severe illness to be determined by study PI or Site AI). A note to file documenting such shall be placed in the subject's study folder and documented in the data collection form.

ADHERENCE TO STUDY ASSIGNMENTS: Adherence to study medication will be assessed via review of the "Study Medication Diary". Compliance will be recorded both in paper format and in the electronic data collection tool. If a subject misplaces their Study Medication Diary, they will be asked to reproduce it from memory to the best of their ability. Subjects will be instructed to bring back all of the bottles regardless of whether there are empty or contain missed doses.

If at any time a subject stops taking their water-soluble cinnamon extract or placebo, they will remain in the study, will be instructed to return any pill bottles, and will continue follow-up in the study. Regardless of the amount of missed doses, all subjects will remain in the study and continue with all the study related visits. Research staff will document the missed doses and subjects will continue in the research study. If the subject decides to re-start their water-soluble cinnamon extract or placebo, they will resume the study at their last documented visit (i.e. subject stops taking water-soluble cinnamon extract or placebo at Visit 4 and decides 1 year later that they wish to resume the study, their next visit would be Visit 5).

If a subject misplaces or loses their study medication, they will be instructed to return to the pharmacy and will be given a new bottle of their assigned study medication. Since the pharmacy is not blinded, they will be able to give the medication that the subject was assigned.

If a subject forgets to bring their study medication in for their visit, they will be instructed to bring it in at their earliest convenience.

DIRECTIONS FOR TAKING MEASUREMENTS: A measuring tape to measure subjects' waist circumference will be provided to the study team. A designated study staff member will obtain the waist circumference measurements to ensure consistent measurements throughout the study.

Directions for taking waist circumference measurement: Have subject take a deep breath, blow out, and hold with abdominals tightened. Tell subjects not to suck in their stomach. Take the measurement around the largest part of their waist. Waist circumference should be recorded to the nearest ½ inch (for example 40.5").

Directions for weighing subjects: Have subject remove his/her shoes and empty pockets of any items prior to stepping on the scale. Weight should be recorded to the nearest ½ pound (for example 150.5#).

Directions for taking height: Have subjects remove their shoes before taking their height. Height should be recorded to the nearest 1/2 inch (for example 60.5").

Directions for taking blood pressure: Have subjects sit for 5 minutes before taking blood pressure.

WITHDRAWAL PROCEDURES: If at any time during the study, the subject decides to withdraw consent they will be referred back to their Primary Care Manager (PCM). If a subject is found to be diabetic during the course of the study, they will be withdrawn and referred to their PCM to initiate standard of care treatment. Standard of care typically follows the DoD Clinical Practice guidelines for self-monitoring of blood glucose. As part of this, the Air Force provides glucometers and supplies at no charge.

ADVERSE EVENTS (AEs) AND DEVIATIONS: The Associate Investigator (AI) at each site is responsible for reviewing, categorizing, and properly reporting to the main PI AEs that occur with their subjects. The "Algorithm for Determining Whether an Adverse Event is an Unanticipated Problem" is attached to assist in guiding the research staff on the categorizing of Adverse Events, Protocol Deviations, and Serious Adverse Events.

Serious Adverse Events (SAEs) and Serious Protocol Deviations are defined as unexpected events that increase the risk to subjects and that were possibly, probably, or definitely related to the research. These must be reported to the WHASC IRB within 5 days. Each site is responsible for reporting these to Col Crawford, the local Site Principal Investigator, and Jill Clark immediately via the "Possible Internal (Local) Reportable Unanticipated Problem Involving Risk to Subjects or Others (UPIRSO)" form.

If a subject experiences an allergic reaction during the study, they will be instructed to stop taking the study medication and seek urgent medical treatment.

Adverse Events (AEs) and Protocol Deviations that do not increase the risks to subjects like those listed in the "risks" section of this protocol are to be reported to Col Crawford, the local Site Associate Investigator and Jill Clark as they occur or no later than the 1st workday of every month via the "WHASC Tracking Log for Adverse Events (AEs)/Protocol Deviations Not Requiring Immediate Reporting. This is done to ensure ongoing monitoring and identification of trends that may arise.

