Protocol Title:	Does Dapagliflozin Augment The Favorable Adaptation To Endurance Exercise Training? Clinical Research Protocol Title: Dapagliflozin Augments The Favorable Adaptation To Endurance Exercise Training
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* * * Continuing review * * *

To renew your protocol: 1. Complete this one-page form; 2. If necessary, update any sections of the protocol that need to be updated for the upcoming year (e.g., change in personnel, location); 3. Electronically "sign" the application by clicking in the check box on the bottom of the "Obligations" page; 4. Remember to click "Submit Form" and confirm your intent to submit by clicking "OK" so that the IRB administrators receive your application. You must answer each question. Input N/A to answer any questions that are not applicable. NOTE: Documents that contain much of the information required to answer the participant number questions below can be found in the "Event History" section of each protocol. The status on your homepage will be "Submitted to IRB" when your submission is successful. IMPORTANT: If the Department Head has changed since your last approval, please be sure to update the Department Head listing on the personnel Information screen of your protocol.

1. **Summary: Number of Participants Associated with the Protocol:**

   a. **Total number of participants approved to date:**
   60

   b. **Number of participants studied since the last approval date:**
   0

   c. **Total number of participants studied since the beginning of the project:**
   57

   d. **Number of participants remaining to study (total number of participants approved LESS the total number of participants studied to date):**
   3

   e. **Please explain if there is a discrepancy in participant numbers (e.g., more participants responded to a survey than had been approved):**

2. a. **Reasons and number of withdrawals from the research (both subject and investigator initiated) since the last approval date.**
   none studied since last approval

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b. Number of subjects lost to follow-up since the beginning of the study.

4

c. Please summarize any protocol deviations/violations or unanticipated problems (UPs)/adverse events (AEs) since the last continuing review or original approval (if this is your first continuing review). Please indicate if any of the unanticipated problems/events are being reported to the IRB for the first time. If you have or will make changes to your protocol as a result of any unanticipated problem/event or adverse event, please summarize those changes in Question #5 below.

Please see AE log. No deviation occurred since the last approval period.

e. Complaints about the research during the last year.

none

3. A summary of any recent findings, literature, or other relevant information (especially pertaining to risks), if applicable.

none

4. Description of the remainder of project:

N Do you plan to recruit more subjects?

Y If "No," have all subjects completed all research-related interventions? Note: Protocols must be renewed to continue recruiting participants and/or collect data from already recruited participants.

Y Are you only performing data analysis? NOTE: If you are analyzing data with no identifiers (i.e., you cannot link your data to individuals), you can close your protocol by submitting a Final Report.

N Does this protocol have a Data Satety Monitoring Board (DSMB)?

If you do have a DSMB, have reports been submitted to the IRB and/or the Sponsor? Upload any DSMB reports that have not yet been submitted to the IRB since the approval or last continuing review.

5. Summarize all approved changes in the protocol since the last continuing review or since the original approval (if this is your first continuing review). For example: Have you amended your protocol during the past year? Are you requesting to make any changes for the upcoming year? Have you

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during the past year? Are you requesting to make any changes for the upcoming year? Have you included any changes as a result of an unanticipated problem/event or Adverse events (AE)? Have there been any personnel changes in the past year (including a change in department head)?

None

If necessary, proceed to the appropriate section(s) of the protocol and make your requested changes. Remember that if you are requesting to revise a document that is already attached, you must delete the already attached document and upload the revised document.

6. List of Protocol Sections (and questions) that have been changed/modified.

None

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* * * Personnel Information * * *

IMPORTANT NOTE: Mandatory Personnel on a protocol are: Principal Investigator and Department Head. Only the Principal Investigator can submit the protocol; although other personnel listed on the protocol can create the protocol. Human Subjects Protection Training is mandatory for Principal Investigator, Co-Principal Investigator, and Key Personnel (as defined by NIH). Training must be updated every three (3) years.

Principal Investigator Mandatory

Name of Principal Investigator (Faculty, Staff or Postdoc)	Degree	Title
Bell, Christopher	Ph.D.	Associate Professor
Email	**Phone**	**Fax**
Christopher.Bell@ColoState.EDU	(970) 491-7522	970-491-0445
Department Name	**Campus Delivery Code**	
Health and Exercise Science	1582	
Human Subjects Training Completed? PIs must complete training every three (3) years.	Y	

CO-Principal Investigator

Name of Co-Principal Investigator (This could be another faculty or a Master's or Ph.D. student)	Degree	Title
Melby, Chris	Dr.P.H.	Professor

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Email	Phone	Fax
Chris.Melby@colostate.edu	(970) 491-6736	

Department Name	Campus Delivery Code
Food Science & Human Nutrition	1571

Human Subjects Training Completed? Training is required for Co-PI. Training must be updated every three (3) years. Y

No training data is available.

Additional Co-Principal Investigator

Name of Additional Co-Principal Investigator	Degree	Title
Gary Luckasen	MD	Medical Monitor

Email	Phone	Fax
gary.luckasen@uchealth.org		

Department Name	Campus Delivery Code (CSU) or off-campus mailing address
244	

Human Subjects Training Completed? Training is required for Co-PI. Training must be updated every three (3) years. Y

Department Head Mandatory

Name of Department Head	Degree	Title
Braun, Barry	Ph.D.	Professor

Email	Phone	Fax
Barry.Braun@colostate.edu	(970)491-7875	

Department Name	Campus Delivery Code
Health and Exercise Science	1582

Human Subjects Training Completed?? Training is not required for Department Head. Select "No" if you do not know if your Department Head has completed training or not. Y

Administrative Contact

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Name of Administrative Contact, Project Director, or Lab Coordinator	Degree:	Title
Biela, Laurie	B.S.	Research Associate III
Email	**Phone**	**Fax**
Laurie.Biela@colostate.edu	970-491-2242	970-491-0445
Department Name	**Campus Delivery Code**	
Health and Exercise Science	1582	
Human Subjects Training Completed? Training is not required for Administrative Contacts		Y

No training data is available.

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* * * Subject Population * * *

Subject Population(s) Checklist

Â Select All That Apply - Note that this is your Targeted Population :

- X Adult Volunteers
- Decisionally Challenged
- Elderly
- X Employees
- Fetuses
- Long-Term Patients
- Mentally Disabled
- Minors (under 18)
- Pregnant Women
- Prisoners
- Soldiers
- X Students
- Other (i.e., non-English Speaking or any population that is not specified above)

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* * * Study Location * * *

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Study Location(s) Checklist

Select All That Apply - NOTE: Check "Other" and input text: 1.) If your study location is not listed, or 2.) If you would like to list details of your already-checked location (e.g., specific school within a school district)

- [ ] Aims Community College
- [ ] Colorado Department of Public Health & Environment
- [X] Colorado State University
- [ ] Colorado State University - Pueblo Campus
- [ ] Denver Public Schools
- [ ] Greeley/Evans School District
- [ ] Poudre School District
- [ ] University of Colorado Health - North (Formerly -Poudre Valley Health System - PVHS)
- [ ] Rocky Mountain National Park
- [ ] Thompson School District
- [ ] University of Colorado - Boulder
- [ ] University of Colorado - Colorado Springs
- [ ] University of Colorado - Denver
- [ ] University of Colorado Health Sciences Center
- [ ] University of Northern Colorado
- [ ] Other (In the box below, list your study location if not checked above. You may also list details of your already-checked location (e.g., specific school within a school district).

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* * * General Checklist * * *

General Checklist

Select All That Apply :

- [X] Proposed Start Date (cannot be before IRB approval): On receipt of IRB Approval
- [X] Sponsored Project (Check if you will be funded OR if you have or plan to submit a grant application in association with this protocol)
- [ ] NSF Sponsored (Please upload mandatory Data Management Plan in the Attachment section)
- [X] FDA or EPA-regulated research. Please contact the CSU Quality Assurance Manager, Cat Bens, at 970-491-5445 to determine if your study is under Good Laboratory, Good Clinical, or Good Manufacturing Practices (GLP, GCP, GMP).
- [ ] Training Grant

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X Clinical Trial. To register your trial on Clinicaltrials.gov, please contact Cat Bens, CSU Quality Assurance Manager and Clinical Trails Administrator at: 970-491-5445.

Project is associated with the Colorado School of Public Health - CSPH(faculty and/or student)

Cooperating/Collaborating Institution(s) Institution where recruitment will occur OR Institution where Collaborating PI will conduct associated research.

Interview

X Questionnaire/Survey

X Subjects will be compensated for participation

Thesis or Dissertation Project

X ÃÂ Radioisotopes/radiation-producing machines, even if standard of care. Please contact Jim Abraham, Radiation Safety Officer for questions related to use of all radiation-producing machine: 970-491-3736; james.abraham@colostate.edu. Upload your radiation-use approval (if available) or your Radiation Safety Training certificate in the attachment section.

X Human blood, cells, tissues, or body fluids. You will need to obtain IBC approval if you check this box. For information regarding IBC approval, contact Christine Johnson, IBC Coordinator: christine.johnson@colostate.edu

Tissues to be stored for future research projects

Tissues to be sent out of this institution as part of a research agreement

Human Embryos. You will need to obtain IBC approval if you check this box. For information regarding IBC approval, contact Christine Johnson, IBC Coordinator: christine.johnson@colostate.edu

Human Embryonic Cells? Provide NIH Code Number(s) or state that no federal funding will be used to support this research. You may need to obtain IBC approval if you check this box. For information regarding IBC approval, contact Christine Johnson, IBC Coordinator: christine.johnson@colostate.edu

Use of Patient-related equipment? If Yes, specify what equipment is being used.

Medical equipment used for human patients/subjects also used on animals. For questions regarding animal use approval, contact Elaine Kim, IACUC Senior Coordinator: 491-0236

Protocol involves studying potentially addicting drugs. For questions regarding approval for possession of controlled substances, contact Chris Giglio, DRC Coordinator: 491-4830; Chris.Giglio@colostate.edu.

Investigational drugs, reagents, or chemicals (IND)

X Commercially available drugs, reagents, or other chemicals administered to subjects (even if they are not being studied)

Investigational Device (IDE)

Cancer Subjects (e.g., clinical trials, behavior/prevention) or Cancer Tissues (e.g., blood, cells, body fluids). You may need to obtain IBC approval if you check this box. For information regarding IBC approval, contact Christine Johnson, IBC Coordinator: christine.johnson@colostate.edu

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Christine Johnson, IBC Coordinator: christine.johnson@colostate.edu

Other (clarify in text box to the right)

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* * * Funding * * *

Please complete this section if: 1. This protocol will be funded, 2. You have submitted or will submit a grant application associated with this protocol. Please be sure to input your PASS/SP1 number to assist Sponsored Programs in setting up an account for your funds.

If this protocol is funded by the NIH or NSF, or will lead to the regulatory involvement of the FDA or EPA, please be certain you are cognizant of any specific regulatory requirements for data acquisition, storage, retention and sharing, as well as research expenditure allowability, with regard to this IRB protocol.

Funding Checklist

NONE

NOTE: Applicable Federal Grant Application, including competing renewals, must be attached in the Attachment Section (#16). Applicable investigator's brochure and sponsor's protocol must also be attached in section #16 for all industry-sponsored clinical trials.

Funding - Grants/Contracts

Funding Administered By	UNIVERSITY
CSU PASS #	120059
Sponsor's ID # (If known)	
Funded By	Other AstraZeneca
Principal Investigator	Bell
Grant/Contract Title if different from Protocol Title	
	For Federal projects, are contents of this protocol the same as described in Federal proposal application?
N	Is this an Umbrella protocol?
N	Is this protocol under an Umbrella protocol?

Funding - Fellowships

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Funding - Other

Gift Funding

Dept. Funding

Other Funding

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* * * Expedited Paragraphs * * *

PLEASE READ: This online application is for projects that will be reviewed by the IRB via the expedite or full-board review process. The criteria for expedited review are listed below. Review and check what expedite criteria is/are appropriate for your project. NOTE: If your research involves or may involve greater than minimal risk, an element of deception, or is FDA-regulated research, do NOT check any of the expedited criteria listed below. Your protocol will then be reviewed by the full-board at their next regularly scheduled meeting. If your project meets the exempt criteria, please submit your exempt application via email to: RICRO_IRB@mail.colostate.edu. Information regarding exempt applications can be found here: http://ricro.colostate.edu/IRB/ExemptReview.html

Expedite Criteria:

1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

   a) Research on drugs for which an investigational new drug application (21 CFR Part 31,32) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

   b) Research on medical devices for which

      i) An investigational device exemption application (21 CFR Part 812) is not required; or
      ii) The medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

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2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

    a) From healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8- week period and collection may not occur more frequently than 2 times per week; or

    b) From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8-week period and collection may not occur more frequently than 2 times per week.

