Retrospective Analysis of Reported Adverse Events Occurring at the Clinical Translational Research Center at the University of Colorado Boulder

Final Thesis

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Abstract

Introduction:

The use of invasive procedures in research settings is essential to enhance and advance our understanding of biological and physiological mechanisms of disease and medical procedures, thus building the foundation for evidence-based medicine. However, such procedures pose a risk to subjects. The benefits gained from performing a procedure must present a greater gain to society than the risks presented to human subjects. When risks of invasive procedures are realized, they are categorized as adverse events. This study analyzes the risk-to-benefit ratio of invasive procedures performed at the Clinical Translational Research Center (CTRC) at CU Boulder, by quantifying the rate and risk of adverse events from 2003-2015. I further compared these rates to other clinical and research settings.

Results:

The rate of adverse events from 2003-2015 was 1 adverse event per 62 procedures. The percentage of adverse events at the CTRC (1.59%) is similar to published research settings and lower than clinical settings. The greatest rate of adverse events over multiple years occurred during GXT protocols, 1 adverse event per 13.51 procedures. However, the symptoms and severity associated with these adverse events were reasonable and largely controllable. The symptoms of GXT adverse events were most commonly abnormal EKGs (ST depressions, hypertension, ventricular ectopy). These symptoms may indicate underlying pathologies in the subject volunteers, but may also be benign. There was no difference between the count of adverse events and sex (50% males, 50% females) and the rate of adverse events between years. The percent of adverse events was highest for elderly people (Age =58-81 years old) for total adverse events (older age group = 50.54%) and GXT (older age group = 69.3%). Further research, including the sex and age of subjects

for the total number of procedures performed, is required to determine the absolute risk of adverse events between age groups and sex in this setting.

Conclusions:

To better assess the cause of an adverse event, a section on negligence should be added to the adverse event reporting form. The risks quantified in this paper may improve informed consent forms at the CTRC, by making the risks of a procedure more precise. Ultimately, the potential benefits of progressing evidence-based medicine by continuing invasive procedures at the CTRC outweigh the accompanied risk incurred by healthy subjects.

Introduction

Clinical Translational Research Center at CU Boulder:

The Clinical Translational Research Center (CTRC) at CU Boulder is a human biomedical research facility where investigators perform a wide variety of invasive procedures that involve risk to subject participants. Typically, the CTRC recruits subjects from non-diseased populations. While the procedures performed are essential in aiding our ability to understand scientific mechanisms of disease or medical procedures, the risks participants may incur have not been comprehensively studied. To determine what is an acceptable risk, we must weigh the potential harm of a procedure versus its potential benefits. To do so requires having an accurate assessment of risk. This study contributes to literature because it quantifies the risk participants take for a given procedure at the CTRC. Quantifying risk will allow Institutional Review Boards (IRB) to better evaluate the risk of a particular procedure, ensure vulnerable populations (such as elderly subjects) are protected, and provide future subjects with a better understanding of the risk he or she takes when agreeing to a given procedure at this *specific* facility. Risks that can occur from these biomedical procedures fall under the category of adverse events.

Definition of an Adverse Event

An adverse event, as defined by the National Cancer Institute (NCI) Common Toxicity Criteria (CTC), is any **unfavorable** symptom, sign, or disease (including an abnormal laboratory finding) **temporarily associated with** the use of a medical treatment or procedure that may or may not be considered related to the medical treatment or procedure[13].

Because the widely used CTC definition serves as a guideline at the Boulder CTRC for collecting and reporting treatment-related adverse events, this is the definition this study will use to define and analyze adverse events. However, unlike the NIC, the CTRC does not report adverse events that are not related to the medical treatment or procedure. Moreover, there are several other definitions of an adverse event[7, 12, 13, 14]. Despite slight discrepancies between these definitions, there is a common consensus that an adverse event is unintended and results in a varying degree of harm to a subject or patient. These events can occur in both research and clinical settings.

Research versus Clinical Settings

The goals of testing in a research setting differ from those of a clinical study. The main difference between a research and clinical setting is the purpose of the test or procedure. On the one hand, the use of invasive procedures in human biomedical research is essential to enhance and advance our understanding of evidence-based medical practices. These tests are administered and driven with the intent to answer a research question and hypothesis. On the other hand, clinical settings typically use invasive procedures to diagnose or treat pathologies. Patients will commonly receive their results from a clinical procedure, and may use them to help make health related decisions. For example, a research setting may use graded exercise tests (GXT) or maximal oxygen consumption tests (VO2max) to investigate the relationship and mechanisms between the effect of exercise training on cardiorespiratory fitness and cardiometabolic risk factors[3]. In

contrast, clinical settings more commonly use such procedures to help make exercise prescriptions or identify underlying cardiovascular disease[10].

It is important to compare the rates of adverse events that occur at the CRTC and clinical settings because the purpose and benefits are assessed differently for the same given procedure. Research at the Boulder CTRC does not typically study diseased populations, whereas clinical diagnostic evaluations do. Thus, how the risks and benefits of treatment are compared is assessed differently.

Risk-to-Benefit Ratio

Evidence-based medicine aims to increase the use of high quality research in clinical decision making[8]. The use of invasive procedures in research settings is essential in strengthening our understanding of physiological mechanisms in evidence-based medicine, but such procedures may pose a risk to subjects. The **risk-to-benefit ratio** asserts that the outcome of a given procedure must present a greater gain to society (i.e. (improving evidence-based medicine) as compared to the risks presented to human subjects[6]. Institutional Review Board (IRB) committees must evaluate the risk-to-benefit ratio when assessing new procedures and protocols. This study will help to quantify the risk-to-benefit ratio specified by the code of research ethics[6]. Comparing the rates of adverse events in both research and clinical settings will give critical insight into determining if there are any modifications or changes that should be made in how we safely conduct human biomedical research.

The risk-to-benefit ratio is especially important in relation to the process of informed consent. Research and clinical testing involves a process of informed consent, in which the patient or subject learns about the testing procedure, the risks and benefits of the test, and the potential consequences of testing. An informed consent form at the CTRC will be more accurate and beneficial if it quantifies the risks incurred by subjects in prior studies at this *specific* research facility.

Relevant Prior Research involving Research Settings

I examined previous studies that reported adverse events occurring during procedures similar to those regularly performed at the CTRC. However, studies analyzing the rate of adverse events for these procedures are limited. In a previous study, Highstead et al. examined the incidence of adverse events in 369 femoral arterial/venous catheterizations and/or muscle biopsies[6]. Highstead and colleagues observed that in the placement of artery and venous catheters, serious complications such as infection, arteriovenous fistula, and vascular insufficiency were not experienced. Furthermore, the study emphasized the importance of femoral catheterization and muscle biopsies in understanding metabolic mechanisms and substrate regulation in a variety of physiological conditions. The rate of experiencing hematoma during a catheterization in this research setting was 1.8%, and pain and discomfort occurred at a rate of 3.2%. Similarly, the rate of pain for muscle biopsies was 3.2%, and ecchymosis occurred 7.5% of the time. This study also found significantly higher incidences of ecchymosis/hematoma in elderly individuals as compared to the younger subjects, but no differences between sexes. Ultimately, Highstead and colleagues concluded the risk posed to subjects in healthy volunteers when placing catheters or muscle biopsies was reasonable.

In a later study, Neves et al. compared the incidence of biopsy-related events between *healthy* and *diseased* individuals[9]. In this study, muscular biopsies were performed in two populations—chronically ill patients suffering from skeletal muscle wasting and healthy volunteers. Neves et al. found the rate of adverse events occurring during muscular biopsies for pain and discomfort was 1.27%, an ecchymosis occurred at a rate of 1.27%. In addition, this group reported the rates did not differ between healthy and chronically ill patients.

In sum, these studies are useful for assessing the performance of arterial/venous catheters and muscle biopsies at the Boulder CTRC relative to subject safety. Comparing the rates of adverse events

between these studies and the CTRC may provide critical insight into determining if there is a systematic risk associated with these procedures. If the rates of adverse events at the CTRC are higher than those published by other research facilities, we must question why? Comparing the rates will give key insight into whether or not the risk of an adverse event during these procedures is reasonably low due to the design of each procedure, or perhaps because of where and who conducted the procedure.

In addition, one cannot necessarily extrapolate these findings to include the more diverse set of procedures performed at Boulder CTRC. Specifically, additional procedures that are routinely performed at the CTRC include the following: phlebotomies, GXT, VO_2max, fat biopsies, systemic infusions, and arterial and venous endothelial cell (EC) harvests. Ultimately, this study seeks to better understand the risk of adverse events involving *all* invasive procedures performed at the CTRC.