Guidance for completing the SAE/AE forms:

- When completing the forms, please ensure that you include as much information as possible, to include:
  - Date the patient reported the event
  - Date the event occurred or the date that you discovered the event happened/began
  - A detailed description of the event including any tests/procedures that were performed with dates
  - Any directions given to the patient including the date
  - Description of the resolution with the date
- When answering the questions:
  - "Was the event unexpected?": Select YES only if the event was NOT already listed in the risks/benefits section of the Protocol or part of an existing disease process.
  - "Did the event cause increased risk to participants or others": Select YES only if the adverse event was serious, which includes events that are life threatening or results in: death, inpatient hospitalization, prolongation of existing hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes above. If the event is not serious but there is a trend that would warrant a change in the protocol/ICD (i.e. several patients experienced a rash), then you would also select YES.
  - "Was the event possibly, probably, or definitely related to the research procedures?": Select YES if it is due to the research itself not underlying disease or disorder. If there isn't adequate information available to assess this, the answer would be NO.

- o "Should the consent form/process be revised": Select YES only if it warrants a revision to the research process or risks/benefits (this should be discussed with Col Crawford if you are selecting YES).
- o "Summary of events in the opinion of the local investigator": please have your Local Site Associate Investigator comment such as "no increased risks to subjects participating in the study" (just an example). Then have your Site Associate Investigator sign, print their name, and date. Then return the scanned copy to Col Crawford and Jill Clark. They will then get the Research Monitor to complete Section 6, and return a copy to be filed in the subjects file.

PREGNANCY: Subjects must agree to take precautions to prevent pregnancy during the course of this study due to the possible effect water soluble cinnamon extract may cause an unborn child. The only completely reliable methods of birth control are total abstinence or surgical removal of the uterus. Other methods, such as the use of condoms, a diaphragm or cervical cap, birth control pills, IUD, or sperm killing products are not totally effective in preventing pregnancy. In addition, women who are breastfeeding may not participate in this study.

If a subject unintentionally becomes pregnant, they will be instructed to cease water-soluble cinnamon extract or placebo, return any pill bottles and will continue follow-up in the study. They will be encouraged to resume taking water-soluble cinnamon extract or placebo and blood work (if they choose) 6 months after delivery of their child. If the subject decides to re-start their water-soluble cinnamon extract or placebo, they will resume the study at their last documented visit (i.e. subject stops taking water-soluble cinnamon extract or placebo at Visit 4 and decides 1 year later that they wish to resume the study, their next visit would be Visit 6).

SUBJECTS ENROLLED NO LONGER PRE-DM: If a subject becomes no longer pre-diabetic while enrolled in the study, they will remain in the study.

SUBJECTS ENROLLED BECOME TYPE II DIABETIC: If a subject becomes Type II diabetic while enrolled in the study, they will be removed from the study.

SUBJECTS COMPLETING THE STUDY: When subjects have completed the study, the Pharmacy will de-identify the information and send to the Investigator for analysis. Each Associate Investigator will send the de-identified data to the Principal Investigator via an encrypted email for analysis.

HYPOGLYCEMIC EPISODES: If the subject experiences a hypoglycemic (low blood sugar) episode, e.g., for example heart palpitations (abnormal heart beats either fast or slow), tremors (involuntary muscle movement), hunger, sweating, they should be instructed to eat 15-20 grams of sugar (e.g., glucose (sugar) tablets, glass of juice or other snack containing sugar) then eat some carbohydrates (e.g., a small meal or cracker with peanut butter).

BLOOD TEST OUTSIDE OF NORMAL REFERENCE RANGE: Research Coordinators at each site will print the blood test results and place in the subject's folder. If any of these results are outside of the normal reference range noted by their lab, they will place a telephone consult for the subject's Primary Care Manager (PCM).

DISPOSAL OF STUDY RELATED PILLS: Subjects will return any remaining study-related pills directly to the Research Coordinator or Principal Investigator. The Research Coordinator or Principal Investigator will be responsible for disposing of the study-related pills. The preferred method of disposal is to have the Pharmacy dispose of them. If the Pharmacy is unable to dispose of them, they will provide directions on safe disposal for the Research Coordinator or Principal Investigator to follow.

OTHER ITEMS: If at any time, a site needs more study medication, they should contact the main site at the Nellis AFB and request. Integrity Nutraceuticals should not be contacted directly. Prior to ordering any standard of care labs, study staff will verify in AHLTA that the subject did not have that lab test within the previous timeframes documented in the study visits above. In addition, CHCS has alerts built in that will alert the person entering the lab test that there is a pending order.

Subjects will take their water-soluble cinnamon extract or placebo daily and will be permitted to have the usual medical care for other co-morbid and acute conditions if applicable. Analysis described above using intention-to-treat principles for any missing data will be used (we will use the carry-forward method to impute missing data).

The placebo will be a gelatin capsule filled with wheat bran, which does not increase the risks to subjects.