3. Prospective collection of biological specimens for research purposes by non-invasive means.

4. Collection of data through non-invasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.)

Examples:

    a) Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy;
    b) Weighing or testing sensory acuity;
    c) Magnetic resonance imaging;
    d) Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography;
    e) Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). (NOTE: Some research in this paragraph may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)

6. Collection of data from voice, video, digital, or image recordings made for research purposes.

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7. **Research on individual or group characteristics or behavior(including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)**

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* * * Purpose,Study Procedures,Background * * *

Original Protocol Number (e.g., 07-226H)

Title (Please indicate if the protocol title is different from the proposal title)

Does Dapagliflozin Augment The Favorable Adaptation To Endurance Exercise Training? Clinical Research Protocol Title: Dapagliflozin Augments The Favorable Adaptation To Endurance Exercise Training

Complete Sections 1 - 16. Specify N/A as appropriate. Do not leave any required sections blank.

1. Purpose of the study

a) **Provide a brief lay summary of the project in <200 words. The lay summary should be readily understandable to the general public, and is, for example, what would be released to a newspaper if requested.**

Exercise is frequently prescribed as a favorable lifestyle intervention to prevent/reverse type 2 diabetes. It is also prescribed in addition to concurrent pharmacological treatment, such as metformin. Recent data (animal and human) suggest that metformin may attenuate the favorable benefits of exercise training. In light of the physiological mechanism of Dapagliflozin (sodium-glucose co-transporter 2 (SGLT2) inhibition), one might speculate that rather than inhibit, it will augment the favorable adaptations to exercise training.

b) **What does the Investigator(s) hope to learn from the study?**

We wish to learn if Dapagliflozin augments the favorable adaptation to endurance exercise training in previously sedentary overweight/obese adult humans.

c) **Proposed Start Date (may not precede IRB approval date):**

On receipt of IRB approval (and FDA approval of IND application).

2.

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Study Procedures (If this is a student project, the methods section of the thesis or dissertation proposal must be attached in section #16 - Attachment section.)

a) **In lay language, describe all the procedures, from screening through end-of-study, that the human subject must undergo in the research project, including study visits, drug treatments, randomization and the procedures that are part of standard of care. Please note: Do NOT respond "See Attachment Section." If you would like to add tables, charts, etc., attach those files in the Attachment section (#16).**

OVERVIEW
This is a randomized, placebo-controlled, double blind, repeated measures study. 30 sedentary adults will be recruited for participation and randomly assigned to one of two 12-week treatments: 1) supervised endurance exercise training 4 days per week plus daily oral administration of Dapagliflozin; 2) supervised endurance exercise training 4 days per week plus daily oral administration of placebo. Prior to and following completion of the treatment the following dependent variables will be quantified: a) maximal aerobic capacity; b) substrate utilization during standardized low-moderate intensity exercise; c) skeletal muscle aerobic enzyme activity; d) body composition; and, e) oral glucose tolerance, fasting glucose and insulin resistance.

Study participants will report to the Human Performance/Clinical Research Laboratory (HPCRL) on 51 separate occasions:

Visit 1: study participants will undergo screening: medical history, 12-lead electrocardiogram and blood pressure assessment at rest and during incremental exercise to volitional exhaustion, blood sampling, and measurement of body composition.

Visit 2: maximal oxygen uptake will be measured.

Visit 3: the metabolic response to standardized exercise will be determined.

Visit 4: an oral glucose tolerance test will be performed, and then skeletal muscle will be sampled.

Visits 5-48: 12 weeks of supervised exercise training. Concurrent with these visits, research participants will ingest, on a daily basis, either Dapagliflozin or placebo.

Visit 49: maximal oxygen uptake and body composition will be measured.

Visit 50: the metabolic response to standardized exercise will be determined.

Visit 51: an oral glucose tolerance test will be performed, and then skeletal muscle will be sampled.

DETAILED DESCRIPTION OF STUDY PROCEDURES

Visit 1: study participants will provide informed consent and undergo screening: medical history, 12-lead electrocardiogram and blood pressure assessment at rest and during incremental exercise to volitional exhaustion, blood sampling, and measurement of body composition.

These screening procedures are standard for our lab. Each of the procedures is currently active in other IRB-approved protocols (e.g. 12-3767H, 08-611H, 14-4756H).

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Health History - Potential participants will complete a standardized health history questionnaire that will address past and present medication use, allergies, past and present medical conditions and physical injuries, and habitual use of alcohol and tobacco.

Body composition - Percent body-fat, fat-free mass, total and regional adipose tissue mass, and total bone mineral density will be determined using a whole-body dual energy x-ray absorptiometry scan (DEXA, Model DPX-IQ Lunar Corp., Madison, WI).

Maximal graded exercise stress testing - A 12-lead ECG, arterial blood pressure (brachial sphygmomanometer) will be obtained during quiet resting conditions in the supine and upright sitting positions, and during incremental stationary cycle ergometer or treadmill exercise until volitional fatigue. During exercise, oxygen consumption, carbon dioxide production and ventilation may be determined by indirect calorimetry. All data from these tests will be will be reviewed by a cardiologist. Only those subjects demonstrating no signs or symptoms of disease will be invited to participate in the study.

Blood sampling – Blood (~ 20 ml) will be sampled from an antecubital or hand vein for subsequent analysis of circulating factors pertinent to inclusion/exclusion criteria, including glucose, aspartate aminotransferase, alanine aminotransferase,and total bilirubin. These blood analyses will be performed in on-site (Piccolo Xpress, Abaxis, Union City, CA). Testing for Hepatitis B/C will be performed at a local, external clinical lab (e.g. University of Colorado-Health North). Per the Medical Monitor's discretion follow up blood draws maybe requested.

Visit 2: Maximal oxygen uptake will be measured.

This procedures is standard for our lab and is currently active in other IRB-approved protocols (e.g. 12-3767H, 08-611H, 14-4756H, 13-4282H).

Maximal oxygen uptake - Oxygen consumption, carbon dioxide production and ventilation will be determined by indirect calorimetry during incremental stationary cycle ergometer exercise until volitional fatigue.

Visit 3: The metabolic response to standardized exercise will be determined.

This procedures is standard for our lab and is currently active in other IRB-approved protocols (e.g. 13-4282H, 13-4234H).

Subjects will perform stationary cycle ergometer exercise. Participants will exercise for 3 consecutive 10-minute periods at an external work rate of 25, 50 and 100 Watts. Respiratory exchange ratio, heart rate, and blood pressure will be recorded during the final 2-minutes of each 10-minute period. During the final 60-seconds of each 10-minute period, ratings of perceived exertion will be recorded. During the final 30-seconds of each 10-minute period, venous blood will be sampled for subsequent determination of circulating concentrations of glucose, lactate, non-esterified fatty acids, glycerol, and insulin.

Visit 4: An oral glucose tolerance test will be performed, followed by muscle sampling.

These procedures are standard for our lab. Each of the procedures is currently active in other IRB-approved protocols (e.g. 14-5201H, 13-4282H, 13-4366H).

Participants will report to the laboratory early in the morning, following a 12-hour fast and 24-hour

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abstention from exercise. An intravenous catheter will be inserted into an antecubital or hand vein and kept patent with a saline drip. Following baseline blood sampling for fasting glucose and insulin, participants will ingest 75 g of dextrose dissolved in 250 ml of water over 10-minutes. Venous blood (~ 9 ml) will be sampled at time 0 (baseline) and 5, 10, 15, 20, 30, 45, 60, 75, 90 105 and 120 minutes for determination of concentration of blood glucose and insulin (commercially available assay).

On completion of the oral glucose tolerance test, skeletal muscle (~ 200 mg of vastus lateralis) will be sampled using standard techniques (Bergström needle) and analyzed for protein content and maximal enzymatic activities.

Visits 5-48: 12 weeks of supervised exercise training. Concurrent with these visits, research participants will ingest, on a daily basis, either Dapagliflozin or placebo.

All participants will complete a 12-week program of supervised exercise training. Exercise will begin with 3 training sessions per week of 20-40 minutes, and progress after 4 weeks to 4 sessions per week of 40-60 minutes. Participants will report their rate of perceived exertion (RPE); the target will be 13-to-15 (somewhat hard to hard). If an RPE indicative of moderate-to-heavy exercise is not achieved by a heart rate equivalent to 70-80% of heart rate reserve, the external work rate will be adjusted to achieve an appropriate training stimulus. Subjects will not be permitted to exercise within 5 beats per minute of their maximum heart rate. The exercise modalities will be treadmill walking/running, stationary cycle ergometer exercise, and elliptical ergometer exercise. The modalities will be varied between (but not within) sessions to avoid boredom and potential overuse injuries. In total, each participant will be scheduled to complete 44 exercise sessions. Every session will begin and end with a 5-minute self-paced warm-up/cool-down. These 5-minute periods will not be included in the training duration (for example, a 20 minute session will consist of a 5 minute warm-up, 20 minutes of exercise training, and 5 minutes of cool-down).

The dose of Dapagliflozin will begin as 5 mg/day for the first 14-days. In the absence of complications, side effects, or unfavorable reactions, the dose will then increase to 10 mg/day for the remainder of the study.

Visit 49: Maximal oxygen uptake will be measured. Body composition will be measured.

See description for Visit 2.

Visit 50: The metabolic response to standardized exercise will be determined.

See description for Visit 3.

Visit 51: An oral glucose tolerance test will be performed, followed by muscle sampling.

See description for Visit 4.

b) Explain why human subjects must be used for this project.

Dapagliflozin is approved for human use. We wish to investigate a potential favorable "side-effect" that may occur in humans who use Dapagliflozin and exercise. Due to potential species differences it would not be appropriate to perform these studies on experimental animals.

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c) **Alternative Procedures. If the proposed study is a clinical trial of a drug, vaccine, device or treatment, describe alternative procedures, if any, that might be advantageous to the subject. Describe the important potential risks and benefits associated with the alternative procedure(s) or course(s) of treatment. Any standard treatment that is being withheld must be disclosed. This information must be included in the consent form.**

There are no appropriate alternative procedures.

d) **If the proposed study is a clinical trial of a drug, vaccine, device or treatment, will it be possible to continue the more (most) appropriate therapy for the subject(s) after the conclusion of the study?**

Not applicable.

e) **Study Endpoint. If the proposed study is a clinical trial of a drug, vaccine, device or treatment, what are the guidelines or end points by which you can evaluate the alternative treatments during the study? If one treatment proves to be clearly more effective than another (or others) will the study be terminated before the projected total subject population has been enrolled? When will the study end if no important differences are detected?**

Not applicable.

f) **State if deception will be used. If so, provide a rationale and describe debriefing procedures. Submit a debriefing script in the Attachment Section (#16).**

There will be no deception. Subjects may receive Dapagliflozin or a placebo; they will not know which treatment (Dapagliflozin or placebo) they receive until study completion.