Relevant Prior Research involving Clinical Settings

This study seeks to determine if the overall rates of adverse events occurring in clinical settings differ from those observed at the CTRC. In addition, understanding the process of how adverse events are reported and analyzed in clinical settings may give insight into ways we may improve doing so in a research setting. For example, adverse events occurring in clinical settings are commonly evaluated for negligence and preventability.

In a retrospective review of adverse events occurring in two British hospitals (n=1014 patients), researchers found that 10.8% of patients experienced an adverse event[14]. In addition, there was no significant difference in sex between patients experiencing and not experiencing adverse events. Patients who experienced adverse events were on average older than subjects who did not. Overall, the study concluded 48% of the reported adverse events were judged to be preventable. However, a limitation of this study is that the investigators did not state how they assessed preventability.

In a Harvard Medical Practice Study, investigators reported that adverse events occurred in 3.7% of hospitalizations in New York in 1984[7]. In a similar Colorado and Utah study, researches found that adverse events occurred in 2.9% of hospitalizations in each state[12]. In these studies, investigators evaluated and quantified if negligence took place during an adverse event. Negligence is defined as the failure to meet a standard of care that is expected of an average physician qualified to take care of the patient in question. In the Harvard study, 28% of the adverse events were judged to have resulted from negligent care; in Utah, 32.6%; in Colorado, 27.4%. Quantifying negligence is an important component of these retrospective studies because it helps investigators and patients determine if risks posed are due to a procedure or due to an error in administration. Interestingly, the CTRC does not determine if negligence or preventability occurred on the reporting form. However, the Boulder CTRC does have a Study Monitoring Committee and IRB review committees in place to evaluate adverse events and assist in the determination of negligence and/or preventability.

Procedures Evaluated in Present Study

This study narrows its focus on the following procedures: phlebotomies, submaximal graded exercise tests (GXT), assessments of maximal oxygen uptake (VO_2max), fat and muscle biopsies, intravenous glucose tolerance testing (IVGTT), and arterial and venous EC harvests (Table 1). These types of procedures are regularly performed in studies conducted at the CTRC. These procedures are essential in our ability to answer scientific questions about physiological or biological mechanisms. The research performed at the CTRC strengthens the foundation for evidence based medical practices.

In addition, exercise is a very common protocol performed at the CTRC. Common exercise protocols include GXT and VO_2max tests. Studying the rates of adverse events occurring during these protocols may also yield key insight into the cardiac risks posed to healthy individuals during submaximal and maximal

exercise. Cardiac adverse events occurring during exercise are termed a risk-paradox because individuals are engaging in the activity known to reduce cardiovascular risk and promote health[5]. Quantifying the rate of adverse events occurring during exercise is important because exercise is performed by people outside of clinical and research settings. Various studies have reported how exercise acutely increases the risk of adverse cardiovascular events, with greater risk associated with vigorous intensity and increased age. For instance, a prior prospective study reported the rates of cardiovascular adverse events occurring during exercise to be from .3 to 6.0 events per 10,000 person-hours of exercise across all age groups for men and women[4]. Most researchers agree the risk of a cardiovascular adverse event occurring during or immediately after exercise is outweighed by the health benefits of high-intensity exercise[5]. This study will help to quantify the cardiac risks of exercise at submaximal and maximal intensities in a research setting. If the risk is low, consistent with current literature, this may help guide clinicians and health professionals in continuing or increasing their support of healthy adults participating in vigorous activity.

Research Question and Hypothesis

This study seeks to determine if the rates of adverse events occurring at the CTRC are significantly different between older/younger populations and males/females. If the rates are significantly higher in older populations, as observed in previous studies, we must ask— what is an acceptable rate of adverse events? Are there proper safeguards in place to protect vulnerable subjects? Can we accept the same or higher rate of adverse events in a non-diseased population as compared to diseased populations?

Although there is a limited amount or literature directly comparing adverse events between research and clinical settings, the rates published in previous research settings were lower than those published in clinical settings. I hypothesize the rates of adverse events at the CTRC to be lower than those reported in clinical settings as well. Furthermore, I predict the rates of adverse events will be higher in older subjects as

compared to younger subjects, but no different between sexes or across years. Finally, I hypothesize that the risks posed to subjects at the CTRC is minimal compared to the scientific insight and benefits we gain from conducting such research.

The ultimate objective of this project is to provide reference data in adverse events occurring at the CTRC at CU Boulder. Procedure risks have not been comprehensively studied in this population, and could be different than those seen in clinical settings. This research will help to quantify the risk-to-benefit ratio dictated by the code of research ethics. Comparing the rates of adverse events in both research and clinical settings will give critical insight into determining if there are any modifications or changes that should be made in how we safely conduct human biomedical research.

This project stands to benefit a number of constituencies. The IRB may use these data to help evaluate proposed research projects at the CTRC. In addition, the IRB may update consent forms to present meaningful statistics that help subjects better assess the risks of a procedure. Also, the greater scientific community may be able to use these results to better evaluate the accompanying risks associated with invasive procedures, which in turn may ensure scientific procedures are performed ethically in human biomedical research settings.

This study was reviewed and approved by the Institutional Review Board at the University of Colorado at Boulder on January 27, 2017.

Methods

Reporting Adverse Events

I evaluated the rate of adverse events that occurred at the CTRC from 2003-2015. The CTRC typically studies non-diseased subjects located near Boulder, CO. Researchers at the CTRC report adverse events by completing the UCB CTRC Adverse Events Reporting Form (Appendix). The scales are based on the National

Cancer Institute (NCI) Common Toxicity Criteria (CTC)[13]. The NCI's CTC is widely used to determine the severity of an adverse event and serves as a guideline for collecting treatment-related adverse events data in research and clinical settings. On the reporting form, researchers identify:

1. Types of adverse event (1 = anticipated, 2= unanticipated)
2. Procedures associated with the adverse event, and the symptoms observed
3. Severity of the adverse event (1 = mild, 2 = moderate, 3=severe and undesirable, 4=life-threatening or disabling, 5= death)
4. Attribution of the adverse event (1= unrelated, 2= unlikely, 3=possible, 4=probable, 5=definite)
5. Acute management outcome of the adverse event (1=unsatisfactory, 2=satisfactory, 3=optimal)

Creating the Dataset

Data collected from the UCB CTRC Adverse Events Reporting Form from 2003-2015 were entered and de-identified into a spreadsheet. This study focuses on adverse events occurring during the following procedures commonly performed at the CTRC: 1. Arterial catheterization 2. Venous Catheterization 3. ECA harvests 4. ECV harvests 5. Muscle biopsies 6. Fat biopsies 7. GXT 8. VO_2 max 9. Phlebotomies and 10. IVGTT (Table 1). However, these ten procedures do not account for *all* of the procedures associated with an adverse event at the CTRC from 2003-2015. Other procedures conducted include microneurography, constant intensity submaximal exercise tests, and administration of oral medications. These were omitted from the major analysis because they are not performed as often, or the total count for the number of times the procedure was performed was not available due to changes in record keeping at the CTRC.

To calculate the total number of times a specific procedure was performed, we entered counts from the CTRC treatment schedules into a spreadsheet. Total counts were available based on individual years for 2011 through 2015, but were grouped together for 2003-June 2007, and July 2007-2010. In addition, totals

for VO2max and GXT (VO2max-GXT) and fat and muscle biopsies (Tissue Biopsies) were grouped together for 2003-June 2007 and could not be separated. Rates and absolute risk were calculated using Excel and R.

Analysis of Risk

397 adverse events were reported at the CTRC from 2003-2015. All adverse events were used to analyze the percent of adverse events based on sex, age, and symptom. Of these 397 events, 297 adverse events (belonging to the ten specified procedures) were used to quantify the risk associated with a given procedure type, and the risk incurred per year.

To determine which procedure type contributed the most to the total number of adverse events across all years, we divided the procedure types into the following general categories: 1. Exercise Protocol (GXT, VO2max, constant intensity submaximal exercise tests) 2. Arterial and Venous Procedures (phlebotomies, arterial and venous catheters) 3. Tissue Biopsies (muscle and fat biopsies) 4. Infusion medications 5. Non-Infusion medications (oral or patch medications) and 6. Other (microneurography, nutrition related events, and all other events).

Analysis of Risk per procedure, per year

The rates of VO2max, GXT, phlebotomies, venous and arterial catheters, muscle and fat biopsies, venous and arterial catheters, and IVGTT were analyzed compared to the total number of times each procedure was performed. I was able to calculate the absolute rate of an adverse event occurring for only these procedures, because totals for the number of times the procedure was preformed, with or without an adverse event occurring were available. A Fisher's exact test was used to determine if the percent of adverse events for a procedure significantly varied between years. VO2max-GXT and tissue biopsies from 2003-2007, and ECA and ECV were excluded because they did not occur over a large enough range of years. To quantify

risk during one of these procedures, I calculated the number of procedures needed to harm, and the rates of an adverse event occurring per 10,000 procedures.