Each site's Laboratory will be responsible for analyzing blood samples obtained at their site for this study. Samples will be labeled as they would for standard laboratory draws. All Laboratories follow Clinical Laboratory Improvement Amendments (CLIA) procedures when processing laboratory specimens mentioned in this research project.

This study involves the use of an investigational product (IP) called Cinnulin PF (water-soluble cinnamon extract). This means that the product has not been approved by the Food & Drug Administration (FDA) for preventing or delaying the onset of

diabetes. However, the FDA has not objected to its use to study its effectiveness. Water-soluble cinnamon extract (Cinnulin PF) is being used to assess its effects on insulin in pre-diabetic subjects. It is being given in a dose that does not increase the risk to the research subjects. There are no known risks associated with water-soluble cinnamon as it is a compound granted GRAS (Generally Recognized As Safe) status by the United States Food and Drug Administration (more information can be found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=582.20).

3.6.1. Interventions, Observations, or Data Sought:
We will assess effect of 1 gram (2-500 mg capsules) of water-soluble cinnamon extract taken once a day for 1 year plus 1 year of follow-up and obtain fasting glucose, Hemoglobin A1c, lipid panel, height, weight, and waist circumference (in inches). Additionally, to assess safety of long term cinnamon use, electrocardiograms will be performed to evaluate for QT prolongation.

3.6.2. Data Collection and Processing:
Subjects will be randomized by the pharmacy. Pharmacist acting as Associate Investigators will be unblinded to study medication assignments. At the conclusion of the study, Pharmacists will provide the blinded information to the Principal Investigator for analysis. Both subjects and Investigators will be blinded to the study assignments. Data will be collected and recorded in a spreadsheet. At the conclusion of the study, all personally identifying information will be removed prior to analysis based on AFI 33-332, "The Air Force Privacy and Civil Liberties Program" and the "National Institute of Standards and Technology Special Publication (NIST SP 800-88) for the approved methods to destroy PII". Each subject will be asked to place their de-identified study-related data into the "Nellis Diabetes Research Data Repository (FWH20110136H)" for future research. If the subject does not give their authorization, then all de-identified study-related data will be destroyed no later than at the closure of the study.

3.6.3. Setting: Mike O'Callaghan Military Medical Center at Nellis AFB.

3.6.4. Date(s): April 2012-April 2018

3.6.5. Source of Research Material:

Source of Research Material per Participant (Procedures)	# Routine Care	# Research Driven	# Total Procedures
Group 1 Only: 1 gram (2-500 mg capsules) water-soluble cinnamon extract (Cinnulin PF) (once a day for 1 year)	0	1 year	1 year
Group 2 Only: 2 placebo pills (once a day for 1 year)	0	1 year	1 year
Fasting glucose	0	3	3
Fasting comprehensive metabolic panel	3	3	6
Hemoglobin A1C	4	5	9
ECG	0	2	2
Lipid panel	4	5	9
Study Medication Diary	0	4	4
RAND 36-Item Health Questionnaire	0	3	3

"All specimens collected at Nellis AFB will be kept at Nellis AFB and handled and disposed of in accordance with federal regulations."

3.6.6. Subjects:
We will recruit male and female subjects Nellis AFB between the ages of 18-65 years with a diagnosis of pre-diabetes. Eligible subjects will be recruited from any form and any stage of "standard" lifestyle intervention for pre-diabetes at an individual base. "Standard" lifestyle intervention for pre-diabetes could include Group Lifestyle Balance (GLB), nutrition classes, Better Body/Better Life, or anything an investigator certifies as standard practice at that base. No special populations (i.e. children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons) will be eligible for this study. There are currently 2,950 diabetic patients empaneled for care at Nellis AFB. Several thousand more are pre-diabetic--many of these will likely attain the diagnosis of diabetes within 36 months.

3.6.7. Inclusion/Exclusion Criteria:

Inclusion:

- Patients will be Nellis AFB DoD beneficiaries between the ages of 18-65 years.
- Diagnosis of pre-diabetes (defined as a fasting plasma glucose (FPG) 100-125mg/dl or hemoglobin A1C 5.7-6.4% or a 2-hour oral glucose tolerance test (OGTT) 140-199).