3. Background

a) **Describe past experimental and/or clinical findings leading to the formulation of the study, if applicable.**

Adults diagnosed with impaired glucose tolerance (pre-diabetes) manifest appreciably decreased insulin sensitivity, are highly likely to develop diabetes, and consequently, face the potential of a life-long burden of increased metabolic and cardiovascular complications. To prevent the transition from impaired glucose tolerance to diabetes, pharmaceutical interventions, such as metformin, are commonly prescribed, often in combination with favorable lifestyle interventions, including habitual aerobic exercise. However, recent evidence (from both animal and human studies) suggests that metformin may attenuate the favorable benefits of exercise training. Specifically, within the mitochondria, metformin is thought to impair the function of complex I in the electron transport chain, thus inhibiting oxidative phosphorylation and potentially limiting gains in aerobic capacity following exercise training (Owen et al., 2000; Brunmair et al., 2004). In humans, when metformin treatment was combined with a single bout of exercise, the exercise-mediated improvement in insulin sensitivity was abolished (Sharoff et al., 2010). Further, 12 weeks of aerobic exercise training decreased blood pressure and high-sensitivity C-reactive protein in adults with impaired glucose tolerance; when metformin was added to exercise training these favorable adaptations were abrogated (Malin et al., 2013). More recently, in a rat model of nonalcoholic fatty liver disease, the beneficial effects of exercise on hepatic mitochondrial function were blunted with the addition of metformin

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(Linden et al., 2014). Collectively, these data raise serious concerns and implications for the combination treatments of metformin and exercise training in adults with impaired glucose tolerance. In contrast, given the physiological mechanism of Dapagliflozin (sodium-glucose co-transporter 2 (SGLT2) inhibition), one might speculate that rather than inhibit, Dapagliflozin will augment the favorable adaptations to exercise training. In addition to improved glucose control, SGLT2 inhibition has been shown to promote weight loss (Idris & Donnelly, 2009; Kilov et al., 2013; Opie, 2014). Recent evidence suggests that the magnitude of improvement in physiological function following initiation of regular exercise may be attenuated with obesity and/or metabolic syndrome and augmented with prior weight loss. For example: compared with lean mice, mice with diet-induced obesity demonstrated a smaller degree of skeletal muscle hypertrophy in response to external loading (i.e. resistance training) (Sitnick et al., 2009). In another study, mice with streptozotocin-induced diabetes exhibited a smaller angiogenic response to treadmill running than the response quantified in healthy mice (Kivela et al., 2008). Perhaps more compelling, in adult humans with metabolic syndrome, there was no detectable improvement in insulin sensitivity following 8 weeks of exercise training compared with the appreciable increase observed in healthy, but previously sedentary adults (Layne et al., 2011). Further, in the adults with metabolic syndrome, muscle glucose transporter 4 increased by only 36% compared with a 67% increase in the previously sedentary controls. Finally, data from a large, recently published study of overweight/obese adults, newly diagnosed with type 2 diabetes, showed that a 12-month exercise plus dietary intervention was no more effective than a dietary intervention alone in improving blood glucose control (glycated hemoglobin A1c concentration) (Andrews et al., 2011). These observations have led some to speculate as to the existence of “cross-talk” between adipose tissue and skeletal muscle that limits the adaptations of skeletal muscle to exercise (Pedersen, 2010; Bell, 2011). That is, adipocyte derived signals, such as circulating inflammatory factors, may interfere with the molecular signaling in skeletal muscle that normally results in favorable adaptions to exercise. Weight loss, mediated by Dapagliflozin, is associated with decreased inflammation, and potentially augmented exercise training responses.

In addition to the benefits derived from weight loss, and in contrast to metformin, SGLT2 inhibition is unlikely to have direct effects on mitochondrial function, and thus should not impair skeletal muscle responses to exercise training. Further, the weight loss associated with Dapagliflozin use may promote fatigue resistance during weight-bearing activities such as walking and jogging in previously sedentary adults.

REFERENCES (Some of which have been provided as attachments)

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b) **Describe any animal experimentation and findings leading to the formulation of the study, if applicable.**

See previous section (3a).

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* * * Radioisotopes or Radiation Machines * * *

You selected NO for Radioisotopes in the General Checklist. If you would like to add Radioisotopes, change the selection to YES in general Checklist.

4.

Radioisotopes or Radiation Machines Please note: For projects requiring radiation procedures, please contact the CSU Radiation Control Office (RCO). For more information see: http://www.ehs.colostate.edu/WRad/Home.aspx :

a) **If applicable, summarize in lay language the radiographic diagnostic and therapeutic procedures associated with this protocol.**

Body composition will be measured by dual energy x-ray absorptiometry (DEXA) on visit 1 and visit 50.

b)

Are the radiation procedures being performed a normal part of the clinical management for the medical condition that is under study (Standard of Care) or are the procedures being performed because the research subject is participating in this project (extra CT scans, more fluoroscopy time, additional Nuclear Medicine Studies, etc.,) (Not Standard of Care)? If some procedures are Standard of Care and some are Not Standard of Care, check both boxes.

NOT STANDARD OF CARE **If it is not standard of care, complete the rest of this section. Provide the CSU RCO approval information**	X	STANDARD OF CARE **If it is only standard of care, skip the rest of this section.**

CSU Radiation Control Office approved protocol number:

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CSU Radiation Control Office protocol approval date:

For more information, see the RCO website at:http://www.ehs.colostate.edu/Wrad/home.aspx or Contact: James Abraham, Radiation Safety Officer, at 970-491-3736.

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* * * Medical Equipment for Human Subjects and Laboratory Animals; Investigatiional Devices * * *

5. Medical Equipment for Human Subjects

If medical equipment is being used for human subjects/patients, describe this equipment and indicate if the use is normal practice for the population under study. You may have already described this equipment in the Study Procedures section. If you have already listed this information in the Study Procedures Section, please do not duplicate this information here. In the space below, input N/A if not applicable, indicate if this is already listed in the Study Procedures Section, or describe the equipment.

N/A

6. Investigational Devices

Please list in the space below all Investigational Devices to be used on Subjects.

Investigational Devices

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* * * Drugs, Reagents, or Chemicals * * *

7. Drugs, Reagents, or Chemicals

a) Please list in the space below all investigational drugs, reagents or chemicals to be administered to subjects during this study.

b) Please list in the space below all commercial drugs, reagents or chemicals to be administered to subjects during this study.

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Drug Name	Dapagliflozin (commercially known as Farxiga)
Source (e.g., Pharmacy, Sponsor, etc.,)	AstraZeneca Pharmaceuticals LP
If not premixed, where will the material be mixed and by whom	Pre-mixed by Bristol-Myers Squibb Company
Manufacturer	Bristol-Myers Squibb Company
IND # (if available)	To be submitted
Dosage	5 mg/day of Dapagliflozin for the first 14-days, and then a dose increase to 10 mg/day of Dapagliflozin for remaining 10 weeks.
Administration Route	Oral
Y	Are these new or different uses of these commercially available drugs, reagents, or chemicals?
Y	IND Regulations

Please read the IND Statements

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* * * Subject Population (a-g) * * *

8.

Subject Population - In the space below, please detail the participants that you are requesting to recruit (include requested participant number and description of each group requested). (Input N/A if not applicable)

a) Requested Participant Description (Include number of participants that you plan to study and description of each group requested, if applicable).

We plan on enrolling 60 participants with estimation that 50% will screen out or not complete the study. We plan to complete the study in 30 overweight/obese adult volunteers (men and women).

b) What is the rationale for studying the requested group(s) of participants?

Adults who are overweight/obese are at the greatest risk of developing type 2 diabetes, thus overweight/obese adults potentially have the most to gain should the outcome of the study prove

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favorable. Inclusion of adults already diagnosed with diabetes might complicate the interpretation of the data; that is, as a consequence of the patho-physiology associated with diabetes, the response to exercise training with or without Dapagliflozin may differ in adults with diabetes compared with adults who are diabetes free.

c) **If applicable, state the rationale for involvement of potentially vulnerable subjects to be entered into the study, including minors, pregnant women, economically and educationally disadvantaged, or decisionally impaired subjects. Specify the measures being taken to minimize the risks and the chance of harm to the potentially vulnerable subjects.**

Potentially vulnerable subjects will not be studied.

d) **If women, minorities, or minors are not included, a clear compelling rationale must be provided. Examples for not including minors: disease does not occur in children; drug or device would interfere with normal growth and development; etc.**

Women and minorities will be invited to participate. Minors will be excluded. The prevalence of type 2 diabetes is greater in adults than minors. Safety and effectiveness of Dapagliflozin in pediatric patients under 18 years of age have not been established.

e) **State if any of the subjects are students, employees, or laboratory personnel. They should be presented with the same written informed consent. If compensation is allowed, they should also receive it.**

If any of the subjects are students, employees, or laboratory personnel they will be presented with the same written informed consent; compensation is allowed, they will also receive it.

f) **Describe how potential subjects will be identified for recruitment (e.g., chart review, referral from individual's treating physician, those individuals answering an ad). How will potential participants learn about the research and how will they be recruited (e.g., flyer, email, web posting, telephone, etc.)? Attach recruitment materials in the Attachment Section (#16). Important to remember: potential subjects may not be contacted before IRB approval.**

Please see examples of recruitment materials in the attachment section.

Potential subjects will be recruited via electronic advertisement (e.g. The Source) and email lists (e.g. CSU genfac). If necessary, potential subjects may also be recruited via newspaper advertisement (e.g. The Coloradoan), clinical trials websites (e.g. clinicaltrials.gov), and/or flyers/posters placed in public places (e.g. coffee shops) in and around the Fort Collins area.

g) **If applicable, provide rationale for the inclusion of healthy volunteers in this study. Specify any risks to which these healthy volunteers may possibly be exposed. Specify the measures being taken to minimize the risks and the chance of harm to these volunteers.**

Adults who are overweight/obese but otherwise healthy will be invited to participate. Inclusion of adults already diagnosed with diabetes might complicate the interpretation of the data; that is, as a consequence of the patho-physiology associated with diabetes, the response to exercise training with or without

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Dapagliflozin may differ in adults with diabetes compared with adults who are diabetes free.

It is not possible to identify all potential risks in research procedures, but the researcher(s) have taken reasonable safeguards to minimize any known and potential (but unknown) risks. The Human Performance Clinical Research Laboratory has emergency supplies including a medicine trolley equipped with heart machines and supplemental oxygen. The research team has a great deal of experience with all of the procedures. Some of the procedures for which you are being asked to volunteer have a number of associated risks:

Body Composition
The risks associated with the DEXA are very low. The maximum radiation dose you will receive in this study is less than 1/1000th of the federal and state occupational whole body dose limit allowed to radiation workers (5,000 mrem). Put another way, the maximum dose from any scan we utilize with this DEXA ranges from 1.2 mrem (Whole body scan) to 12.2 mrem (for several of the regional scans, such as lumbar, femur, and forearm scans). The average annual background radiation you already receive is at least 620 mrem/year. The more radiation you receive over the course of your life, the more the risk increases of developing a fatal cancer or inducing changes in genes. The radiation in this scan is not expected to significantly increase these risks, but the exact increase in such risks is not known. There are no discomforts associated with this procedure. Women who are or could be pregnant should receive no unnecessary radiation and should not participate in this study.

Women will complete a pregnancy test before participating in a DEXA scan.

Exercise Tests and Exercise Training
There is a very small chance of an irregular heartbeat during exercise (< 1% of all subjects). Other rare risks of a stress test are heart attack (< 5 in 10,000) and death (<2 in 10,000). Wearing a mouthpiece and nose-clip can sometimes cause dryness in the mouth and mild discomfort. Difficult exercise may make you feel very tired, light headed and nauseous. Exhausting exercise will, by definition, make you feel very tired. After any exercise your muscles might ache.

ACSM guidelines pertinent to the requirement of physician supervised exercise (stress) testing will be followed.

Blood Collection
When the needle goes into a vein, it may hurt for a short period of time (a few seconds). Also there may be minor discomfort of having the needle/plastic tube taped to your arm. In about 1 in 10 cases, a small amount of bleeding will occur under the skin that will cause a bruise. The risk of forming a blood clot in the vein is about 1 in 100, and the risk of significant blood loss is 1 in 1,000. Additionally, there is a risk that you may faint while having blood collected or having the catheter inserted in your vein.

Only trained research personnel will be permitted to perform phlebotomy.

Muscle Biopsy
During the procedure you may feel discomfort associated with the injection of the numbing drug (the anesthetic) but during the actual muscle removal the discomfort should be minimal. There is a risk that you may faint during the procedure. There is also a risk of muscle cramp, bleeding, of loss of feeling in your leg, and of damage to a skin (cutaneous) nerve. The risk of infection and bruising is extremely small if you follow the instructions for caring for the incision. A very small and minor scar will remain as a result of the incision, but may not be noticeable. These procedures will be performed under surgically clean conditions.

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Emergency medical equipment will be available. You will be screened prior to the procedure for history of allergic reactions to Novocain (Lidocaine).

Only trained research personnel will be permitted to perform muscle biopsies.

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* * * Subject Population (h-m) * * *

8. Subject Population (Input N/A if not applicable)

h) Inclusion and Exclusion Criteria (e.g., Participants must have 20/20 vision, Participants must be 30-45 years of age, etc.)

Identify inclusion criteria.