Analysis of Risk based on Age and Sex

I calculated the percent distribution of age or sex for all adverse events and by specific procedure type. The age groups were defined as: younger [18-37 years old], middle-aged [38-59 years old], and older [60-81 years old]. These age categories were assigned based on a previous experiment, which addressed aging and habitual exercise, conducted at the University of Colorado at Boulder[11]. The age and sex of subjects were not available for the total number of times a procedure was performed. Therefore, this study makes the assumption that the CTRC draws from roughly equal numbers of men and women, and across age groups. Absolute risks were not calculated based on sex or age. For example, to quantify the risk of an adverse event based on age during a VO2max, we compared the number of adverse events that occurred for a particular age group to the total number of VO2max adverse events.

Severity, Expectation, Attribution, Acute Management, and Symptoms

I calculated counts for the ratings of severity, expectation, attribution, acute management, and symptoms of an adverse event. Symptoms were available for adverse events that occurred from 2009-2015. VO2max and GXT symptoms were further disaggregated if they were associated with cardiovascular disease (CVD) or not definitively associated with CVD. A symptom was deemed 'not definitively associated with a CVD' if the symptom is not indisputably related to cardiac function. These included symptoms such as pain/discomfort, vomiting, lightheadedness, and falling. I then analyzed the percent distribution of age groups based on CVD symptoms.

Results

All Adverse Events

397 adverse events were recorded at the CTRC from 2003-2015. Subjects experiencing an adverse event ranged from 18 to 81 years of age. The average age of a subject who experienced an adverse event was 52.7 $\pm$ 17.0 years old, the median age was 58 years old. 94.4% of the adverse events were anticipated, 85.5% were of mild-severity (severity =1), 44.0% were 'definitely' attributed to the procedure, and 93.9% handled 'optimally' by the investigator (Table 2). Exercise protocols are the most common procedures performed at the CTRC, and account for 32.4% of all procedures performed. 49% of the adverse events were experienced during an exercise protocol, and 22% during an arterial or venous procedure (Figure 1A). However, when GXT adverse events were removed from the exercise protocols, arterial and venous protocols account for the greatest percentage of adverse events (34%), (Figure 1B).

Rates of Adverse Events for Specific Procedures:

The percent of adverse events occurring at the CTRC from 2003-2015 for the ten specified procedures is 1.59%. This correlates to an absolute risk of 1 adverse event per 62 procedures or 159 adverse events per 10,000 procedures. Of the ten specified procedures, GXTs have the highest occurrence of an adverse event (7.40%) (Table 3). The greatest risk of experiencing an adverse event occurs during a GXT, 1 adverse event per 13.51 GXTs (Table 4). The second highest risk posed to subjects is during fat biopsies, with 1 adverse event per 20 fat biopsies. The lowest risk posed to subjects is during an ECV, with 1,000 adverse events needed to harm 1 subject. The percentage of venous and arterial catheterization adverse events across all years was 1.20% and 4.70% respectively (Table 3). The percent of adverse events for muscle biopsies was 3.90%. When evaluating the incidence of these adverse events based on symptoms from 2011-2015, 0.31% of catheterizations resulted in pain and discomfort, and 0.27% resulted in hematoma. Similarly, 2.56% of muscle biopsies induced pain/discomfort and 5.13% resulted in bruising.

Risk of Adverse Event by Year

When the percent of total adverse events were disaggregated by year, there was no apparent trend (Figure 2). A Fisher's exact test was run for VO2max, GXT, arterial catheters, venous catheters, phlebotomies, muscle and fat biopsies, and IVGTT. The percent of adverse events during a GXT and venous catheters varied significantly between years ($P<0.05$), but there was no apparent trend across all years (Figure 3). The percent of adverse events occurring across all years from a venous catheterization ranged from 0-1.4%, while GXTs ranged from 2.5 -10.5%.

Risk of Adverse Event by Age

Older adults accounted for a greater percentage of total adverse events (50.54%) as compared to the other age groups (Younger group = 21.5%, Middle-Aged = 27.9%) (Figure 4). In addition, older adults made up a greater percentage of the adverse events for a GXT (69.3%) compared to the younger age group (2.14%) and middle-aged group (28.57%) (Figure 5). In contrast, the younger adults accounted for the greatest percentage of adverse events during a VO2max test (42.2%), phlebotomy (66.6%), and venous catheterization (57.1%) as compared to the two older groups (Figure 6). There was no observed trend between arterial catheterizations and age. In the younger group, a greater count of adverse events occurred during a VO2max (19 of the 45 VO2max adverse events) as compared to a GXT (3 of the 140 GXT adverse events). In contrast, the older group experienced more adverse events during a GXT (97 of the 140 GXT adverse events) compared to a VO2max test (17 of the 45 VO2max adverse events) (Figure 5).

Risk of Adverse Event by Sex

Of the 384 adverse events that reported a sex on the reporting form, there was no difference between the percent of adverse events occurring between males and females (50% female, 50% male) (Figure 7). The greatest disparity between sex for a given procedure was during a VO2max, where females accounted for 68.08% of adverse events. Males accounted for a greater percentage of adverse events for GXT,

phlebotomies, venous catheterizations, and fat biopsies. Conversely, women accounted for a greater percentage of adverse events for VO2max, arterial catheters, ECA, and ECV procedures (Figure 7).

Symptoms

The symptoms associated with each procedure type from 2009-2015 were compiled and summarized (Table 1). GXT and VO2max test subject's experienced the greatest range of symptoms. Of the symptoms reported during a GXT, the most common were ST depressions (38.1%), hypertension (21.2%), and ventricular ectopy (16.9%). The GXT and VO2max symptoms were disaggregated by symptoms associated with cardiovascular disease (CVD) or not definitively associated with CVD. Symptoms that were associated with CVD during a GXT or VO2max include ST depression, hypertension, ST elevation, vasovagal, bundle branch blocking, T-Wave inversions, supraventricular trachycardia, chest pain, and ventricular ectopy. Symptoms that were excluded include headaches, vomiting, lightheadedness, pain/discomfort, or falling. 107 of the 118 symptoms (90.7%) reported were associated with CVD for a GXT, and 22 of the 28 (78.6%) were associated for a VO2max. Of the CVD reported symptoms, a greater percentage occurred in the older groups. 80.9% of the CVD symptoms during a GXT occurred in subjects over 58 years old. 73.9% of the CVD symptoms during a VO2max occurred in subjects over 58 years old.

Severity Ratings

The highest severity rating reported for all events was of 'moderate-severity' (Table 2). 15.4% of the all adverse events were graded as 'moderate-severity'. A 'moderate-severity' severity rating accounted for 42.9% (n=3 of the 7 adverse events) of the severity fat biopsies ratings. In addition, a 'moderate-severity' grade accounted for a greater percentage of total arterial catheterization adverse events (23.7%, n= 9 of the 29 adverse events) compared to venous catheterization adverse events (11.8%, n= 4 of the 30 adverse events) (Figure 8).

Discussion

GXT and Informed Consent

The absolute risk posed to a subject during a GXT is 1 adverse event per 13.51 GXT procedures (7.40%) (Table 3). While this risk may seem high, the symptoms observed during a GXT differ from those experienced during other procedures. Symptoms that warrant the report of an adverse event include ST depressions, ventricular ectopy, and hypertension, among others (Table 1). However, these symptoms indicate risk factors of cardiovascular disease, but do not necessarily indicate the same degree of harm as other procedures. The most common symptoms reported during a GXT are abnormal EKGs, which may or may not indicate underlying pathologies. Perhaps, these symptoms would be better reported as "abnormal findings", rather than as adverse events. For instance, ventricular ectopy (arrhythmia) during exercise has yet to be linked with increased risk of a cardiovascular adverse event in healthy populations[5]. Exercise protocols (VO2max, GXT, and constant intensity submaximal exercise) account for the greatest percent of adverse events across all years (49%), and are the most common type of procedure performed at the CTRC (32.4%). However, when analyzing the percent of adverse events occurring at the CTRC excluding GXTs (due to the unique symptoms that warrant report), arterial and venous procedures account for the greatest percent of adverse events (34%) (Figure 1). In addition, fat biopsies, arterial and venous catheterizations also reported higher 'moderate severity' ratings (Fat biopsy = 42.9%, arterial catheterizations = 23.6%, venous catheterizations = 11.8%) compared to GXT (10.4%) (Figure 8). This data indicate that the severity of risk posed to subjects during a catheterization or biopsy may be greater than the risk posed during an exercise protocol. Therefore, although the absolute risk of a GXT adverse event occurring is relatively high, the severity of the risk incurred by a subject is low. The CTRC should still document these events as they give insight into cardiac and hemodynamic responses during exercise, however they may not want to consider them as 'adverse events'.