Exclusion:

- Patients who are less than 18 yrs of age or greater than 65 years of age
- Patients who are known to have or develop during the study any of the following upon review of their medical record:
    - Diabetes Mellitus (defined as fasting plasma glucose (FPG) ≥126mg/dl, hemoglobin A1C ≥6.5%, or a 2-hour oral glucose tolerance test (OGTT) ≥200mg/dl)

    - Stage 3 kidney disease or worse
    - Renal insufficiency defined as a glomerular filtration rate (gfr) of less than 60ml
    - Celiac disease
    - Insulinoma
    - Cushing's disease
    - Hyperthyroidism
    - Acromegaly
    - Pheochromocytoma
    - Addison's disease
    - Galactosemia
    - Glycogen storage disease
    - Hereditary fructose intolerance
- Patients taking any of the following:
    - Cinnamon as a dietary supplement
    - Daily oral steroids
    - Warfarin
    - Hypoglycemic medication
    - Weight loss medication
    - Digoxin, lithium, phenytoin, and theophylline (due to their narrow therapeutic index)
- Patients who are pregnant or breast feeding
- Patients with a known allergy to cinnamon
- Patients with a known allergy to wheat

3.6.8. Instrumentation: N/A

4.0. Human Subject Protection:

4.1. Recruitment:
All potentially eligible patients will be offered an opportunity to participate. Primary Care Managers (PCMs) who are not part of the research team will be informed about the study and provided information on the inclusion/exclusion criteria. PCM referrals and posted advertisements will be utilized for recruiting subjects to the study. Some patients may be patients of the PI or AI, however, they will have the study staff recruit their patients to prevent any misconception of coercion or undue influence. If a potential subject is identified by the treating PCM and is interested in obtaining more information about the study, the patient will either be provided a contact number to the Research Staff, the Research Staff will be given the potential subject's contact information by the PCM with the patient's oral or written authorization, or the PCM will come and get the Research Staff to speak with the patient directly. Lifestyle Intervention instructors will also provide referrals with the patient's oral or written authorization. We will also utilize the Marquees on base (the marquee will state: Pre-Diabetic, Contact (insert contact) for Cinnamon Trial, (insert phone number) for recruitment.

We are requesting a HIPAA Waiver so we are able to review the AHLTA schedule for potential participants. The data collected will only be used for recruiting and will be destroyed after contact with individual patients has been made. The clinical research coordinator will review the schedules of clinicians to find eligible patients within their schedule. The coordinator will proceed to inform the clinician of any possibly eligible subjects for the study. Each participating clinic will mail their pre-diabetic patients a letter informing them of the Cinnamon trial, and giving them the opportunity to participate or opt out. The mailing of these letters will be tasked to a study team member at the study site. We are also requesting to obtain a list from the Disease Management nurse on behalf of Family Medicine and Family Health Clinics. This list will be used to mail out letters to potential participants to increase recruitment

4.2. Consent Processes:
Informed consent and HIPAA authorization will be sought in advance from each prospective subject. Informed consent will be appropriately documented. [32 CFR 219.117] After discussion with the Investigator, the subject will be given the opportunity to consent. The Investigator will provide a written copy of the consent form and allow the subject to read it, review it with the subjects, and answer questions. The subject may decline to consent, and no pressure will be applied. If the subject consents, the proper signatures will be obtained, and a copy will be given to the subject.

4.3 Participation Compensation: Subjects will not be paid for participation in this study.

4.4. Assent Process: N/A

4.5. Benefits:
The benefits to the subjects may include lower hemoglobin A1c levels and improvement of long-term health by decreasing the risk of developing diabetes.

4.6. Risks:

Risks to the subject are minimal as the subjects have been diagnosed with pre-diabetes and will have to be treated regardless if they participate in this study or not. There are no known risks associated with water-soluble cinnamon, as it is a compound granted GRAS (Generally Recognized as Safe) status by the United States Food and Drug Administration. Potential risks include the inadvertent disclosure of personal health information and a potential for a cinnamon allergy that is not already known by the subject. The risks associated with the blood draw include bleeding, feeling light-headed, and bruising at the blood draw site and infection. Risks and side effects related to the water-soluble cinnamon extract include those, which are:

Less likely and not serious:

- **Hypoglycemia** (low blood sugar):
  - Heart palpitations (abnormal heart beats either fast or slow)
  - Tremors (involuntary muscle movement)
  - Hunger
  - Sweating

*If a subject experiences any of these symptoms, they are instructed to eat 15-20 grams of sugar [for example glucose (sugar) tablets], a glass of juice or other snack containing sugar, and then eat some carbohydrates (for example a small meal or cracker with peanut butter).