For inclusion in the study subjects should fulfill the following criteria:
1.Provision of informed consent prior to any study specific procedures.
2.Aged 18-50 years.
3.No known Type 2 Diabetes
4.Body mass index 25-45 kg/m^2, inclusive
5.Sedentary (maximum of 2/week regularly scheduled activity sessions of < 20 minutes during the previous 2 years)
6.Completion of a screening visit consisting of medical history, physical examination, and 12-lead electrocardiogram and blood pressure assessment at rest and during incremental exercise to volitional exhaustion (Note: Subjects with abnormal screening values may be eligible if the results are not clinically significant, as judged by the investigator or medical monitor)
7.Agree to abide by the study schedule and dietary restrictions and to return for the required assessments
8.Be willing and able to repeatedly perform exercise
9.Women of childbearing potential must have negative pregnancy test and be using acceptable contraception

Identify exclusion criteria.

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:
1.Evidence of clinically significant cardiovascular, respiratory, renal, hepatic, pulmonary, gastrointestinal, haematological, neurological, psychiatric, or other disease that may interfere with the objectives of the study or the safety of the subject, as judged by the investigator in agreement with the sponsor or medical monitor, have been hospitalized in the past 2 years as a result of these conditions, or are receiving pharmacological treatment for these conditions.
2.Use of prescription drugs (see exceptions listed below) or herbal preparations in the 2 weeks before study commencement.
PPermitted Prescription Drugs
•Birth Control
•Less than 7 days, short course antibiotics. Note: Rifampin is not permitted.

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•Less than 7 days, short course antibiotics. Note: Rifampin is not permitted.
•Other medicines, for GERD, depression, seasonal allergies and OTC analgesics, may be allowed, but will be approved on a case-by-case basis.
3.Is currently enrolled in another clinical study for another investigational drug or has taken any other investigational drug within 30 days before the screening visit.
4.Habitual and/or recent use (within 2 years) of tobacco.
5.Being considered unsuitable for participation in this trial for any reason, as judged by the investigator or medical monitor.
6.History of serious hypersensitivity reaction to Dapagliflozin.
7.Severe renal impairment, end-stage renal disease, or dialysis.
8.Pregnant or breastfeeding patients.
9.Severe hepatic insufficiency and/or significant abnormal liver function defined as aspartate aminotransferase (AST) >3x upper limit of normal and/or alanine aminotransferase (ALT) >3x upper limit of normal.
10.Total bilirubin >2.0 mg/dL (34.2 umol/L).
11.Positive serologic evidence of current infectious liver disease including Hepatitis B viral antibody IGM, Hepatitis B surface antigen and Hepatitis C virus antibody.
12.Estimated Glomerular Filtration Rate <60 mL/min/1.73 m^2 (calculated by Cockcroft-Gault formula).
13.History of bladder cancer.
14.Recent cardiovascular events in a patient, including any of the following: acute coronary syndrome within 2 months prior to enrolment; hospitalization for unstable angina or acute myocardial infarction within 2 months prior to enrolment; acute stroke or trans-ischemic attack within two months prior to enrolment; less than two months post coronary artery revascularization; congestive heart failure defined as New York Heart Association class IV, unstable or acute congestive heart failure. Note: eligible patients with congestive heart failure, especially those who are on diuretic therapy, should have careful monitoring of their volume status throughout the study.
15.Blood pressure at enrolment: Systolic blood pressure ≥165 mmHg and/or diastolic blood pressure ≥100 mmHg.
16.Blood pressure at randomization: Systolic blood pressure ≥165 mmHg and/or diastolic blood pressure ≥100 mmHg
17.Patients who, in the judgment of the medical monitor, may be at risk for dehydration.

i) Describe your screening procedures. Attach your screening document(s) (e.g., health history questionnaire) in the Attachment Section (#16).

Please see attached screening document. Subjects will be provided with the option of receiving an electronic version of the screening document in advance of visit 1.

j) Describe how you will be cognizant of other protocols in which subjects might be participating. Please explain if subjects will be participating in more than one study.

Subjects will asked if they are participating in another study or if they intend to enroll in another study. Subjects will be permitted to participate in other studies when participation does not interfere with the current study - that is, no possible interaction with Dapagliflozin or exercise, no increase risk to subject safety, etc.

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k) **Compensation. Explain the amount and schedule of compensation, if any, that will be paid for participation in the study. Compensation includes food, gift cards, money, tokens, etc. Include provisions for prorating payment, if applicable. Compensation should be prorated if several activities are involved for different time periods (e.g., $10 for session #1, and $10 for session #2).**

Subjects are provided with the following information: "If you complete all 51 of the visits, and all of the procedures as described, you may receive $300 in total. This payment will be paid in installments and prorated as follows: you will not receive compensation for visit 1 (the screening visit). You will receive $80 on completion of visits 2, 3 and 4. You will not receive compensation for visits 5-48; nor will you be charged for this supervised exercise training. You will receive $60 for completion of visit 49. You will receive $60 for completion of visit 50. You will receive $60 for completion of visit 51. If you attend 100% of your scheduled visits, and arrive no later than 10 minutes after the scheduled appointment time for all appointments, you will receive a bonus of $40."

l) **Costs. Please explain any costs that will be charged to the subject.**

Subjects are provided with the following information: "Other than transport to and from the lab, your participation should incur no costs. You will not be charged for your supervised exercise training." The commercial cost for 12-weeks of supervised exercise training is approximately $1,200.

m) **Estimate the probable duration of the entire study. This estimate should include the total time each subject is to be involved and the duration the data about the subject is to be collected (e.g., This is a 2-year study. Participants will be interviewed 3 times per year; each interview will last approximately 2 hours. Total approximate time commitment for participants is 12 hours). These times should be consistent with the time commitment listed on the consent document.**

The study will take place over approximately 2 years. Subjects will be involved for approximately 4 months and will be asked to visit the Human Performance Clinical Research Laboratory on 52 different days. Visits will last between 30 minutes and 3 hours.

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* * * Risks * * *

9. Risks (Input N/A if not applicable)

US Department of Health & Human Services (HHS) Regulations define a subject at risk as follows: "...any individual who may be exposed to the possibility of injury, including physical, psychological, or social injury, as a consequence of participation as a subject in any research, development, or related activity which departs from the application of those accepted methods necessary to meet his needs, or which increases the ordinary risks of daily life, including the recognized risks inherent in a chosen occupation or field of service."

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a) PI's evaluation of the overall level of Risk. (Please check one: minimal or > minimal.)

Minimal (everyday living)

Y **> Minimal (greater than everyday living)**

b)

For the following categories include a scientific estimate of the frequency, severity, and reversibility of potential risks. Wherever possible, include statistical incidence of complications and the mortality rate of proposed procedures. Where there has been insufficient time to accumulate significant data ON risk, a statement to this effect should be included. (In describing these risks in the consent form to the subject, it is helpful to use comparisons which are meaningful to persons unfamiliar with medical terminology.) Address any risks related to:

1. **Use of investigational devices. Please include the clinical adverse events (AEs) associated with each of the devices with an indication of frequency, severity and reversibility. This information can often be found in the Investigator(s) brochure.**

N/A

2 **Use of investigational drugs. Please include the clinical AEs associated with each of the drugs with an indication of frequency, severity and reversibility. This information can often be found in the Investigator(s) brochure.**

N/A

3 **Use of commercially available drugs, reagents or chemicals. Please include the clinical AEs associated with each of the drugs with an indication of frequency, severity and reversibility. This information can often be found in the package insert provided by the manufacturer.**

Please see the package insert provided by the manufacturer for further information.

Adverse reactions in placebo-controlled studies reported in more than 2% but less than 8.5 % of patients treated with Dapagliflozin include:

•Female genital mycotic infections, such as (listed in order of frequency reported): vulvovaginal mycotic infection, vaginal infection, vulvovaginal candidiasis, vulvovaginitis, genital infection, genital candidiasis, fungal genital infection, vulvitis, genitourinary tract infection, vulval abscess, and vaginitis bacterial.

•Nasopharyngitis (cold-like symptoms)

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•Urinary tract infections, such as (listed in order of frequency reported): urinary tract infection, cystitis, Escherichia urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection, and prostatitis.

•Back pain

•Increased urination

•Male genital mycotic infections, such as (listed in order of frequency reported): balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection male, penile infection, balanoposthitis, balanoposthitis infective, genital infection, and posthitis.

•Influenza

•Nausea

•Dyslipidemia

•Constipation

•Discomfort with urination

•Pain in extremity

In addition, use of Dapagliflozin is also associated with a risk of weight loss (up to 10 lbs over 12 weeks).

4 When performing procedures, please include all investigational, non-investigational and non-invasive procedures (e.g., surgery, blood draws, treadmill tests).

Subjects are provided with the following information pertaining to risks:

Body Composition
The risks associated with the DEXA are very low. The maximum radiation dose you will receive in this study is less than 1/1000th of the federal and state occupational whole body dose limit allowed to radiation workers (5,000 mrem). Put another way, the maximum dose from any scan we utilize with this DEXA ranges from 1.2 mrem (Whole body scan) to 12.2 mrem (for several of the regional scans, such as lumbar, femur, and forearm scans). The average annual background radiation you already receive is at least 620 mrem/year. The more radiation you receive over the course of your life, the more the risk increases of developing a fatal cancer or inducing changes in genes. The radiation in this scan is not expected to significantly increase these risks, but the exact increase in such risks is not known. There are no discomforts associated with this procedure. Women who are or could be pregnant should receive no unnecessary radiation and should not participate in this study.

Exercise Tests and Exercise Training
There is a very small chance of an irregular heartbeat during exercise (< 1% of all subjects).

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Other rare risks of a stress test are heart attack (< 5 in 10,000) and death (<2 in 10,000). Wearing a mouthpiece and nose-clip can sometimes cause dryness in the mouth and mild discomfort. Difficult exercise may make you feel very tired, light headed and nauseous. Exhausting exercise will, by definition, make you feel very tired. After any exercise your muscles might ache.

Blood Collection
When the needle goes into a vein, it may hurt for a short period of time (a few seconds). Also there may be minor discomfort of having the needle/plastic tube taped to your arm. In about 1 in 10 cases, a small amount of bleeding will occur under the skin that will cause a bruise. The risk of forming a blood clot in the vein is about 1 in 100, and the risk of significant blood loss is 1 in 1,000. Additionally, there is a risk that you may faint while having blood collected or having the catheter inserted in your vein.

Muscle Biopsy
During the procedure you may feel discomfort associated with the injection of the numbing drug (the anesthetic) but during the actual muscle removal the discomfort should be minimal. There is a risk that you may faint during the procedure. There is also a risk of muscle cramp, bleeding, of loss of feeling in your leg, and of damage to a skin (cutaneous) nerve. The risk of infection and bruising is extremely small if you follow the instructions for caring for the incision. A very small and minor scar will remain as a result of the incision, but may not be noticeable. These procedures will be performed under surgically clean conditions. Emergency medical equipment will be available. You will be screened prior to the procedure for history of allergic reactions to Novocain (Lidocaine).

5 **Radioisotopes/radiation-producing machines(e.g., X-rays, CT scans, fluoroscopy).**

Body Composition
The risks associated with the DEXA are very low. The maximum radiation dose you will receive in this study is less than 1/1000th of the federal and state occupational whole body dose limit allowed to radiation workers (5,000 mrem). Put another way, the maximum dose from any scan we utilize with this DEXA ranges from 1.2 mrem (Whole body scan) to 12.2 mrem (for several of the regional scans, such as lumbar, femur, and forearm scans). The average annual background radiation you already receive is at least 620 mrem/year. The more radiation you receive over the course of your life, the more the risk increases of developing a fatal cancer or inducing changes in genes. The radiation in this scan is not expected to significantly increase these risks, but the exact increase in such risks is not known. There are no discomforts associated with this procedure. Women who are or could be pregnant should receive no unnecessary radiation and should not participate in this study.

c)

For the following categories, include an estimate of the potential risk, if applicable.