Current informed consent forms at the CTRC cite that 4 in 10,000 people have chest pain or a heart attack and 1 in 10,000 people die during an exercise test. In addition, these consent forms tell patients that an exercise test can cause fatigue and minor discomfort. In this study, I found only 3 incidents of chest pain were reported during a GXT (n=1239 from 2009-2015). This can be phrased as a risk of 1 adverse event of chest pain per 413 GXT. In addition, no subjects have experienced a heart attack or died at the CTRC in the past 12-years. Although the current statistics cite risks of adverse exercise events, updating informed consent forms to include this data may be beneficial in ensuring subject understand all of the risks they may incur, and the common symptoms they may experience when agreeing to participate at this *specific* research facility.

Risk-Paradox of Exercise and Age

The percent distribution of total adverse events and GXT adverse events increased with age (Figure 4, 5). This was not the trend observed during a VO2max. Rather, the percent of VO2max adverse events was more equally distributed between the younger group (42.2%) and older group (37.9%). This may be because there is a pre-screening test for a VO2max testing at the CTRC for older subjects. Typically a subject 45 years or older must complete a GXT prior to participating in a VO2max test. This pre-screening likely prevents adverse events from occurring during a VO2max test in older subjects by ensuring older subjects are physically fit enough to perform a maximal exercise protocol. Younger age groups are not typically required to complete a pre-exercising test prior to a VO2max test. Overall, this may explain why the count for adverse events is higher for VO2max as compared to GXT within the younger group (Figure 5). In contrast to previous research, the younger adults accounted for the greatest percentage of adverse events during a phlebotomy (66.7%) and venous catheterization (57.14%) as compared to the two older groups (Figure 6) [6,7,9]. The symptoms associated with the event were vasovagal and nausea. One potential reason there was a higher

percent of adverse events in the younger group may be because the total number of procedures performed for these protocols was higher in younger adults. However, I hypothesize it may be because younger subjects typically have had less exposure to arterial and venous procedures throughout their medical histories compared to older adults. Thus, younger subjects may be more sensitive to the symptoms of the test. For example, vasovagal was the most common symptom reported during a phlebotomy (n=6). Of the reported instances of vasovagal, 80% occurred in the younger group. Therefore, we may see a higher percent of adverse events occurring in the younger group because they are most sensitive to the procedures. To ensure that younger populations at the CTRC are not at a higher risk of experiencing an adverse event during one of these procedures, the CTRC should begin recording the age of subjects for all procedures performed in an accessible dataset. This is essential because my findings contrasts other research and clinical studies who reported higher rates of adverse events in *older* groups due to changes in vasculature as one ages[6,7,9].

There was a greater percentage of CVD associated symptoms in the older groups during VO2max tests (73.9%) and GXT (80.9%) compared to younger age groups. This finding supports that the risk of a cardiovascular adverse event during exercise increases with age[5]. During an exercise protocol, no severity rating above 'moderate severity' was reported, and there were no heart attacks or cardiovascular deaths (n=4,088 exercise protocols). This indicates that although exercise protocols may induce CVD symptoms, especially in older subjects, these risks are reasonable. In addition, the rate of an adverse event occurring during an exercise protocol is low (VO2max = 1.50%, GXT = 7.40%, VO2-GXT= 5.70%). Moreover, scientific evidence demonstrating the beneficial effects of exercise on overall health is indisputable[3,4,5,10]. Taken together, the data from exercise protocols performed at the CTRC support that the risk of experiencing a cardiac adverse event during graded and maximal exercise is less than the potential benefits gained from exercising in healthy populations.

Percent of Adverse Events based on Sex

There was no observed difference between the counts of adverse events occurring in males and females (50% male, 50% female). This finding is congruent with previous literature in clinical and research settings[6,9,14]. The greatest disparity between male and female adverse events for a specific procedure was VO2max testing. Females accounted for 68.1% of the adverse events experienced. I speculate this difference may be because more females performed a VO2max test than males. In addition, typically a physician will supervise a VO2max test for men over the age of 40, and females over the age of 50. Given that the counts of adverse events are higher for women during a VO2max, perhaps the IRB should consider adjusting the age at which females are supervised. To determine if the risk of a VO2max test adverse event is higher in females, the CTRC should comprise a dataset with the sex of the total number of procedures performed. Because the percent of males vs. female adverse events do not differ drastically between most procedures types, and are exactly equal for all adverse events, overall the data support there is no difference between males and females experiencing an adverse event.

Risk of Adverse Event per Year

There is no apparent trend between the overall risks of an adverse event occurring and individual year (Figure 2). The percent of adverse events occurring each year may vary because the total number or procedures differed year to year, different studies drew from different populations (i.e. elderly populations), or studies used a greater number of higher risk procedures. For example, fat biopsies were only conducted from 2007-2012. Fat biopsies in these years had relatively higher risks of adverse events compared to other procedures (2007-2010 = 7.00%, 2011 = 2.90%, 2012= 8.30%) (Table 3). This may explain why the percent of adverse events during these years are higher than others (Figure 2). The risk of an adverse event occurring during a GXT or venous catheterization did significantly differ between years ($P<0.05$). A statistically

significant result indicates that the null hypothesis (there is no difference in the percent of adverse events between years) can be rejected at some level of certainty. However, it is easier to find statistical significance with larger sample sizes, (i.e. the statistical power increases with sample size). Because the sample size for a GXT (n=1,293) and venous catheterization (n=2,924) were relatively large, this may have resulted in statistical significance but the effect size was small. The effect size describes the changes in the percent of adverse events between years. The percent of adverse events occurring across all years from a venous catheterization ranged from (0-1.4%), while GXTs ranged from (2.5 -10.5%) (Figure 3). Because this range is so small, and the sample sizes so large, I do not believe that this statistical significance describes an important relationship between the percent of adverse events between years. In addition, there is no trend between the rate of adverse events during a GXT or venous catheterization and year. Differences between the rates of adverse events may occur because studies performing venous catheterizations and GXTs drew from different populations (older vs. younger) from year to year.

Rates of Adverse Events at CTRC Compared to Other Research Settings

The rate adverse events that occurred during venous or arterial catheterizations at the CTRC were 1.20% and 4.70%, respectively. Common symptoms were vasovagal, pain/discomfort, hematoma, bruising, and numbness/tingling (Table 1). From 2011-2015, 0.31% of catheterizations induced pain/discomfort, and 0.27% led to hematoma. Highstead et. al reported higher rates and symptoms for catheterizations (hematoma = 1.8% of instances, Pain/Discomfort = 3.2% of instances). Conversely, I found the percent occurrence of pain related adverse event during a CTRC muscle biopsy to be 2.56%, and bruising occurred 5.12% of the time. These rates of pain/discomfort and bruising were higher than the Neves et al. study (percent occurrence of pain =1.27%, ecchymosis =1.27%), but lower than those published in the Highstead et al. study (Pain = 3.2%, ecchymosis = 7.5%). This suggests that muscle biopsies may pose a higher risk to

subjects at the CTRC compared to other research facilities. However, the CTRC reports symptoms of bruising, which are related but not necessarily the same as ecchymosis. Ecchymosis is a sizeable discoloration of the skin resulting from bleeding underneath, typically caused by bruising. Thus comparing these rates is useful, but imperfect. The rates of adverse events may have been higher than the Neves et al. study because muscle biopsies are not performed often at the Boulder CTRC (n =51 from 2007-2015). In addition, in the Neves study, one may argue that the successful outcomes are related to the fact that only two physicians were responsible for performing all the biopsies (n=496) over one year. Muscle biopsies at the CTRC were likely performed by a variety of physicians over the time frame, which may increase risk. Since the rates of adverse events at the CTRC are higher than biopsies performed in a different research settings, there may be a need to either strengthen the selection criteria for muscle biopsies, or increase staff training in the future. This proposed idea requires further comparison of the rates of adverse events at the CTRC to a greater number of research facilities. The symptoms experienced during a biopsy (pain/discomfort, bruising) do not pose an apparent severe long-term risk to subjects. In addition, the overall rate of adverse events is low (3.90%). Therefore, my results support that the risk associated with catheterizations and muscle biopsies in healthy volunteers is still reasonable and largely controllable. The risks posed during catheterizations may be low because they were performed in skilled hands, in a defined setting. 94.3% of all adverse events reported were handled 'optimally' by the investigator, indicating a high-quality staff at the Boulder CTRC. My findings indicate performing catheterizations at the Boulder CTRC poses no higher risk to subjects compared to other research settings. Muscle biopsies had a higher risk of adverse events compared the Neves et al. study.. However, the risk incurred to subjects is still relatively low at the CTRC (1 adverse event per 25.64 procedures), and symptoms pose minor clinical relevance. Future studies should examine the rates of adverse events in other clinical translational research centers to determine if there is a higher systematic risk associated with these

procedures in different research settings. Comparing the rate of adverse events during a muscle biopsy to other research settings is necessary to definitively determine if the risk is reasonable at the CTRC. In addition, comparing the rates of adverse events among the physicians performing the biopsy would give insight into determining if there is a need to strengthen the training of investigators who are allowed to perform a biopsy procedure.