Less Likely and serious

- **Cinnamon and Wheat Bran**: There may be a risk that the subject has an allergy to cinnamon and wheat bran that they are not aware of currently. The signs and symptoms of an allergic reaction include:
  - Shortness of breath
  - Hives (itchy rash)
  - Runny nose
  - Watery eyes
  - Sore eyes
  - Asthma
  - Lip swelling
  - Tongue swelling
  - Nausea
  - Brochospasm (a bronchial spasm is a sudden constriction of the muscles in the walls of the bronchioles)
  - Anaphylaxis (whole-body allergic reaction that has the following signs and symptoms):
    - Abdominal pain or cramping
    - Abnormal (high-pitched) breathing sounds
    - Anxiety
    - Confusion
    - Cough
    - Diarrhea
    - Difficulty breathing
    - Difficulty swallowing
    - Fainting, light-headedness, dizziness
    - Hives
    - Itchiness
    - Nasal congestion
    - Nausea, vomiting
    - Palpitations
    - Skin redness
    - Slurred speech
    - Wheezing

*If the subject experiences any of these symptoms, they are instructed to stop taking the study medication and seek urgent medical treatment.

Rare and serious

- **RAND-36 Health Questionnaire**: Risks and side effects related to the RAND-36 item Health Questionnaire include those which are:
  - There is a risk (although rare) that the questionnaire may identify a subject as at risk for a mental health condition and result in a referral to mental health. Occasionally a person diagnosed with a mental health condition may be disqualified from active duty and a Medical Examination Board (MEB) referral.

4.7. Costs: There will be no additional costs to subjects for their participation in this research study.

4.8. Safeguards for Protecting Information:

How will coded or identifiable data/specimens be stored?	

[X]	Paper data, including completed consent forms	The research consents and HIPAA Authorization Documents will be stored in a locked cabinet in a locked room with restricted access.
[X]	Electronic data	Medical records will be annotated to reflect the subject's participation in a research study. All coded, de-identified research data will be electronically stored separately from the Master Key of identifiable patient demographics and PHI/PII.
[X]	Long-term storage (following completion of the study and inactivation of IRB approval)	The research data will be coded and any links to identifiable data will be destroyed (an approved shredding bin) as soon as possible or no later than at the closure of the study, with the exception of those study subjects that consent to place their de-identified research data into the "Nellis Diabetes Research Data Repository (FWH20110136H) for future research. The anonymized research data will not be utilized for further research activity beyond the protocol stipulations without additional IRB approval. All de-identified research data will be maintained for 3 years following study closure.

4.9. Safeguards for Protecting Subjects:
The Principal Investigator will be responsible for the protocol safety monitoring. The PI will make study documents (*e.g.*, consent forms, data pulls) and pertinent hospital or clinical records readily available for inspection by the local IRB and over sight staff for confirmation of the study data. Integrity Nutraceuticals, Inc. will not have access to subjects' medical records.

4.9.1. Minimizing Risks:
Risks in this study are minimal and only relate to a blood draw and water-soluble cinnamon extract. Subjects will have access to study personnel should they have any issues. If there are any issues, they will be immediately reported to one of the Investigators and an applicable medical evaluation will be initiated. There is also a risk of inadvertent breach of confidentiality.

4.9.2. Vulnerable Populations: No vulnerable populations will be recruited.

4.9.3. Clinical Care:
If a subject experiences any injury, adverse event, or unexpected clinical finding, a PI, AI, or Primary Care Manager will be available to assess the subject and initiate proper clinical care.

4.9.4. Injury Compensation: Subjects will not be compensated for injuries.

4.9.5. Data Safety Monitoring:
The trial will be conducted in compliance with this protocol, International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), and any applicable national and international regulatory requirements. The Principal and Associate Investigators will be monitoring all aspects of the study in accordance with the appropriate regulations and will have regular meetings with periodic quality control of data documentation and collection. The objectives of the monitoring meetings will be:

1) To verify the prompt reporting of all data points, including reporting SAE's and checking availability of signed informed consent,
2) To compare individual subject records, data pulls and/or the study source documents/case report forms (supporting data, laboratory specimen records and medical records to include physician progress notes, nurses' notes, subjects' hospital charts),
3) To ensure protection of study subjects, compliance with the protocol, and accuracy and completeness of records.

David Moss, DO, Capt (Primary) and Matthew Hawks, MD, Capt (alternate) will be the research monitors assigned to this study.

The PI will make study documents (*e.g.*, consent forms, data pulls) and pertinent hospital or clinical records readily available for inspection by the local IRB and over sight staff for confirmation of the study data.

5.0. Alternatives: The alternative is not to participate in this study.

6.0. Data Analysis:
6.1. Outcome Measures:

We will be assessing the effect of 1 gram (2-500 mg capsules) of water-soluble cinnamon extract (Cinnulin PF) on pre-diabetic subjects and obtaining hemoglobin A1c, lipid panel, height, weight, and waist circumference measurements (in inches).