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1. **Physical well-being.**

Subjects are provided with the following information pertaining to risks to physical well-being:

Body Composition
The risks associated with the DEXA are very low. The maximum radiation dose you will receive in this study is less than 1/1000th of the federal and state occupational whole body dose limit allowed to radiation workers (5,000 mrem). Put another way, the maximum dose from any scan we utilize with this DEXA ranges from 1.2 mrem (Whole body scan) to 12.2 mrem (for several of the regional scans, such as lumbar, femur, and forearm scans). The average annual background radiation you already receive is at least 620 mrem/year. The more radiation you receive over the course of your life, the more the risk increases of developing a fatal cancer or inducing changes in genes. The radiation in this scan is not expected to significantly increase these risks, but the exact increase in such risks is not known. There are no discomforts associated with this procedure. Women who are or could be pregnant should receive no unnecessary radiation and should not participate in this study.

Exercise Tests and Exercise Training
There is a very small chance of an irregular heartbeat during exercise (< 1% of all subjects). Other rare risks of a stress test are heart attack (< 5 in 10,000) and death (<2 in 10,000). Wearing a mouthpiece and nose-clip can sometimes cause dryness in the mouth and mild discomfort. Difficult exercise may make you feel very tired, light headed and nauseous. Exhausting exercise will, by definition, make you feel very tired. After any exercise your muscles might ache.

Blood Collection
When the needle goes into a vein, it may hurt for a short period of time (a few seconds). Also there may be minor discomfort of having the needle/plastic tube taped to your arm. In about 1 in 10 cases, a small amount of bleeding will occur under the skin that will cause a bruise. The risk of forming a blood clot in the vein is about 1 in 100, and the risk of significant blood loss is 1 in 1,000. Additionally, there is a risk that you may faint while having blood collected or having the catheter inserted in your vein.

Muscle Biopsy
During the procedure you may feel discomfort associated with the injection of the numbing drug (the anesthetic) but during the actual muscle removal the discomfort should be minimal. There is a risk that you may faint during the procedure. There is also a risk of muscle cramp, bleeding, of loss of feeling in your leg, and of damage to a skin (cutaneous) nerve. The risk of infection and bruising is extremely small if you follow the instructions for caring for the incision. A very small and minor scar will remain as a result of the incision, but may not be noticeable. These procedures will be performed under surgically clean conditions. Emergency medical equipment will be available. You will be screened prior to the procedure for history of allergic reactions to Novocain (Lidocaine).

2. **Psychological well-being.**

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N/A

3. **Economic well-being.**
N/A

4. **Social well-being.**
N/A

d) **In case of overseas research, or working with a specific race/ethnicity in the United States, provide background on what experience the Investigator(s) have with the proposed population. Describe qualifications/preparations that enable the Investigator(s) to evaluate cultural appropriateness and estimate/minimize risks to subjects.**
N/A

e) **Special Precautions. Describe the planned procedures for protecting against or minimizing potential risks. If appropriate, include the standards for termination of the participation of the individual subject. Discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects.**
N/A

f)

Data Safety Monitoring

N **Is there a Data Safety Monitoring Board (DSMB)?**

If yes, describe its role and indicate who set up the Data Safety Monitoring Board (e.g., sponsor or Protocol Director).

Describe the data and safety monitoring plan developed to ensure the safety of participants and the validity and integrity of research data. Monitoring should be commensurate with risks and with the size and complexity of the trials.

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* * * Benefits, Procedures to Maintain Confidentiality * * *

10. Benefits (Input N/A if not applicable)

a) **Describe the potential benefit(s) to be gained by the subjects. If there is no direct benefit to the subjects describe how the results of the study may benefit society or a particular group.**

The benefits of participation in this study may include: benefits from nutrition and exercise training; the patient population in general may benefit from the knowledge provided by the results of this study.

11. Procedures to Maintain Confidentiality

a) **Describe the procedures that protect the privacy of the subjects and maintain the confidentiality of the data. If a linked list is used, explain when the linked list will be destroyed. Provide a sample of the code that will be used, if applicable.**

Participants will be identified only on a signed consent form and initial screening form that will be kept locked and separate from other research data. Each subject will be assigned a randomly generated code (e.g. 12698afd) that will be used to identify them in association with all other research data and blood or tissue samples. Records identifying individuals will be kept in Dr. Bell's office/laboratory in a locked cabinet and will be destroyed (shredded) following completion/publication of the project. Data will only be released to regulatory/governmental entities authorized to inspect research records, such as the FDA.

b) **If information derived from the study will be provided to the subject's personal physician, a government agency, or any other person or group (other than the research team), describe to whom the information will be given and the nature of the information, if applicable.**

Unless ordered by an agent of the law, no information will be shared specific to a subject without that subject's written permission. Anonymous data will only be released to regulatory/governmental entities authorized to inspect research records, such as the FDA.

c) **Specify where and under what conditions study data will be kept, how samples will be labeled, who has access to the data, and what will be available and to whom. Federal regulations require that study data and consent documents be kept for a minimum of three (3) years after the completion of the study by the PI. For longitudinal projects and federally regulated studies, the PI may be required to keep the data and documents for a longer time period.**

Research records and data will be stored on file in locked cabinets in Dr. Bell's office/laboratory, or digitally on a password protected central server. Only members of the research team will have access to these records. The materials will be archived for a minimum of three years after completion of the project.

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* * * Potential Conflict of Interest * * *

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12. Potential Conflict of Interest

Although you have already submitted CSU's official Conflict of Interest form (FCOI/COI/COC) to the University, it is the IRB's responsibility to ensure that conflicting interests related to submitted protocols do not adversely affect the protection of participants or the credibility of the human research protection program at CSU. Please answer questions a-d below. Please note that if you indicate that you have a potential financial or professional conflict of interest in relation to this protocol, your CSU FCOI/COI/COC Reporting Form must reflect this potential conflict. Link to CSU's Conflict of Interest policy: :http://www.facultycouncil.colostate.edu/files/manual/sectiond.htm#D.7.7

a)	N	**In connection with this protocol, do you or any of the protocol investigators or their immediate family members (i.e., spouse and legal dependents, as determined by the IRS) have a potential financial or professional conflict of interest?**
b)	N/A	**If you do have a potential conflict of interest, is this reported in your current FCOI/COI/COC?**
c)	N/A	**If you do have a potential conflict of interest, is there a management plan in place to manage this potential conflict?**
d)	N/A	**If you do have a potential conflict of interest, is this potential conflict of interest included in your consent document (as required in the Management Plan)?**

If you have reported a possible conflict of interest, the IRB will forward the title of this protocol to your Research Associate Dean to complete your COI file.

For more information on CSU's policy on Conflict of Interest, please see the Colorado State University Academic Faculty and Administrative Professional Manual Sections D.7.6 & D.7.7. :http://www.facultycouncil.colostate.edu/files/manual/sectiond.htm#D.7.7

Link to CSU's Conflict of Interest Policy: http://www.provost.colostate.edu/index.asp?url=faculty_affairs.

*** * * Informed Consent * * ***

13. Informed Consent

NOTE: In order to complete this protocol, you must upload either a Consent Form or an Alteration of Consent Form (i.e., Cover Letter or Verbal Script) OR (if neither of those apply to your project) you must complete the Waiver of Consent information.

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In the space below, please provide consent process background information for each Consent Form(s), Alteration of Consent Form(s), or Waiver(s).

Informed Consent

Title	14-5529H Bell Consent 01July2016	
Consent Information Type	Consent	
Sponsor's Consent Version Number: (if any)		
Consent Form Template	X Attachment	14-5529H Bell Consent 01July2016 (6) IRB 01112017

<a href='http://ricro.colostate.edu/IRB/ConsentAssentTemplates.html' target=_blank Consent Form Samples

Who is obtaining consent? The person obtaining consent must be knowledgeable about the study and authorized by the PI to consent human subjects.

How is consent being obtained?

What steps are you taking to determine that potential subjects are competent to participate in the decision-making process?

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* * * Assent Background * * *

14. Assent Background (Complete if applicable)

All minors must provide an affirmative consent to participate by signing a simplified assent form, unless the Investigator(s) provides evidence to the IRB that the minor subjects are not capable of assenting because of age, maturity, psychological state, or other factors.

See sample consent/assent forms at http://ricro.colostate.edu/IRB/ConsentAssentTemplates.html

Provide assent process background information, in the space below, for each Assent Form, Alteration Form (i.e., Cover Letter or Verbal Script), and Waiver.

Assent Background

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* * * HIPAA * * *

15. HIPAA

Are you using PHI*? (See definition below)

N

Colorado State University is a hybrid entity and does not have a research-related HIPAA policy. If you will be working with a HIPAA covered entity (e.g., Poudre Valley Health System), you will need to follow their HIPAA guidelines. If your project will involve a HIPAA-regulated entity, in the Attachment section (#16) please attach that entity's required HIPAA consent and/or each waiver of authorization or alteration of authorization requested (e.g., waiver of authorization for access to medical records). Include HIPAA authorization language in the consent document(s) as appropriate (e.g., when enrolling subjects).

*Protected Health Information (PHI) is health information with one or more of the following identifiers. For more information see: http://www.hhs.gov/ocr/hipaa/

1. Names
2. Social Security numbers
3. Telephone numbers
4. All geographic subdivisions smaller than a State, including street address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code, if, according to the current publicly available data from the Bureau of the Census: (1) The geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and (2) The initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000
5. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older
6. Fax numbers
7. Electronic mail addresses
8. Medical record numbers
9. Health plan beneficiary numbers
10. Account numbers
11. Certificate/license numbers
12. Vehicle identifiers and serial numbers, including license plate numbers
13. Device identifiers and serial numbers
14. Web Universal Resource Locations (URLs)
15. Internet Protocol (IP) address numbers
16. Biometric identifiers, including finger and voice prints

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17. Full face photographic images and any comparable images; and
18. Any other unique identifying number, character, or code (note this does not mean the unique code assigned by the Investigator(s) to code the research data)

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* * * Attachments * * *

16. Attachments

Attach relevant documents here. These could include: Collaborating Investigator's IRB approval and approved documents; Conflict of Interest information; Debriefing Script; Grant/Sub-contract; HIPAA Authorization Form from HIPAA-covered entity; Interview/Focus Group Questions; Investigator's Brochure; Letters of Agreement/Cooperation from organizations who will help with recruitment; Methodology section of associated Thesis or Dissertation project; Questionnaires; Radiation Control Office approval material; Recruitment Material (e.g., flyers, email text, verbal scripts); Sponsor's Protocol; Surveys; Other files associated with the protocol (you can upload most standard file formats: xls, pdf, jpg, tif, etc.) Please be sure to attach all documents associated with your protocol. Failure to attach the files associated with the protocol may result in this protocol being returned to you for completion prior to being reviewed. Students: Be sure to attach the Methods section of your thesis or dissertation proposal. If this protocol is associated with a grant proposal, please remember to attach your grant.

To update or revise any attachments, please delete the existing attachment and upload the revised document to replace it.