Rates of Adverse Events at CTRC Compared to Clinical Rates

The percentage of adverse events occurring at the CTRC from 2003-2015 (1.50%) is lower compared to those reported in clinical settings (Britain = 10.8%, New York = 3.7%, Colorado and Utah = 2.9%). While clinical settings typically perform similar procedures as those performed at the CTRC (phlebotomies, arterial and venous catheters, tissue biopsies, etc.), hospitals also perform a set of more invasive procedures in diseased populations. Therefore, it is sensible that the observed Boulder CTRC rate is lower than those reported by hospitals.

Retrospective studies of adverse events occurring in hospitals typically evaluate for preventability and if negligence occurred[7,12,14]. Risk occurring from error is not the same as negligence. Negligence occurs when the degree of error surpasses an accepted norm. Evaluation of negligence in these retrospective studies was essential in determining if an adverse event occurred due to an unpreventable event or due to operational or administrative error. This is one area in which the CTRCs guidelines do not align with clinically reported adverse events. Adverse events at the CTRC are reported by the primary personnel involved in the event, which may introduce bias when filling out a form. While personnel report if an adverse event was expected and how the event was handled, there is no section on the reporting form that indicates if an adverse event was due to an unreasonable error by the researchers. I believe a section on negligence should be added to the CTRC form because it will more clearly define the *cause* of an adverse event. This may in turn better

inform patients of the risk they take when agreeing to a procedure. For example, an adverse event was reported in 2015 at the CTRC due to the mislabeling of a medication bottle. A section on negligence or preventability would be beneficial in this circumstance because it would clearly indicate how the adverse event was *not* caused by an adverse reaction to the prescribed drug. In this case, it is clear that some degree of negligence occurred. However, not all reported adverse events are as easy to retrospectively analyze. The Harvard Study evaluated negligence on a 3-point scale on which 1 = slight degree of negligence, 2 = moderate degree, and 3 = severe degree. A grading system similar to the Harvard study would allow IRB committees to quantify and distinguish if the risk a patient takes is due to a procedural error that exceeds an expected norm. The Study Monitoring Committee or IRB, who oversee all reported adverse events, should fill out this proposed section of the form with the primary personnel who were present at the event, to avoid reporting bias.

Future Recommendations for Specific Procedures

Fat biopsies have the greatest percent contribution moderate-severity ratings (42.9%). The severity rating of 'moderate-severity' was relatively higher, compared to other procedures (Figure 8). Furthermore, when excluding GXTs from analysis, fat biopsies presented the greatest risk to subjects, 1 adverse event per 20 procedures. Fat biopsies have not been included in any research study at the CTRC since 2013. However, IRB committees should consider this risk when evaluating proposed research studies that involve fat biopsies.

A severity ranking of a 'moderate-severity' accounted for a greater percentage of adverse events for arterial catheters (23.7%) as compared to venous catheters (11.8%). This suggests arterial catheters pose a more severe risk to subjects than venous catheters. IRB committees should take this into account, and recommend venous over arterial catheters if both are plausible options.

Conclusions:

The risk-to-benefit ratio, as specified by the research code of ethics, states that the outcome of a given procedure must present a greater gain to society as compared to the risks presented to the human subject. The rate of an adverse event occurring at the Boulder CTRC were similar to those found in other research settings, and lower than those published in clinical settings. Further research, quantifying the rates of adverse events for similar invasive procedures is necessary to determine how rates of adverse events at the Boulder CTRC compare to other research settings. 94.4% of adverse events were reported to be of 'mild-severity', and no adverse events over the 12-year span were reported as severe and undesirable, life threatening or disabling, or leading to death. On an informed consent form, the CTRC may include the risk of a procedure type, common symptoms experienced by previous subjects at the CTRC, and the percent of a mild-severity ranking to better inform subjects of the specific risks they may incur at this specific research facility. Although the apparent risk of a GXT appears to be high (1 per 13.51 procedures), it must be clear that the symptoms and severity associated with a GXT adverse event are less critical, and most commonly occur in older individuals. In addition, given the relatively low percentage of cardiac adverse events and low severity-ratings that occur during exercise protocols, the cardiac risks of exercise are minimal. Clinicians and health-care providers should continue to increase the promotion of vigorous exercise in healthy individuals in a sensible and gradual progression, as the benefits of performing exercise outweigh the accompanied cardiac risks. To better assess the cause of an adverse event, a section on negligence should be added to the adverse event reporting form. Overall, the risks posed to a subject at the CTRC during an invasive clinical procedure are reasonable. Because research at the Boulder CTRC contributes to enhancing and advancing our understanding of evidence-based medicine, the benefits of continuing these procedures outweigh the risks posed to subjects.

Limitations

The dataset on adverse events created for this study has several limitations. First, not all procedures had available total counts due to changes in record keeping. In addition, the total counts for procedure totals from 2003-2010 were grouped into two sections of years, 2003- June 2007 and July 2007-2010. These groups of years could not be separated into individual years. In addition, from 2003- June 2007, the total number of VO2max and GXT (VO2-GXT), and total number of muscle and fat biopsies (Tissue Biopsy) were combined, and could not be teased apart.

The sex and age of the total counts were not available for this study; therefore, I made the assumption the CTRC studies a roughly equal distribution of males/females, and older/younger people. However, the populations studied at the CTRC may vary from year to year, or may not draw from roughly equal numbers of males/females, and older/younger people. Thus, the counts of adverse events based on age and sex may not be representative of the true rate of adverse events experienced in these groups. This potential confounding variable may explain why I saw a greater percentage of adverse events during phlebotomies and venous catheterizations in the younger group compared to older groups. Moreover, the amount of statistical analysis in this project was limited. I could not perform odds or risk ratios to determine the relative risk a subject takes because totals for people who experience a specific adverse event (i.e bruising) without experiencing the procedure (i.e. phlebotomy) are not available.

In addition, there were no age gaps between the younger, middle-aged, and older groups. I cannot confidently conclude the physiology between end group ages (i.e. 37 vs. 38 years old) is significantly different. Hence, the trends observed might not accurately reflect the increased risk of adverse events that occurs due to aging effects.

Finally, symptoms were only available from 2009-2015. The greatest count of VO2max adverse events in the younger group occurred from 2003-June 2007 (n=13 of the 19 total VO2max adverse events in younger

group). Therefore, we cannot determine if these younger subjects also experienced associated CVD symptoms, which may change the observed relationship between older people experiencing the greatest percentage of CVD associated symptoms during a VO2max.

Acknowledgements

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Figures and Tables:

Table 1. Common procedures performed at the CTRC, an explanation of how and why they are performed, and symptoms associated and reported on the UCB CTRC Adverse Events Reporting Form.

Procedure Type	Procedure Explanation	Common Symptoms
Graded Exercise Test (GXT)	An exercise test in which the intensity increases at regular intervals. Submaximal GXT never exceed 85% of maximal heart rate. Used to determine aerobic fitness levels, and heart's response to exercise.	ST Depression, Hypertension, Ventricular Ectopy, ST Elevation, Bundle Branch Blocking, Pain/Discomfort, Lightheadedness/Dizziness, Vomiting, Headache, Supraventricular Tachycardia, Vasovagal
Maximal Oxygen Consumption (VO2max)	Measure of the maximal capacity to transport and utilize oxygen during dynamic exercise involving a large muscle mass	Ventricular Ectopy, Bundle Branch Blocking, Vomiting, Pain/Discomfort, Vasovagal, ST Depression, Supraventricular Tachycardia, Hypertension, Falling,
Phlebotomy	Puncture of a vein in order to withdraw blood or introduce fluid.	Vasovagal, Nausea
Arterial Catheter	Catheter is inserted into an artery, most commonly to monitor blood pressure directly or to obtain samples for arterial blood gas analysis.	Vasovagal, Pain/Discomfort, Numbness/Tingling, Hematoma, Rash, Bruising
Venous Catheter	Catheter is inserted into large vein and is threaded to the thoracic portion of the vena cava or in the right atrium of the heart. Typically used to administer systemic infusions, monitor blood pressure, and estimate cardiac output and vascular resistance	Vasovagal, Pain/Discomfort, Hematoma, Misplacement, Rash
Muscle Biopsy	Small needle or incision is made to remove a small sample of muscle. May be used to study muscle metabolic processes.	Pain/Discomfort, Bruising
Fat Biopsy	Small needle or incision is made to remove a small piece of fat tissue.	Pain/Discomfort, Redness, Hematoma
Endothelial Cell Harvest	Using a small umbilical cord vessel to remove endothelial cells from arteries (ECA) or veins (ECV).	Rash
Intravenous Glucose Tolerance Test (IVGTT)	Glucose is injected into vein as a way to measure the body's ability to metabolize glucose.	Lightheaded/Dizziness, Hypoglycemia, Diaphoresis

Table 2. Counts of expectation, severity, attribution, and acute management for all adverse events occurring at the CTRC from 2003-2015 (n=397). These scales are based on the National Cancer Institute (NCI) Common Toxicity Criteria (CTC). 94.4% of adverse events were anticipated, 85.5% were of mild-severity (severity =1), 44.0% were 'definitely' attributed to the procedure, and 94.3% handled 'optimally' by the investigator.