6.2. Sample size estimation/power analysis:
A priori power for $H_0$1 was assessed using G*Power Version 3.0.10 [1]. The results indicate 214 subjects per group with 8 repeated measures for a total sample size of 3424 will achieve a power of approximately 0.99 to detect a small effect size of 0.10 at $\alpha = 0.0004$.

A priori power for $H_0$2 was assessed using the method described by Glantz[2] to calculate sample size for a two-sample log-rank test to detect differences in the time to event. Based on this design, it will require a minimum of 214 subjects per group to detect a difference between a 17.5% conversion in the Placebo + lifestyle and an 11.5% conversion in the Cinnulin + lifestyle group at $\alpha = 0.05$ (one-sided) and power of 0.80.

We are enrolling 557 subjects total, for an expected 428 completing the study. We estimate 129 subjects' will either withdraw consent or drop out of the study.

6.3. Statistical Analysis: Statistical Analysis Plan

Protocol	Assessment of the effe**C**t of l**I**festyle i**N**tervention plus water-soluble ci**N**n**AM**on extract **O**n loweri**N**g blood glucose in pre-diabetics: A randomized, double-blind, multicenter, placebo controlled **TRIAL**.
Principal Investigator(s)	Lt Col Paul Crawford, USAF, MC 99th MDG
Statistical Analysis Plan	Mr. Danny Sharon, Ctr AFMSA/SG5M South
Statistical Analysis	Mr. Ken Williams, Ctr AFMSA/SG5M South

Technical Objective: The objective of this study is to compare Cinnulin PF, a cinnamon extract, in combination with a lifestyle management program, to a placebo and life style management program, and to evaluate the prevention or delay the development of Type 2 diabetes in persons with pre-diabetes.

Sample: Subjects will be a random sample of males and females between the ages of 18-65 years with a diagnosis of pre-diabetes seen in certain Air Force medical treatment facilities. The subjects are presumed to be randomly selected from the population of patients obtaining similar care at all Air Force medical treatment facilities.

Hypothesis:
$H_0$1 – No difference in means of continuous dependent variables between and among treatment groups
$H_0$2 – Cinnulin + Life Style and Placebo + Life Style groups have identical survival functions for the time to reach the Type 2 diabetes conversion event.

Study Design: The experimental design of this study is a mixed effects, randomized complete block design with repeated measures. Subject is a random effect as the subjects are a sample randomly selected and randomly assigned to a treatment group. Fixed effects are treatment group and time of repeated measure as these effects cannot be generalized to other treatments and times. Subjects will be randomly assigned to each treatment group.

Factors:
1. Subject
2. Treatment: Cinnulin PF + Life Style Management versus Placebo + Lifestyle Management
3. Repeated Measurements: Laboratory and physical measurements obtained from each subject at fixed intervals for the duration of the study (N=8).

[1] Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*. 2007; 39 (2): 175-191.
[2] Glantz SA. *Primer of Biostatistics*. McGraw-Hill, 2002, 438-440.

Outcome Variables:

1. Diabetic indicators
    a. Glucose
    b. Hemoglobin A1c
    c. Lipid panel (cholesterol, triglycerides, HDL, LDL)
    d. Waist circumference
2. Type 2 diabetes conversion: Yes/No

Other Variables of Interest among Subjects

1. Subject Demographics
    a. Age (years)
    b. Marital Status (single versus married)
    c. Gender
    d. Race/Ethnicity (African American, European American, or Hispanic, 2 parameters)
    e. Specialty codes (categorized into office work, logistics, or combat specialties, 2 parameters)
    f. Military Grade (Officer grades categorized into company, field or higher ranks; enlisted into E1 – E6 or E7 – E9).

Sample Size Estimation and Power Analysis: A priori power for $H_0 1$ was assessed using G*Power Version 3.0.10 [3]. The results shown below indicate 214 subjects per group with 8 repeated measures for a total sample size of 3424 will achieve a power of approximately 0.99 to detect a small effect size of 0.10 at α = 0.0004.