Document Type	**Investigator's Brochure**
Attachment	Investigator's Brochure Dapagliflozin Edition 10 (3)
Document Name	Investigator's Brochure Dapagliflozin Edition 10 (3)

Document Type	**Other Protocol Material**
Attachment	Farxiga Dapagliflozin
Document Name	Farxiga Dapagliflozin

Document Type	**Other Protocol Material**
Attachment	SGLT2 Dapagliflozin
Document Name	SGLT2 Dapagliflozin

Document Type	**Other Protocol Material**
Attachment	SGLT2 Inhibitors T2 Diabetes
Document Name	SGLT2 Inhibitors T2 Diabetes

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Document Type	**Other Protocol Material**
Attachment	SGLT2 Inhibitors Diabetes
Document Name	SGLT2 Inhibitors Diabetes

Document Type	**Other Protocol Material**
Attachment	SGLT2 Inhibitors New Diabetes Drug
Document Name	SGLT2 Inhibitors New Diabetes Drug

Document Type	**SOP**
Attachment	HP-03-R1 Reporting AEs SOP
Document Name	HP-03-R1 Reporting AEs SOP

Document Type	**Recruitment Material (e.g., flyers, email text, verbal scripts)**
Attachment	14-5529H Recruitment Examples 02062015
Document Name	14-5529H Recruitment Examples 02062015

Document Type	**Other Protocol Material**
Attachment	Id cards for subjects
Document Name	Id cards for subjects

Document Type	**Sponsor's Protocol**
Attachment	Protocol ISSDAP0010-02062015
Document Name	Protocol ISSDAP0010-02062015

Document Type	**Other Protocol Material**
Attachment	FDA-1572_508(7.13)_05June2015
Document Name	FDA-1572_508(7.13)_05June2015

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Document Type	**Sponsor's Protocol**
Attachment	Bell 0010 IISR FINAL
Document Name	Bell 0010 IISR FINAL

Document Type	**Other Protocol Material**
Attachment	Important Communication from AZ regarding DKA other T2D studies 3 July 2015
Document Name	Important Communication from AZ regarding DKA other T2D studies 3 July 2015

Document Type	**Other Protocol Material**
Attachment	AZ Email 07072015
Document Name	AZ Email 07072015

Document Type	**Questionnaire/Survey**
Attachment	Screening Med History 08262015
Document Name	Screening Med History 08262015

Document Type	**Other Protocol Material**
Attachment	FDA safety warning 04Dec2015
Document Name	FDA safety warning 04Dec2015

Document Type	**Other Protocol Material**
Attachment	CDC Hepatitis B Fact Sheet
Document Name	CDC Hepatitis B Fact Sheet

Document Type	**Recruitment Material (e.g., flyers, email text, verbal scripts)**
Attachment	Recruitment_AZ_Exercise
Document Name	Recruitment_AZ_Exercise

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Document Type Other Protocol Material
Attachment delegation of authority log 22April2015
Document Name delegation of authority log 22April2015

Document Type Other Protocol Material
Attachment NTF Interpretation of Hep B results gjl 29 oct 2015
Document Name NTF Interpretation of Hep B results gjl 29 oct 2015

Document Type Other Protocol Material
Attachment 14-5529H BS-EX-003 AE headache
Document Name 14-5529H BS-EX-003 AE headache

Document Type Other Protocol Material
Attachment 14-5529H BS-EX-003 AE kicked foot
Document Name 14-5529H BS-EX-003 AE kicked foot

Document Type Other Protocol Material
Attachment 14-5529H BS-EX-003 con-meds
Document Name 14-5529H BS-EX-003 con-meds

Document Type SOP
Attachment QAIR 14-5529H drug dispensing 23Feb2016
Document Name QAIR 14-5529H drug dispensing 23Feb2016

Document Type Email Correspondence
Attachment FW_ ISSDAPA0009 and ISSDAPA0010 - Allergy Meds
Document Name FW_ ISSDAPA0009 and ISSDAPA0010 - Allergy Meds

Document Type Questionnaire/Survey

Protocol Title: Does Dapagliflozin Augment The Favorable Adaptation To Endurance Exercise Training? Clinical Research Protocol Title: Dapagliflozin Augments The Favorable Adaptation To Endurance Exercise Training

Protocol Type: Biomedical

Date Submitted: 11/01/2018

Approval Period: 11/06/2018-11/05/2019

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Attachment 14-5529H Medical Screening Form 01July2016
Document Name 14-5529H Medical Screening Form 01July2016

Document Type **Investigator's Brochure**
Attachment Investigator's Brochure Dapagliflozin Edition 13
Document Name Investigator's Brochure Dapagliflozin Edition 13

Document Type **Other Protocol Material**
Attachment 14-5529 Protocol deviation Incorrect intervention dosage 20July2016
Document Name 14-5529 Protocol deviation Incorrect intervention dosage 20July2016

Document Type **Other Protocol Material**
Attachment 14-5529 Deviation Prescribed Iron Supplement 03Jan2017
Document Name 14-5529 Deviation Prescribed Iron Supplement 03Jan2017

Document Type **Other Protocol Material**
Attachment 14-5529 Event Log cont review 01_05_2017
Document Name 14-5529 Event Log cont review 01_05_2017

Document Type **Investigator's Brochure**
Attachment Investigator's Brochure Dapagliflozin Edition 12
Document Name Investigator's Brochure Dapagliflozin Edition 12

Document Type **Other Protocol Material**
Attachment 14-5529 Continuation.Form 11_10_2017
Document Name 14-5529 Continuation.Form 11_10_2017

Protocol Title: Does Dapagliflozin Augment The Favorable Adaptation To Endurance Exercise Training? Clinical Research Protocol Title: Dapagliflozin Augments The Favorable Adaptation To Endurance Exercise Training

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Document Type	**Other Protocol Material**
Attachment	14-5529 Event Log v.3 ET Verified
Document Name	14-5529 Event Log v.3 ET Verified

Document Type	**Other Protocol Material**
Attachment	14-5529 Protocol Deviation OGTT and MET EX RH-EX-023 11_03_2017
Document Name	14-5529 Protocol Deviation OGTT and MET EX RH-EX-023 11_03_2017

Document Type	**Other Protocol Material**
Attachment	14-5529 Event Log v.3 ET Verified cont review 11_2018
Document Name	14-5529 Event Log v.3 ET Verified cont review 11_2018

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* * * Obligations * * *

Obligations (Researcher's Responsibilities)

The Principal Investigator is ultimately responsible for the conduct of the project. Obligations of the Principal Investigator are:

Conduct the research involving human subjects as presented in the protocol, including modifications, as approved by the Department and Institutional Review Board. Changes in any aspect of the study (for example project design, procedures, consent forms, advertising materials, additional key personnel or subject populations) will be submitted to the IRB for approval before instituting the changes (PI will submit the "Amendment/Revision" form);

Provide all subjects a copy of the signed consent form, if applicable. Investigators will be required to retain signed consent documents for three (3) years after close of the study;

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Maintain an approved status for Human Subjects Protection training. Training must be updated every three (3) years (Contact RICRO to check your current approval/renewal dates). For more information: Human Subjects Training Completed?

Submit either the "Protocol Deviation Form" or the "Report Form" to report protocol Deviations/Violations, Unanticipated Problems (UPs) and/or Adverse Events (AEs) that occur in the course of the protocol. Any of these events must be reported to the IRB as soon as possible, but not later than five (5) working days. Note that if an event resulted in life threatening injury or death OR an event resulted in substantive harm to the safety, rights or welfare to human subjects, this must be reported to the IRB within 24 hours;

Submit the "Continuing Review" Form in order to maintain active status of the approved protocol. This form must be submitted annually at least four (4) weeks prior to expiration, five (5) weeks for protocols that require full review. If the protocol is not renewed before expiration, all activities must cease until the protocol has been re-reviewed;

Notify the IRB that the study is complete by submitting the "Final Report" form.

X The Principal Investigator has read and agrees to abide by the above obligations.

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* * * Event History * * *

Event History

Date	Status	View Attachments	Letters
12/27/2014	NEW FORM CREATED		
01/02/2015	NEW FORM SUBMITTED	Y	
01/05/2015	NEW FORM PANEL ASSIGNED		
01/09/2015	NEW FORM REVIEWER(S) ASSIGNED		
01/09/2015	NEW FORM REVIEWER(S) ASSIGNED		

Protocol Title: Does Dapagliflozin Augment The Favorable Adaptation To Endurance Exercise Training? Clinical Research Protocol Title: Dapagliflozin Augments The Favorable Adaptation To Endurance Exercise Training

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02/10/2015	NEW FORM SUBMITTED (CYCLE 1)	Y	
02/10/2015	NEW FORM REVIEWER(S) ASSIGNED		
02/24/2015	NEW FORM SUBMITTED (CYCLE 2)	Y	
03/02/2015	NEW FORM APPROVED	Y	Y
03/02/2015	NEW FORM UNDO APPROVED		
03/02/2015	NEW FORM MOVED		
03/02/2015	NEW FORM APPROVED	Y	Y
06/03/2015	AMENDMENT 1 FORM CREATED		
06/10/2015	AMENDMENT 1 FORM SUBMITTED	Y	
06/15/2015	AMENDMENT 1 FORM REVIEWER(S) ASSIGNED		
06/15/2015	AMENDMENT 1 FORM MOVED		
06/15/2015	AMENDMENT 1 FORM APPROVED	Y	Y
07/07/2015	AMENDMENT 2 FORM CREATED		
07/07/2015	AMENDMENT 2 FORM SUBMITTED	Y	
07/10/2015	AMENDMENT 2 FORM REVIEWER(S) ASSIGNED		
07/16/2015	AMENDMENT 2 FORM APPROVED	Y	Y
07/16/2015	AMENDMENT 2 FORM UNDO APPROVED		
07/16/2015	AMENDMENT 2 FORM MOVED		
07/16/2015	AMENDMENT 2 FORM APPROVED	Y	Y
08/26/2015	AMENDMENT 3 FORM CREATED		

Protocol Title: Does Dapagliflozin Augment The Favorable Adaptation To Endurance Exercise Training? Clinical Research Protocol Title: Dapagliflozin Augments The Favorable Adaptation To Endurance Exercise Training

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08/26/2015	AMENDMENT 3 FORM SUBMITTED	Y	
08/26/2015	AMENDMENT 3 FORM REVIEWER(S) ASSIGNED		
08/31/2015	AMENDMENT 3 FORM APPROVED	Y	Y
12/11/2015	CONTINUING REVIEW 1 FORM CREATED		
12/14/2015	CONTINUING REVIEW 1 FORM SUBMITTED	Y	
12/14/2015	CONTINUING REVIEW 1 FORM REVIEWER(S) ASSIGNED		
01/06/2016	CONTINUING REVIEW 1 FORM APPROVED	Y	Y
01/06/2016	CONTINUING REVIEW 1 FORM UNDO APPROVED		
01/06/2016	CONTINUING REVIEW 1 FORM APPROVED	Y	Y
01/26/2016	DEVIATION 1 FORM CREATED		
01/26/2016	DEVIATION 1 FORM SUBMITTED	Y	
01/26/2016	AMENDMENT 4 FORM CREATED		
01/28/2016	AMENDMENT 4 FORM SUBMITTED	Y	
01/28/2016	AMENDMENT 4 FORM REVIEWER(S) ASSIGNED		
02/01/2016	DEVIATION 1 FORM REVIEWER(S) ASSIGNED		
02/05/2016	DEVIATION 1 FORM APPROVED	Y	N
02/05/2016	AMENDMENT 4 FORM APPROVED	Y	Y
02/24/2016	DEVIATION 2 FORM CREATED		

Protocol Title: Does Dapagliflozin Augment The Favorable Adaptation To Endurance Exercise Training? Clinical Research Protocol Title: Dapagliflozin Augments The Favorable Adaptation To Endurance Exercise Training

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02/24/2016	DEVIATION 2 FORM SUBMITTED	Y		
02/25/2016	DEVIATION 3 FORM CREATED			
02/25/2016	DEVIATION 3 FORM SUBMITTED	Y		
02/29/2016	AMENDMENT 5 FORM CREATED			
02/29/2016	AMENDMENT 5 FORM SUBMITTED	Y		
03/04/2016	AMENDMENT 5 FORM REVIEWER(S) ASSIGNED			
03/09/2016	DEVIATION 3 FORM REVIEWER(S) ASSIGNED			
03/14/2016	AMENDMENT 5 FORM APPROVED	Y		Y
03/16/2016	AMENDMENT 6 FORM CREATED			
03/16/2016	AMENDMENT 6 FORM SUBMITTED	Y		
03/17/2016	AMENDMENT 6 FORM REVIEWER(S) ASSIGNED			
03/17/2016	REPORT 1 FORM CREATED			
03/17/2016	REPORT 1 FORM SUBMITTED	Y		
03/18/2016	REPORT 1 FORM REVIEWER(S) ASSIGNED			
04/15/2016	REPORT 1 FORM REVIEWER(S) ASSIGNED			
04/15/2016	AMENDMENT 6 FORM REVIEWER(S) ASSIGNED			
04/15/2016	REPORT 1 FORM REVIEWER(S) ASSIGNED			

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04/15/2016	DEVIATION 2 FORM REVIEWER(S) ASSIGNED		
04/15/2016	DEVIATION 3 FORM REVIEWER(S) ASSIGNED		
05/06/2016	AMENDMENT 6 FORM SUBMITTED (CYCLE 1)	Y	
05/06/2016	AMENDMENT 6 FORM REVIEWER(S) ASSIGNED		
05/13/2016	DEVIATION 4 FORM CREATED		
05/13/2016	DEVIATION 4 FORM SUBMITTED	Y	
05/16/2016	DEVIATION 2 FORM MOVED		
05/16/2016	AMENDMENT 6 FORM MOVED		
05/16/2016	AMENDMENT 6 FORM APPROVED	Y	Y
05/16/2016	DEVIATION 2 FORM APPROVED	Y	N
05/16/2016	DEVIATION 4 FORM REVIEWER(S) ASSIGNED		
05/17/2016	DEVIATION 3 FORM APPROVED	Y	N
05/17/2016	REPORT 1 FORM APPROVED	Y	N
06/02/2016	AMENDMENT 7 FORM CREATED		
06/02/2016	AMENDMENT 7 FORM SUBMITTED	Y	
06/03/2016	AMENDMENT 7 FORM APPROVED	Y	Y
07/01/2016	AMENDMENT 8 FORM CREATED		
07/06/2016	AMENDMENT 8 FORM SUBMITTED	Y	