	Expectation	Severity	Attribution	Acute Management
1	372 (94.4%)	334 (85.5%)	13 (3.31%)	2 (0.51%)
2	22 (5.58%)	61 (15.44%)	24 (6.11%)	22 (5.63%)
3			57 (14.5%)	367 (93.9%)
4			126 (32.1%)	
5			173 (44.0%)	
Totals	394	395	393	391

Expectation: 1 = anticipated, 2= unanticipated. Severity: 1 = mild, 2 = moderate, 3=severe or undesirable, 4=life-threatening or disabling, 5= death. Attribution of the adverse event: 1= unrelated, 2= unlikely, 3=possible, 4=probable, 5=definite. Acute management outcome of the adverse event: 1=unsatisfactory, 2=satisfactory, 3=optimal.

Table 3. Percent of adverse events that occur during a specific procedure. This percent was measured by comparing the counts of adverse events to the total number of procedures performed. Blank spaces indicate the total count was not available or applicable for the procedure type.

	Rates of Adverse Events (%)											
Date	VO2max	VO2 GXT	GXT	Phleb	V Cath	A Cath	Muscle Biopsy	Fat Biopsy	Tissue Biopsy	ECA	ECV	IVGTT
2003-2007		5.70%		0.20%	1.40%	5.20%			3.20%			
2007-2010	1.40%		10.50%	0.30%	0.80%	3.20%		7.00%				
2011	1.90%		5.00%	0%	0.20%	5.90%	4.50%	2.90%		0%	0%	0%
2012	0%		2.50%	0%	0%	1.50%	0%	8.30%		0%	0%	0%
2013	3.00%		6.80%	0.20%	0%	1.30%	5.90%			0%	0%	6.00%
2014	1.50%		6.40%	0.20%	0.70%	2.60%	0%			1.40%	0.50%	2.10%
2015	1.70%		8.40%	0.40%	0%	1.00%	0%			0%	0%	6.30%
Total	1.50%	5.70%	7.40%	0.40%	1.20%	4.70%	3.90%	5.00%	3.20%	0.30%	0.10%	2.50%

VO2max = assessment of maximal oxygen consumption, Phleb = phlebotomy, V Cath = Venous Catheter, A Cath = Arterial Catheter, GXT = graded exercise test, ECA = arterial endothelial cell harvest, ECV = venous endothelial cell harvest, IVGTT = intravenous glucose tolerance test.

Table 4. The number of procedures needed to cause an adverse events based on procedure type. The greatest risk is associated with a GXT, whereas the lowest risk is associated with an ECV.

Procedure Type	# Procedures needed to Harm
VO2max	66.67
GXT	13.51
Phleb	250.00
V Cath	83.33
A Cath	21.28
Muscle Biopsy	25.64
Fat Biopsy	20.00
ECA	333.33
ECV	1000.00
IVGTT	40.00

VO2max = maximal oxygen consumption test, GXT = graded exercise test, Phleb = phlebotomy, V Cath = venous catheter, A Cath = arterial catheter, ECA = arterial endothelial cell harvest, ECV = venous endothelial cell harvest, IVGTT = intravenous glucose tolerance test.

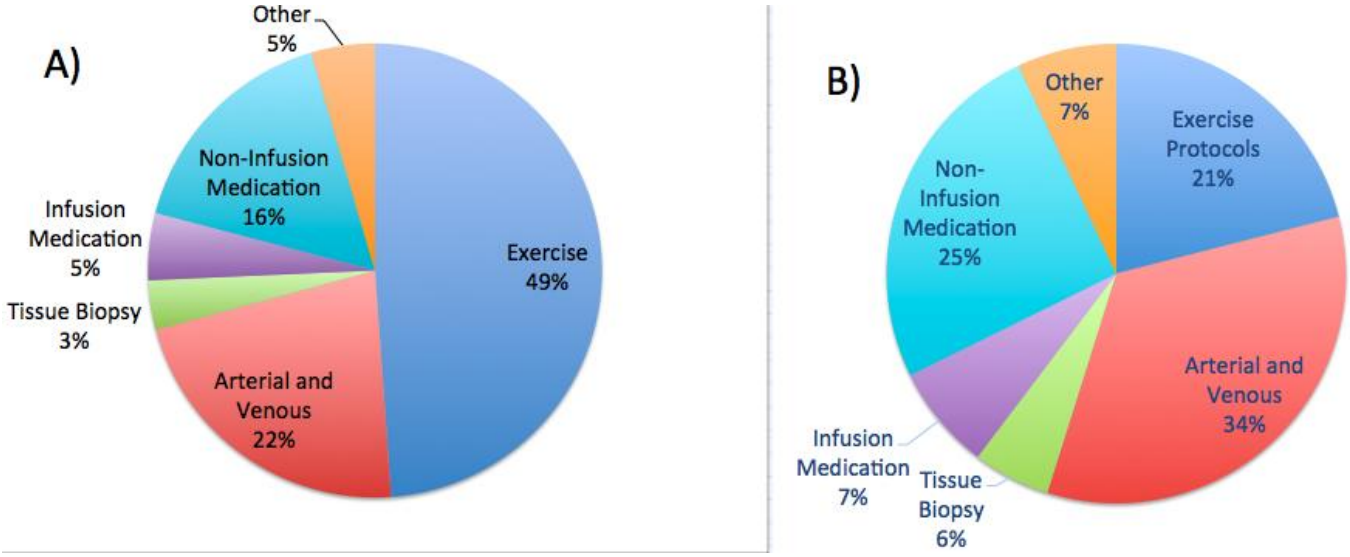

Figure 1. Panel A) Percent of all adverse events occurring at the CTRC from 2003-2015 based on general procedure type (n=397). Exercise procedures include GXT, VO2max, and constant intensity submaximal exercise tests. Arterial and venous procedures include phlebotomies, arterial and venous catheters. Tissue Biopsies include fat and muscle biopsies. Non-infusion medications include oral or patch medications. Other procedures include microneurography procedures, nutrition related events, and all other events. Exercise related procedures account for the greatest portion of adverse events that occur at the CTRC. **Panel B)** Percent of all adverse events occurring at the CTRC from 2003-2015 based on general procedure type, excluding GXT (n=257). Exercise procedures include VO2max and constant intensity submaximal exercise tests.

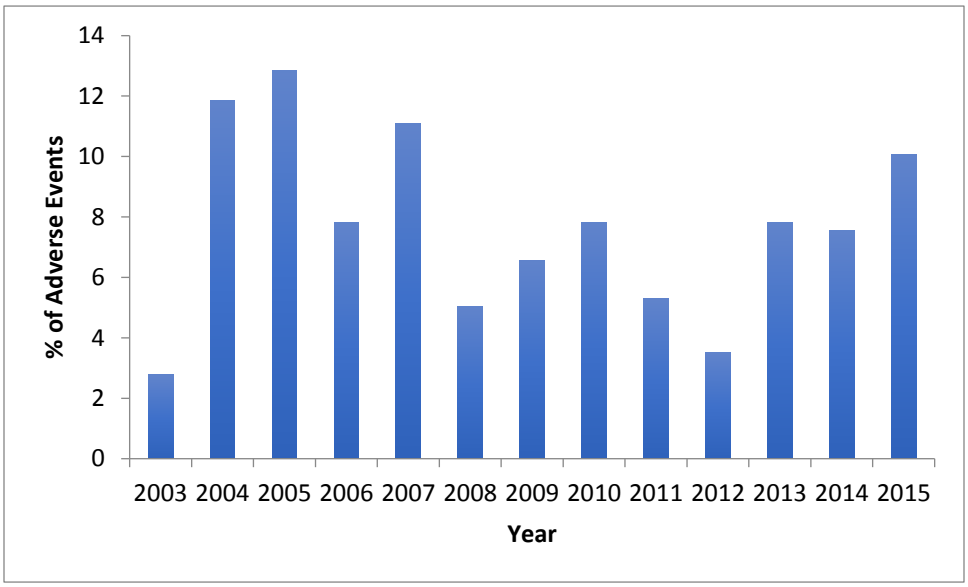

Figure 2. The percent of total adverse events (n=397) based on year (2003-2015). There is no apparent trend in the total number of adverse events and the year they occurred.