Input:	Effect size f	=	0.1
	β/α ratio	=	4
	Total sample size	=	3424
	Number of groups	=	2
	Repetitions	=	8
	Corr among rep measures	=	0.8
Output:	Noncentrality parameter λ	=	41.503030
	Critical F	=	12.389225
	Numerator df	=	1.000000
	Denominator df	=	3422
	α err prob	=	0.000437447
	β err prob	=	0.00174979
	Power (1-β err prob)	=	0.998250

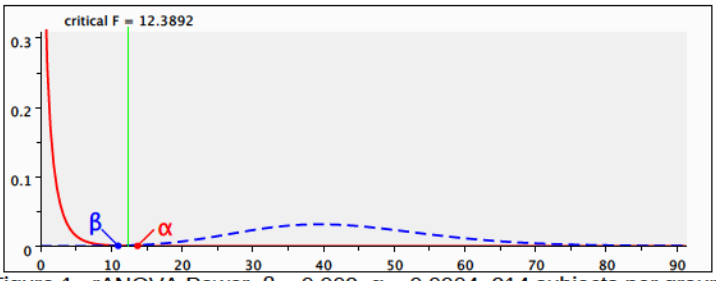

Figure 1. rANOVA Power, β = 0.002, α = 0.0004, 214 subjects per group

Post hoc analyses to evaluate differences within clinically significant time intervals will be tested with one-tailed t-tests for independent samples. The power analysis, using G*Power Version 3.0.10[4], is shown below and shows 214 subjects per group will achieve a power of approximately 0.85 to detect a small effect size of 0.20. To lessen the probability of a false negative, a β/α ratio of 1 was employed.

t tests - Means: Difference between two independent means (two groups)

Analysis:	Compromise: Compute implied α & power		
Input:	Tail(s)	=	One
	Effect size d	=	0.2
	β/α ratio	=	1
	Sample size group 1	=	214
	Sample size group 2	=	214
Output:	Noncentrality parameter δ	=	2.068816
	Critical t	=	1.035015
	Df	=	426
	α err prob	=	0.150624
	β err prob	=	0.150624
	Power (1-β err prob)	=	0.849376

[3] Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods*. 2007; 39 (2): 175-191.
[4] Ibid.

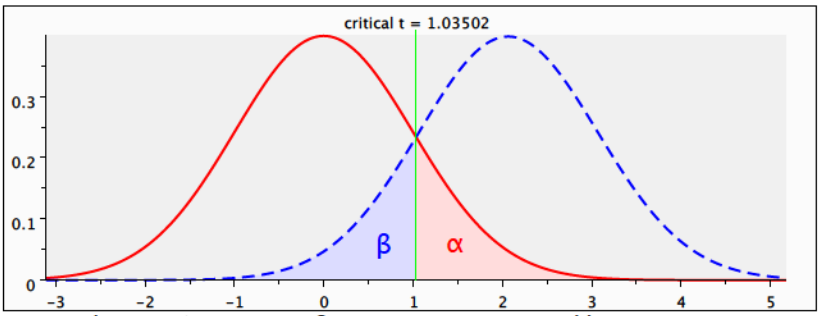

Figure 2. *t*-test Power, β = 0.15, α = 0.15, 214 subjects per group

A priori power for $H_0$2 was assessed using the method described by Glantz[5] to calculate sample size for a two-sample log-rank test to detect differences in the time to event. Based on this design, it will require a minimum of 214 subjects per group to detect a difference between a 17.5% conversion in the placebo + lifestyle and an 11.5% conversion in the cinnulin + lifestyle group at α = 0.05 (one-sided) and power of 0.80.

Power Analysis Log-Rank Test for Two Samples	
α	0.050
$Z_{.05(2)}$	1.64
1-β	0.80
$Z_{.80(upper)}$	-0.842
$S_2(\infty)$	0.885
LnS2(∞)	-0.122168
$S_1(\infty)$	0.825
LnS2(∞)	-0.192372
ψ	0.6350597
d (primary endpoint events) =	124
n (sample size to achieve this number of events) =	428
Groups/Treatments	2
Subjects required per group/treatment	**214**

Steps of Analysis

Descriptive statistics: Sample means and standard errors of measurement of interval variables will be calculated, and frequency distributions of nominal variables will be calculated and graphed for the total sample and for the Cinnulin/Lifestyle Management groups. Homogeneity of the groups will be tested with a two-tailed *t*-test and two-tailed Fisher's exact test for interval and nominal variables respectively.

Hypothesis Testing

$H_0$1– This hypothesis will be tested by a mixed effects repeated measures analysis of variance (rANOVA).

$H_0$2– This hypothesis will be tested by developing Kaplan-Meier survival curves and survival functions compared with a log-rank test.

Post Hoc Tests: In the event $H_0$1 is rejected, contrasts will be used to investigate effects and differences within clinically significant time intervals. In the event multiple univariate tests are used to investigate effects, the Bonferroni[6] or Holm's method[7] will be used to correct the level of significance for multiple comparisons.