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07/08/2016	AMENDMENT 8 FORM REVIEWER(S) ASSIGNED		
07/28/2016	AMENDMENT 8 FORM SUBMITTED (CYCLE 1)	Y	
08/17/2016	AMENDMENT 8 FORM MOVED		
08/17/2016	AMENDMENT 8 FORM APPROVED	Y	Y
10/07/2016	DEVIATION 4 FORM APPROVED	Y	N
10/08/2016	REPORT 2 FORM CREATED		
10/12/2016	REPORT 2 FORM SUBMITTED	Y	
10/14/2016	REPORT 2 FORM REVIEWER(S) ASSIGNED		
01/02/2017	CONTINUING REVIEW 2 FORM CREATED		
01/05/2017	CONTINUING REVIEW 2 FORM SUBMITTED	Y	
01/06/2017	CONTINUING REVIEW 2 FORM REVIEWER(S) ASSIGNED		
01/07/2017	REPORT 2 FORM APPROVED	Y	N
01/10/2017	CONTINUING REVIEW 2 FORM REVIEWER(S) ASSIGNED		
01/12/2017	CONTINUING REVIEW 2 FORM APPROVED	Y	Y
01/13/2017	AMENDMENT 9 FORM CREATED		
01/13/2017	AMENDMENT 9 FORM SUBMITTED	Y	
01/13/2017	AMENDMENT 9 FORM APPROVED	Y	Y
11/29/2017	CONTINUING REVIEW 3 FORM CREATED		
11/29/2017	CONTINUING REVIEW 3 FORM SUBMITTED	Y	

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11/29/2017	CONTINUING REVIEW 3 FORM APPROVED	Y	Y
11/01/2018	CONTINUING REVIEW 4 FORM CREATED		
11/01/2018	CONTINUING REVIEW 4 FORM SUBMITTED	Y	
11/06/2018	CONTINUING REVIEW 4 FORM APPROVED	Y	Y

Methods of statistical analyses

Two-way analysis of variance (before training *vs*. after training, and Dapagliflozin *vs*. Placebo) with repeated measures on one factor (before *vs*. after) are used to examine differences in primary outcomes resulting from exercise training and/or drug treatment. Multiple comparisons of factor means will be performed using the Newman-Keuls test.

Consent to Participate in a Research Study
Colorado State University

TITLE OF STUDY:

Does Dapagliflozin Augment The Favorable Adaptation To Endurance Exercise Training?

CO-PRINCIPAL INVESTIGATORS:

Christopher Bell, Ph.D.
Health & Exercise Science
Colorado State University
Email: physiology@cahs.colostate.edu
Telephone: 970-491-3495

Christopher L. Melby, Dr.P.H.
Food Science & Human Nutrition
Colorado State University
Email: chris.melby@colostate.edu
Telephone: 970-491-6736

WHY AM I BEING INVITED TO TAKE PART IN THIS RESEARCH?

You are aged between 18-50 years, your body mass index is between 25 and 45 kg/m^2, you are free of diabetes, you are not pregnant, and/or you are not a regular exerciser, but would like to be.

WHO IS DOING THE STUDY?

Drs. Bell and Melby are running the study; local medical doctors, other researchers, and a team of trained graduate and undergraduate students are helping. AstraZeneca Pharmaceuticals LP, a company that makes medicine, is providing financial support for the study.

WHAT IS THE PURPOSE OF THIS STUDY?

Dapagliflozin **(**commercially known as Farxiga; pronounced: far-see-gah) is a new medicine for treating type 2 diabetes. The purpose of the study is to discover if taking Dapagliflozin will improve people's response to regular exercise. That is, if people perform regular exercise while using Dapagliflozin, will they become fitter and leaner than similar people who perform the same exercise but do not use Dapagliflozin?

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WHERE IS THE STUDY GOING TO TAKE PLACE AND HOW LONG WILL IT LAST?

The study will take place in the Human Performance/Clinical Research Laboratory (HPCRL) and in the Health and Exercise Science Cardiovascular Training Room, both of which are located in the Department of Health and Exercise Science, Moby Complex, on the main campus of Colorado State University, Fort Collins, Colorado.

The study will take place over approximately 2 years. You will be involved for approximately 4 months and will be asked to visit the Human Performance Clinical Research Laboratory on 51 different days.

WHAT WILL I BE ASKED TO DO?

Here is a brief summary of what you will be asked to do:

You will report to the Human Performance Clinical Research Laboratory (HPCRL) on 51 separate days:

Visit 1: you will undergo screening: medical history, 12-lead electrocardiogram and blood pressure assessment at rest and during incremental exercise to volitional exhaustion, blood sampling, and measurement of body composition.

Visit 2: maximal oxygen uptake will be measured.

Visit 3: the metabolic response to standardized exercise will be determined.

Visit 4: an oral glucose tolerance test will be performed, and then skeletal muscle will be sampled.

Visits 5-48: 12 weeks of supervised exercise training. Concurrent with these visits, you will ingest, on a daily basis, either Dapagliflozin or placebo.

Visit 49: maximal oxygen uptake and body composition will be measured.

Visit 50: the metabolic response to standardized exercise will be determined.

Visit 51: an oral glucose tolerance test will be performed, and then skeletal muscle will be sampled.

Outline and timing of study visits:

Days -14 to -1 (Weeks -2 to 0)				Day 1 (Week 1) for 12 weeks	Days 85 to 91 (Week 13)		
Screening	VO_{2max}	Response to standardized exercise	OGTT & Biopsy	Initiation of treatment (Placebo or Dapagliflozin plus exercise)	VO_{2max}	Response to standardized exercise	OGTT & Biopsy

VO_{2max}: Maximal oxygen uptake. OGTT: Oral glucose tolerance test.

Here is a detailed description of what you will be asked to do:

Visit 1 – Screening Visit / Medical History / Stress Test / Blood Test / Body Composition

The first visit to the Human Performance Clinical Research Lab (HPCRL) will be a screening visit. During this visit we will make sure that participation in this study is right for you.

This screening visit will include the following procedures:

Medical Questionnaire
You will be asked to answer several pages of questions related to your health, any illness you may have or have had, and medications you use or have used in the past.

Blood Pressure
We will measure your blood pressure using a standard blood pressure cuff (the same as in a doctor's office). Blood pressure will be measured during all of the tests performed in the lab with the exception of body composition. There are no known risks associated with this procedure. (Duration: 5 minutes)

Body Composition
We will measure how much fat you have in your body using a test called dual energy x-ray absorptiometry (DEXA). The DEXA test requires you to lie quietly on a padded table while a small probe gives off low-level x-rays and sends them over your entire body. This test gives very accurate measurements of your body fat and bone mineral density. We will also measure the circumference of your waist and hip using a tape measure. (Duration: ~ 15 minutes)

Pregnancy Test (Women Only)
Women who are or could be pregnant should not participate in this study. Before the body composition test(s) women will be asked to use a pregnancy test (urine test) to confirm they are not pregnant.

Blood Test
During this visit we will be taking blood from you. We will be taking approximately 20 ml (~1.5 table spoons); this is a lot less than the amount that is typically taken when a person donates blood. Your blood will be tested for various things to make sure you are healthy enough to consume Dapagliflozin. Your blood will be taken from veins in your arms or hands using needles and hollow plastic tubes called catheters. As per the medical monitor's discretion, you may be asked to have your blood tested periodically during the intervention period.

Exercise Stress Test
You will be asked to perform a vigorous exercise test. This test will tell us if your heart is healthy. You will be asked to walk on a motorized treadmill or ride an exercise cycle (cycle ergometer) for approximately 10-15 minutes. The exercise will become more difficult every 2 minutes. While you are walking/riding we will measure your heart rate with an electrocardiogram (ECG) and your blood pressure with a cuff placed around your upper arm. We will also ask you to wear a nose clip (something that stops you breathing through your nose) and ask you to breathe through a mouthpiece. This will let us measure the gases you breathe. Depending on your age, a physician may supervise the test. If we do not think your heart is healthy you will be referred to your primary care physician for further testing. There is a chance that you may not be allowed to take part in our study. (Duration: ~ 60 minutes)

Visit 2 – Maximal Aerobic Capacity

You will be asked to perform a vigorous exercise test. You will be asked to ride an exercise cycle (cycle ergometer) for approximately 10-15 minutes. The exercise will become more difficult every 2 minutes. You will be asked to exercise until you become so tired you are unable to push the pedals more than 40 revolutions per minute. While you are riding we may measure your heart rate with an electrocardiogram (ECG) and your blood pressure with a cuff placed around your upper arm. We will also ask you to wear a nose clip (something that stops you breathing through your nose) and ask you to breathe through a mouthpiece. This will let us measure the gases you breathe. (Duration: ~ 60 minutes)

Visit 3 – Metabolic Response To Standardized Exercise

You will be asked to ride a stationary exercise bike for approximately 30 minutes. For the first 10 minutes the intensity will be very, very light. During the second 10 minutes the intensity will be increased but will still be moderate. During the final 10 minutes the intensity will be increased again such that it is quite difficult, but still achievable. Throughout the entire ride we may measure your heart rate with an electrocardiogram (ECG) and your blood pressure with a cuff placed around your upper arm. We will also ask you to wear a nose clip (something that stops you breathing through your nose) and ask you to breathe through a mouthpiece. This will let us measure the gases you breathe. You will only wear the mouthpiece during the final 5 minutes of each 10-minute period.

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During this visit we will be taking blood from you. We will be taking approximately 80 ml (~6 table spoons); this is a lot less than the amount that is typically taken when a person donates blood. Your blood will be tested for various things that are involved with your nerves, the amount of calories you burn at rest, and insulin and glucose (blood sugar). Your blood will be taken from veins in your arms or hands using needles and hollow plastic tubes called catheters.

You will be provided with additional food to eat prior to this visit.

Visit 4 – Oral Glucose Tolerance Test and Skeletal Muscle Sampling

You will be asked to drink water (300 ml or ~ 10 oz) in approximately 5 minutes. A small amount of sugar (75 g of glucose) will have been added to the water. This will make it taste sweeter and also increase your blood sugar.

After drinking the water you will sit/lie quietly for 2 hours. You will be able to read and/or watch TV and/or listen to music. We will collect blood from you over the 2 hours. Your blood will be analyzed for concentrations of sugar (glucose), insulin (something that helps control blood sugar), and other things that may be help control blood sugar. Your blood will be taken from veins in your arms or hands using needles and hollow plastic tubes called catheters.

We will then sample a small piece of your muscle. This test is commonly called a muscle biopsy. During the muscle biopsy a drug (an anesthetic) will be injected into an area of your thigh to make it feel numb. A small incision (roughly 1/4 inch) will be made using a sharp sterile blade. A sterile probe will be inserted into your leg and a little piece of muscle (roughly the size of a sweet corn kernel) will be removed.

The whole visit will last approximately 3 hours.

Visits 5 – 48 – Supervised Exercise Training

You will report to the Health and Exercise Science Cardiovascular Training Room on 44 separate occasions, spread out over 12-weeks, for supervised exercise training. Exercise will begin with 3 training sessions per week of 20-40 minutes, and progress after 4 weeks to 4 sessions per week of 40-60 minutes. The exercise will be difficult enough to increase your heart rate to 70-80% of your maximum measured heart rate reserve. This will feel like moderate-to-difficult exercise, with a measured rate of perceived exertion (RPE) falling between 13-15. If an RPE indicative of moderate-to-difficult exercise is not achieved by a heart rate at 70-80% of heart rate reserve, the exercise intensity will be adjusted to achieve an appropriate difficulty of exercise. The exercise will be treadmill walking/running, stationary cycle ergometer exercise (exercise bike), and elliptical ergometer exercise. The exercise will be varied between, but not within, sessions to avoid boredom and potential overuse injuries. In total, you will be scheduled to complete 44 exercise sessions. If you fail to complete 40 sessions (~90%),

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or two sessions within a 7-day period you will be removed from the study. Every session will begin and end with a 5-minute self-paced warm-up/cool-down. These 5-minute periods will not be included in the training duration (for example, a 20 minute session will consist of a 5-minute warm-up, 20 minutes of exercise training, and 5 minutes of cool-down).