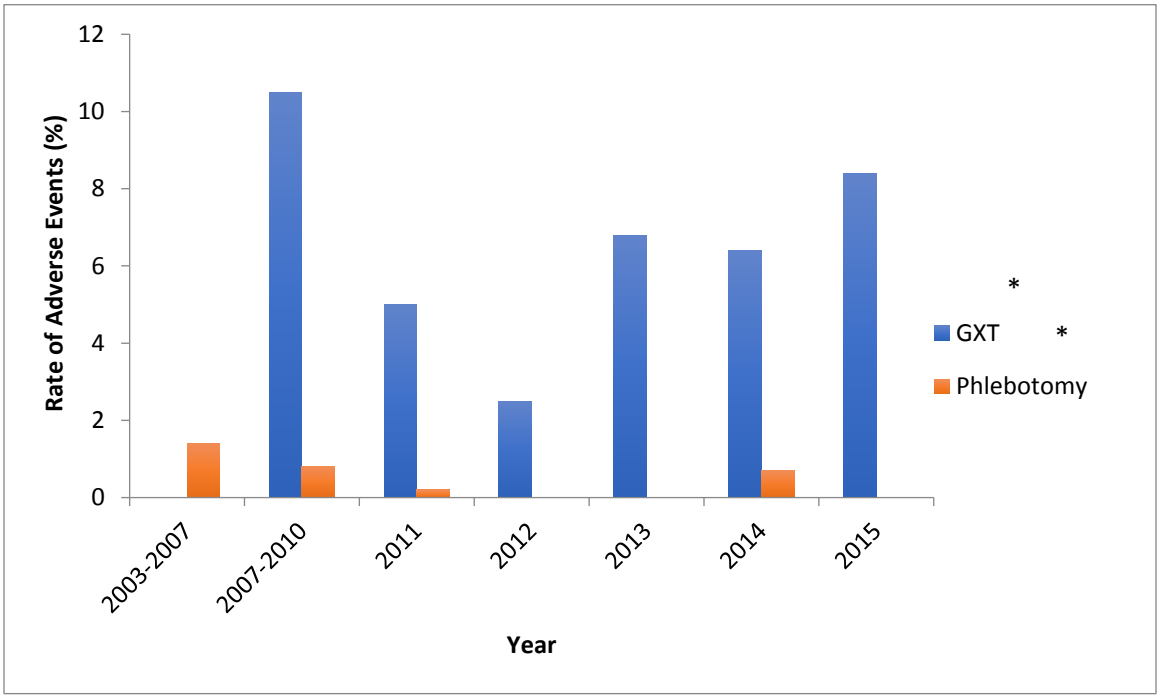

Figure 3. Percent rates of adverse events occurring during a GXT or phlebotomy per year. These percentages were found by dividing the number of adverse events by the total number of times the procedure was performed in the same year. To test if the percent of an adverse event differed between years, a Fisher exact test was run for all available procedures. GXT and phlebotomy were the only procedures to significantly differ between years ($P<0.05$). There is no apparent trend across years. * $p<0.05$

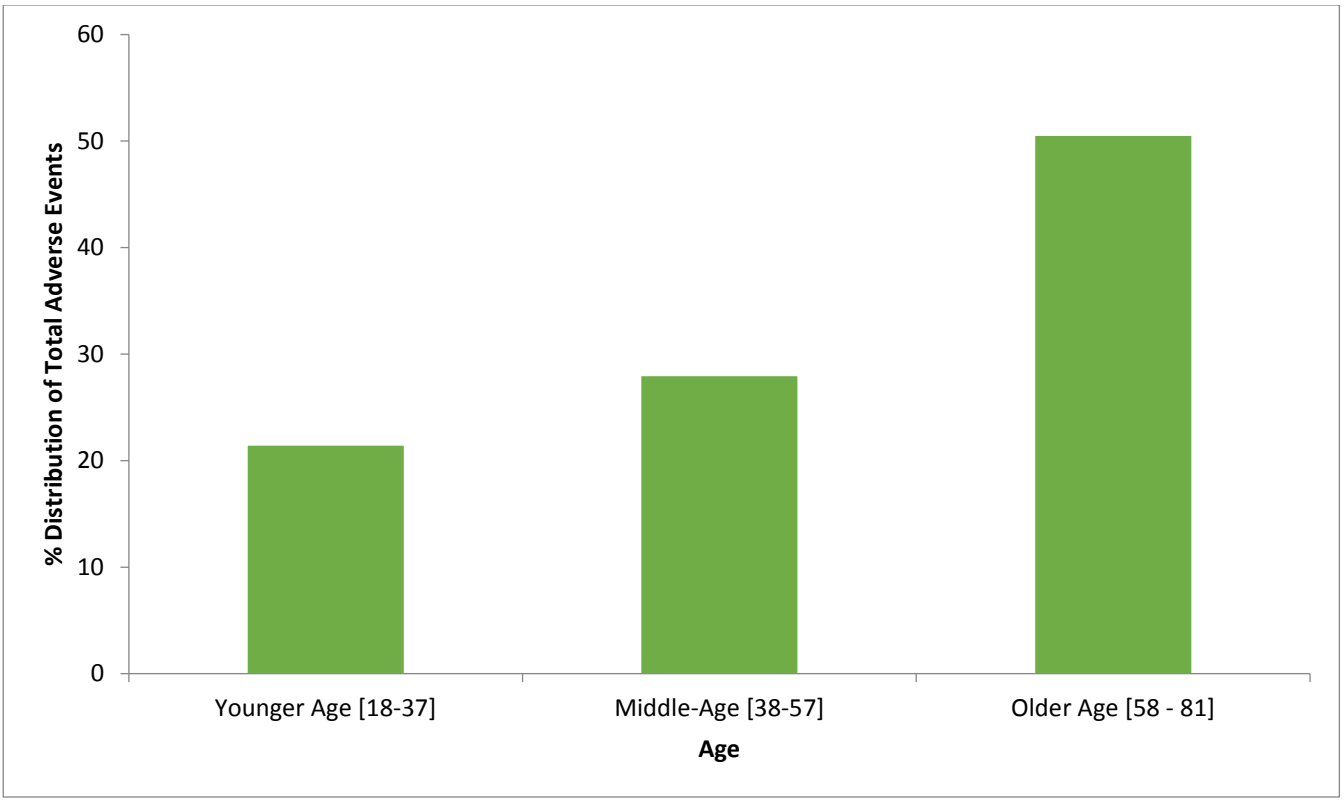

Figure 4. Distribution of all adverse events recorded at the CTRC from 2003-2015 based on age (younger, middle-age, older) (n=368). 29 of the 397 events were excluded from analysis because an age was not available. The count of adverse events increases with age. 50.5% of all the adverse events occurred within the elderly age group compared to the middle-aged group (27.9%) and younger-group (21.5%).