Analysis Tools:

SAS Version 9.2 for Windows (SAS Institute, Cary, North Carolina)
R Version 2.13.1 (R Foundation for Statistical Computing)
Microsoft Excel (Microsoft Corporation, Seattle, Washington)

6.4 Number of Subjects:

Number of subjects recruited at WHASC	46

[5] Glantz SA. *Primer of Biostatistics*. McGraw-Hill, 2002, 438-440.
[6] Abdi H. Bonferroni and Šidák. Corrections for multiple comparisons. In N.J. Salkind (ed.). *Encyclopedia of Measurement and Statistics*. 2007; Thousand Oaks, CA: Sage.
[7] Holm, S. 1979. A simple sequential rejective multiple test procedure. *Scand. J. Statistics*, 6: 65-70.

Number of subjects recruited at Nellis AFB	106
Number of subjects recruited at DGMC	76
Number of subjects recruited atEglin (actual)	53
Numerb of subject recruited at Offutt	2

TOTAL NUMBER OF SUBJECTS: 557 (nation-wide/study-wide): **428** (completing the study)

7. Duration of Study: Approximate duration of the study: 6 years

8. Intramural Funding/Local Support Services Required:
We received a grant for Intramural funding from the AFMSA/SG9S in the amount of approximately $639,036.36. We received a second grant from the 59MDW/ST for approximately $618,000 over 2 years. This is to support the salaries of four Medical Assistants, costs associated with Group Lifestyle Balance training, and site monitoring visits.

9. Extramural Funding/External Support Services Required:
Integrity Nutraceuticals, Inc. will provide Cinnulin PF and placebo to Geneva Research Foundation who will administer the grant. Collaborating Institution Support: This study will be sponsored by Integrity Nutraceuticals, Inc. The collaborative research will be executed in accordance with 15 USC 3710a through a Cooperative Research and Development Agreement, (pending approval) between the 99th MDG and Integrity Nutraceuticals, Inc. Integrity Nutraceuticals, Inc. shall provide the Air Force activity: 1 gram (2-500 mg capsules) Cinnulin PF tablets for approximately 279 subjects taking once a day for 1 year ($280,370.00) and Placebo pills for approximately 279 subjects taking once a day for 1 year ($1,870.00) to include shipping costs to the Air Force Activity. The estimated fair market value of the support is $282,240.00.

10. Financial Conflict of Interest: No financial conflicts of interest exist.

11. Use of an Investigational New Drug, use of a Drug for a non-FDA approved purpose, use of an investigative device or use of a placebo:
This research uses an Investigational New Drug **[x] YES [] NO**
This research uses a FDA approved drug for a non-FDA approved purpose **[] YES**
[x] NO
This research uses an Investigational Device **[] YES [x] NO**
This research uses a placebo. **[x] YES**
[] NO

12. Medical Research Area for the Study: (Pick as many as appropriate)

[] Analytical Chemistry	[] Anatomy	[] Anesthesiology	[] Biochemistry
[] Cardiovascular Surgery	[] Cardiology	[] Cell Biology	[] Dentistry
[] Dermatology	[] Dietetics	[] Electrophysiology	[x] Endocrinology
[] Emergency medicine	[] Gastroenterology	[] General Surgery	[] Hematology
[] Histology	[] Immunology/Allergy	[] Infectious Disease	[] Microbiology
[] Molecular Biology	[] Neonatology	[] Neurology	[] Neurosurgery
[] Nursing	[] OB/GYN	[] Occupational Medicine	[] Occupational Therapy
[] Oncology	[] Ophthalmology	[] Oral/Maxillofacial Surgery	[] Orthopedics
[] Pathology	[] Pediatrics	[] Pharmacology	[] Physical Therapy
[] Mental Health	[] Radiology/Imaging	[] Urology	[] Wellness
[] Other (state): Family Medicine, Internal Medicine, Family Health Clinic			

13. Attachments:
1. Study Medication Diary
2. Certificate of Compliance
3. Informed Consent Document
4. HIPAA Authorization Form
5. Placebo justification
6. Advertisement flyer
7. Letter for Mailing
8. Travis AFB Advertisement Flyer
9. Investigational New Drug Worksheet
10. H33-Local and External Support Document
11. H32 Intramural and Extramural Funding Support Document
12. RAND 36-Item Health Questionnaire
13. Form A2-Study Personnel
14. Medication Disposal

15. Algorithm for Determining Whether an Adverse Event is an Unanticipated Problem
16. Form J HIPAA Waiver or Alteration