At the same time as Visits 5 – 48: Daily Ingestion of Dapagliflozin or Placebo

During the 12 weeks of exercise training you will swallow a pill every day. The pill may be Dapagliflozin or a placebo, a pill that has no effect. Neither you, nor the investigators, will know which pill you are swallowing. If you are chosen to swallow Dapagliflozin, for the first 2-weeks the dose will be 5 mg/day. For the next 10-weeks the dose will be 10 mg/day. For a description of Dapagliflozin, see below.

Visit 49 – Maximal Aerobic Capacity and Body Composition

You will repeat the procedures described in visit 2. You will also undergo measurement of body composition (as described in visit 1).

Visit 50 – Metabolic Response to Standardized Exercise

You will repeat the procedures described in visit 3.

Visit 51 – Oral Glucose Tolerance Test and Skeletal Muscle Sampling

You will repeat the procedures described in visit 4.

What is Dapagliflozin?

Dapagliflozin is a new medicine that is used to treat people who have type 2 diabetes (high blood sugar and/or difficulty controlling blood sugar). Dapagliflozin works by limiting the body's ability to absorb sugar from food and beverages. It does this by changing the ability of the kidneys to absorb sugar. The sugar that is not absorbed is removed from the body in urine.

ARE THERE REASONS WHY I SHOULD NOT TAKE PART IN THIS STUDY?

You will not be allowed to take part in the study for any of the following reasons:

1. Evidence of serious (clinically significant) heart (cardiovascular), lung (respiratory), kidney (renal), liver (hepatic), stomach (gastrointestinal), blood (hematological), nerve (neurological), mental (psychiatric), or other disease, or if you have been hospitalized in the past 2 years as a result of these conditions, or are receiving medicine (pharmacological treatment) for these conditions.

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2. Use of prescription drugs (see exceptions listed below) or herbal preparations in the 4 weeks before study commencement.

Permitted Prescription Drugs

- Birth Control
- Less than 7 days, short course antibiotics. **Note: Rifampin is not permitted.**

Other medicines, for GERD, depression, seasonal allergies and OTC analgesics, may be allowed, but will be approved on a case-by-case basis.

3. You are currently enrolled in another clinical study for another investigational drug or have taken any other investigational drug within 30 days before the screening visit.

4. You are a smoker: Habitual and/or recent use (within 2 years) of tobacco.

5. You are considered unsuitable for participation in this trial for any reason, as judged by the investigator or medical monitor.

6. You have a history of serious hypersensitivity reaction to Dapagliflozin.

7. You have severe kidney problems: renal impairment, end-stage renal disease, or dialysis.

8. You are pregnant or breastfeeding.

9. You have severe hepatic insufficiency and/or significant abnormal liver function based on blood tests.

10. You have a history of bladder cancer.

11. Your blood pressure during visit 1: Systolic blood pressure ≥165 mmHg and/or diastolic blood pressure ≥100 mmHg.

12. Your blood pressure before visit 5: Systolic blood pressure ≥165 mmHg and/or diastolic blood pressure ≥100 mmHg

13. Patients who, in the judgment of the medical doctor, may be at risk for dehydration.

WHAT ARE THE POSSIBLE RISKS AND DISCOMFORTS?

It is not possible to identify all potential risks in research procedures, but the researcher(s) have taken reasonable safeguards to minimize any known and potential (but unknown) risks. The Human Performance Clinical Research Laboratory has emergency supplies including a medicine trolley equipped with heart machines and supplemental oxygen. The research team has a great deal of experience with all of the procedures. Some of the procedures for which you are being asked to volunteer have a number of associated risks:

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Body Composition

The risks associated with the DEXA are very low. The maximum radiation dose you will receive in this study is less than 1/1000th of the federal and state occupational whole body dose limit allowed to radiation workers (5,000 mrem). Put another way, the maximum dose from any scan we utilize with this DEXA ranges from 1.2 mrem (Whole body scan) to 12.2 mrem (for several of the regional scans, such as lumbar, femur, and forearm scans). The average annual background radiation you already receive is at least 620 mrem/year. The more radiation you receive over the course of your life, the more the risk increases of developing a fatal cancer or inducing changes in genes. The radiation in this scan is not expected to significantly increase these risks, but the exact increase in such risks is not known. There are no discomforts associated with this procedure. **Women who are or could be pregnant should receive no unnecessary radiation and should not participate in this study.**

Exercise Tests and Exercise Training

There is a very small chance of an irregular heartbeat during exercise (< 1% of all subjects). Other rare risks of a stress test are heart attack (< 5 in 10,000) and death (<2 in 10,000). Wearing a mouthpiece and nose-clip can sometimes cause dryness in the mouth and mild discomfort. Difficult exercise may make you feel very tired, light headed and nauseous. Exhausting exercise will, by definition, make you feel very tired. After any exercise your muscles might ache.

Blood Collection

When the needle goes into a vein, it may hurt for a short period of time (a few seconds). Also there may be minor discomfort of having the needle/plastic tube taped to your arm. In about 1 in 10 cases, a small amount of bleeding will occur under the skin that will cause a bruise. The risk of forming a blood clot in the vein is about 1 in 100, and the risk of significant blood loss is 1 in 1,000. Additionally, there is a risk that you may faint while having blood collected or having the catheter inserted in your vein.

Muscle Biopsy

During the procedure you may feel discomfort associated with the injection of the numbing drug (the anesthetic) but during the actual muscle removal the discomfort should be minimal. There is a risk that you may faint during the procedure. There is also a risk of muscle cramp, bleeding, of loss of feeling in your leg, and of damage to a skin (cutaneous) nerve. The risk of infection and bruising is extremely small if you follow the instructions for caring for the incision. A very small and minor scar will remain as a result of the incision, but may not be noticeable. These procedures will be performed under surgically clean conditions. Emergency medical equipment will be available. You will be screened prior to the procedure for history of allergic reactions to Novocain (Lidocaine).

Dapagliflozin

Adverse reactions in placebo-controlled studies reported in more than 2% but less than 8.5% of patients treated with Dapagliflozin include:

- Female genital mycotic infections (fungal or yeast infections), such as (listed in order of frequency reported): vulvovaginal mycotic infection, vaginal infection, vulvovaginal candidiasis, vulvovaginitis, genital infection, genital candidiasis, fungal genital infection, vulvitis, genitourinary tract infection, vulval abscess, and vaginitis bacterial.

- Nasopharyngitis (cold-like symptoms)

- Urinary tract infections, such as (listed in order of frequency reported): urinary tract infection, cystitis, *Escherichia* urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection, and prostatitis.

- Back pain

- Increased urination

- Male genital mycotic infections (fungal or yeast infections), such as (listed in order of frequency reported): balanitis, fungal genital infection, balanitis candida, genital candidiasis, genital infection male, penile infection, balanoposthitis, balanoposthitis infective, genital infection, and posthitis.

- Influenza (Flu)

- Nausea (Upset stomach)

- Dyslipidemia (High Cholesterol)

- Constipation

- Discomfort with urination

- Pain in extremity

In a study of 5,936 patients with type 2 diabetes, one patient became ill with diabetic ketoacidosis (a metabolic sickness). If you experience any of the following sensations/symptoms you should seek immediate medical help and contact the investigator: sickly or queasy (nausea), vomiting, stomach (abdominal) pain, confusion, change in breathing pattern and unusual tiredness (fatigue) or sleepiness.

In addition, use of Dapagliflozin is also associated with a risk of weight loss (up to 10 lbs over 12 weeks).

ARE THERE ANY BENEFITS FROM TAKING PART IN THIS STUDY?

There are no direct benefits in participating, however you will receive a copy of your results and information pertinent to your body composition (i.e. height and weight), and metabolic and cardiovascular risk factors. For example, in blood we will measure concentrations of glucose. You will be provided with a copy of your DEXA scan; you may wish to have this interpreted by a medically qualified professional. Finally, this study has the potential to identify an additional benefit for people who use Dapagliflozin to treat their type 2 diabetes.

DO I HAVE TO TAKE PART IN THE STUDY?

Your participation in this research is voluntary. If you decide to participate in the study, you may withdraw your consent and stop participating at any time without penalty or loss of benefits to which you are otherwise entitled.

WHAT WILL IT COST ME TO PARTICIPATE?

Other than transport to and from the lab, your participation should incur no costs. You will not be charged for your supervised exercise training.

WHO WILL SEE THE INFORMATION THAT I GIVE?

We will keep private all research records that identify you, to the extent allowed by law. For this study, we will assign a code to your data (e.g. 1234ABCD) so that the only place your name will appear in our records is on the consent and in our data spreadsheet that links you to your code. Only the research team will have access to the link between you, your code, and your data. The only exceptions to this are if we are asked to share the records of the study for audit purposes with the Food and Drug Administration, Health and Human Services, AstraZeneca, and/or the CSU Institutional Review Board ethics committee, if necessary. In addition, for funded studies, the CSU financial management team may also request an audit of research expenditures. For financial audits, only the fact that you participated would be shared, not any research data. When we write about the study to share it with other researchers, we will write about the combined information we have gathered. You will not be identified in these written materials. We may publish the results of this study; however, we will keep your name and other identifying information private.

Your identity/record of receiving compensation (NOT your data) may be made available to CSU officials for financial audits.

CAN MY TAKING PART IN THE STUDY END EARLY?

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If you do not complete 40 exercise sessions (approximately 90%), or two exercise sessions within a 7-day period, you will be removed from the study. If you fail to ingest 90% of your Dapagliflozin or placebo (75/84 pills) you will be removed from the study. Your participation in the study will end if you become pregnant.

WILL I RECEIVE ANY COMPENSATION FOR TAKING PART IN THIS STUDY?

If you complete all 51 of the visits, and all of the procedures as described, you may receive $300 in total. This payment will be paid in installments and prorated as follows: you will not receive compensation for visit 1 (the screening visit). You will receive $80 on completion of visits 2, 3 and 4. You will not receive compensation for visits 5-48; nor will you be charged for this supervised exercise training. You will receive $60 for completion of visit 49. You will receive $60 for completion of visit 50. You will receive $60 for completion of visit 51. If you attend 100% of your scheduled visits, and arrive no later than 10 minutes after the scheduled appointment time for all appointments, you will receive a bonus of $40.

Should your participation in the study end early, you will still receive feedback pertaining to your health and fitness.

WHAT HAPPENS IF I AM INJURED BECAUSE OF THE RESEARCH?

We will arrange to get you medical care if you have an injury that is caused by this research.

CSU will pay for medical expenses for the treatment of a personal injury that is a direct result of the administration of the study drug (CSU will be reimbursed by AstraZeneca). CSU will not provide compensation for lost wages or for any other damages, expenses or losses, or for medical expenses that have been covered by medical insurance.

Should you sustain an injury that is not the direct result of the study drug, you or your insurance company may have to pay for the required care. The Colorado Governmental Immunity Act determines and may limit Colorado State University, University of Colorado Denver and University of Colorado Hospital's legal responsibility if an injury happens because of this study. Claims against the University must be filed with Colorado State University within 180 days of the injury.

WHAT IF I HAVE QUESTIONS?

Before you decide whether to accept this invitation to take part in the study, please ask any questions that might come to mind now. Later, if you have questions about the study, you can contact the investigator, Dr. Bell via email: physiology@cahs.colostate.edu. If you have any questions about your rights as a volunteer in this research, contact the CSU IRB at: RICRO_IRB@mail.colostate.edu; 970-491-1553. We will give you a copy of this consent form to take with you.

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WHAT ELSE DO I NEED TO KNOW?

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

Your signature acknowledges that you have read the information stated and willingly sign this consent form. Your signature also acknowledges that you have received, on the date signed, a copy of this document containing 12 pages.

_____ _____
Signature of person agreeing to take part in the study Date

_____ _____
Printed name of person agreeing to take part in the study Time of Day

_____ _____
Name of person providing information to participant Date

_____
Signature of Research Staff

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