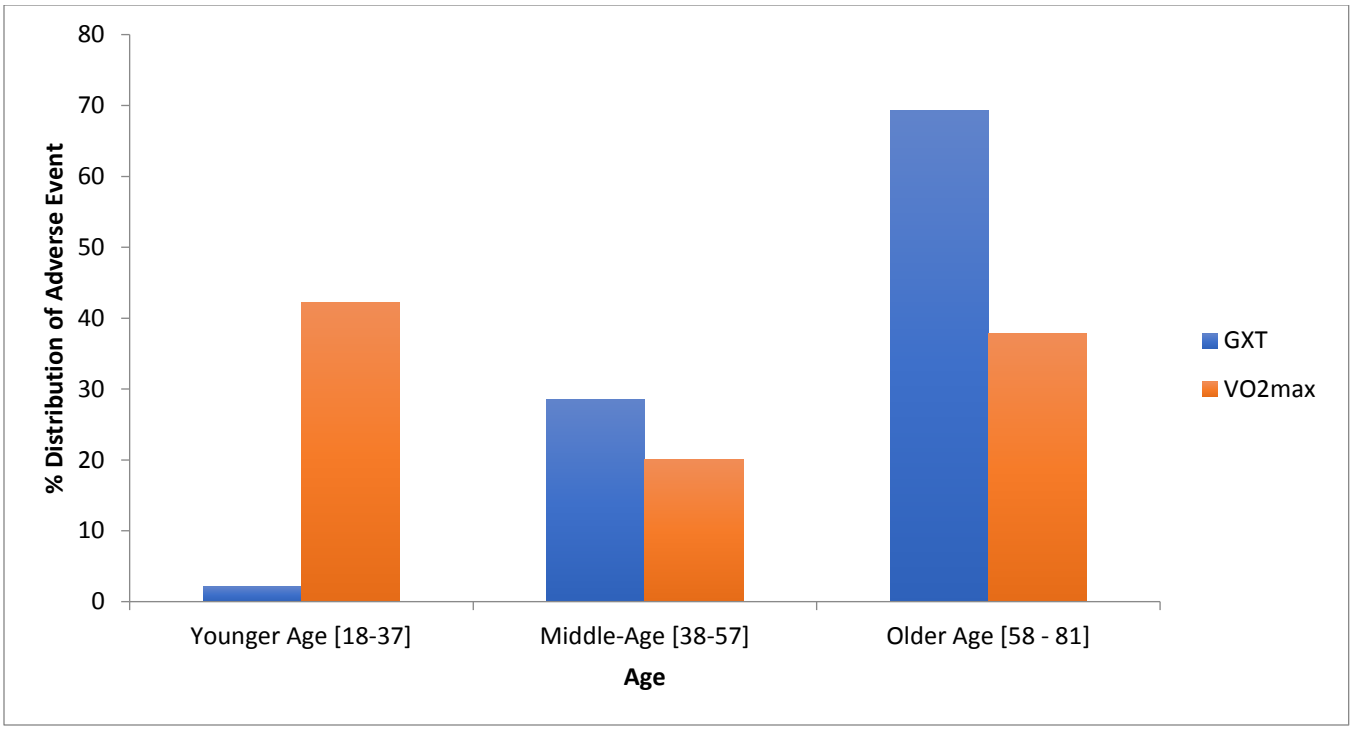

Figure 5. Percent of adverse events occurring during a GXT (n=140) and VO2max test (n=45) based on age group (younger, middle-aged, older) from 2003-2015. Two VO2max adverse events were excluded from analysis because age was not available. The number of adverse events increases with age during a GXT, but not during a VO2max test. The greatest number of adverse events that occurred during a GXT was in the elderly group (69.3%). The greatest number of adverse events that occurred during a VO2max was in the younger group (42.2%).

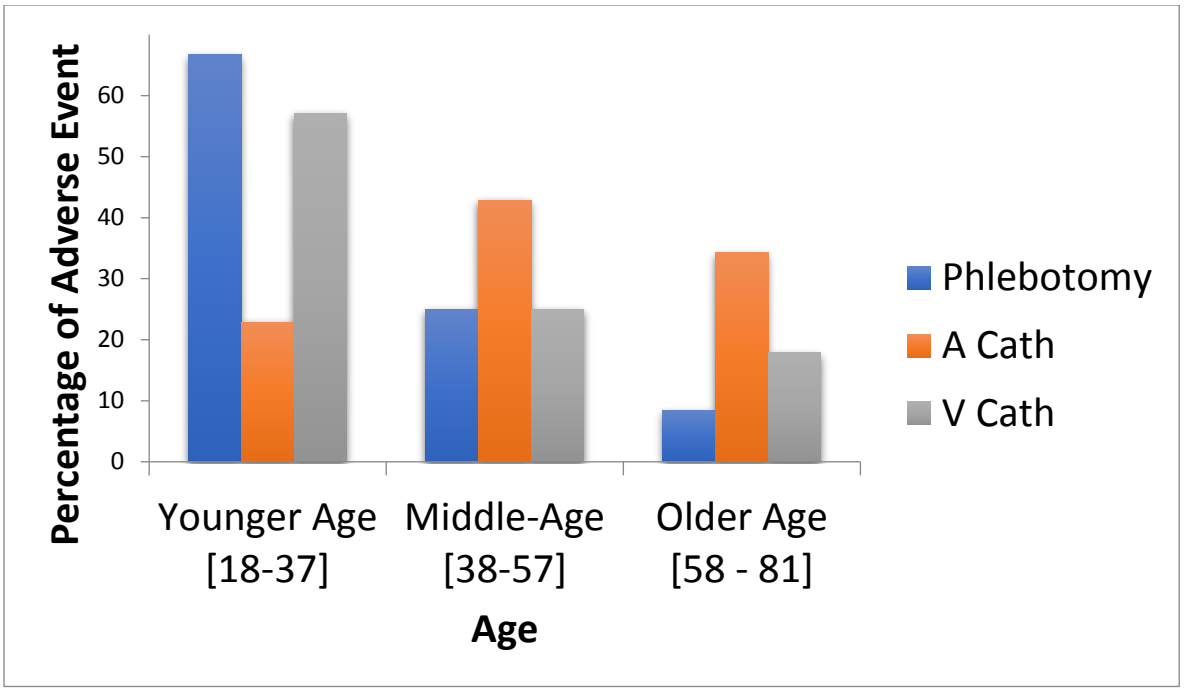

Figure 6. Percentage of adverse events occurring during a phlebotomy (n=12), arterial (A Cath) (n=35) or venous catheterization (V Cath) (n=28) based on age. There are a greater percentage of phlebotomies and venous catheterizations adverse events that occur in the younger group (Phlebotomy = 66.7%, V Cath = 57.14%) compared to the older groups (Middle-aged Phleb = 25%, Middle-aged V Cath = 25%, Older age Phleb = 8.3%, Older age V Cath = 17.9%).

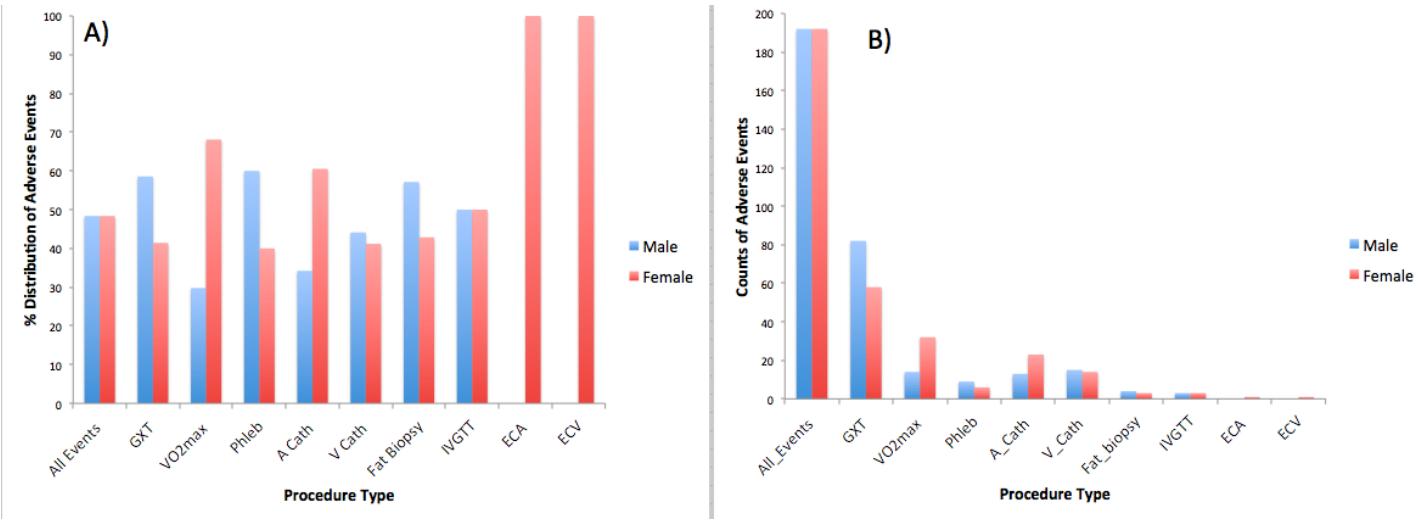

Figure 7. Panel A). Percent of adverse events occurring at the CTRC from 2003-2015 based on sex. 384 adverse events were reported with a sex, 192 adverse events occurred in females and males. 68.1% of VO2max adverse events occurred in females. 100% of the ECA (n=1) and ECV (n=1) adverse events occurred for a female. **Panel B)** Counts of adverse events by sex. The sample size of adverse events was relatively smaller for fat biopsies, IVGTT, ECA, and ECV compared to the other procedures. VO2max= maximal oxygen consumption test, GXT = graded exercise test, Phleb = phlebotomy, V Cath = venous catheter, A Cath = arterial catheter, ECA = arterial endothelial cell harvest, ECV = venous endothelial cell harvest, IVGTT = intravenous glucose tolerance test.

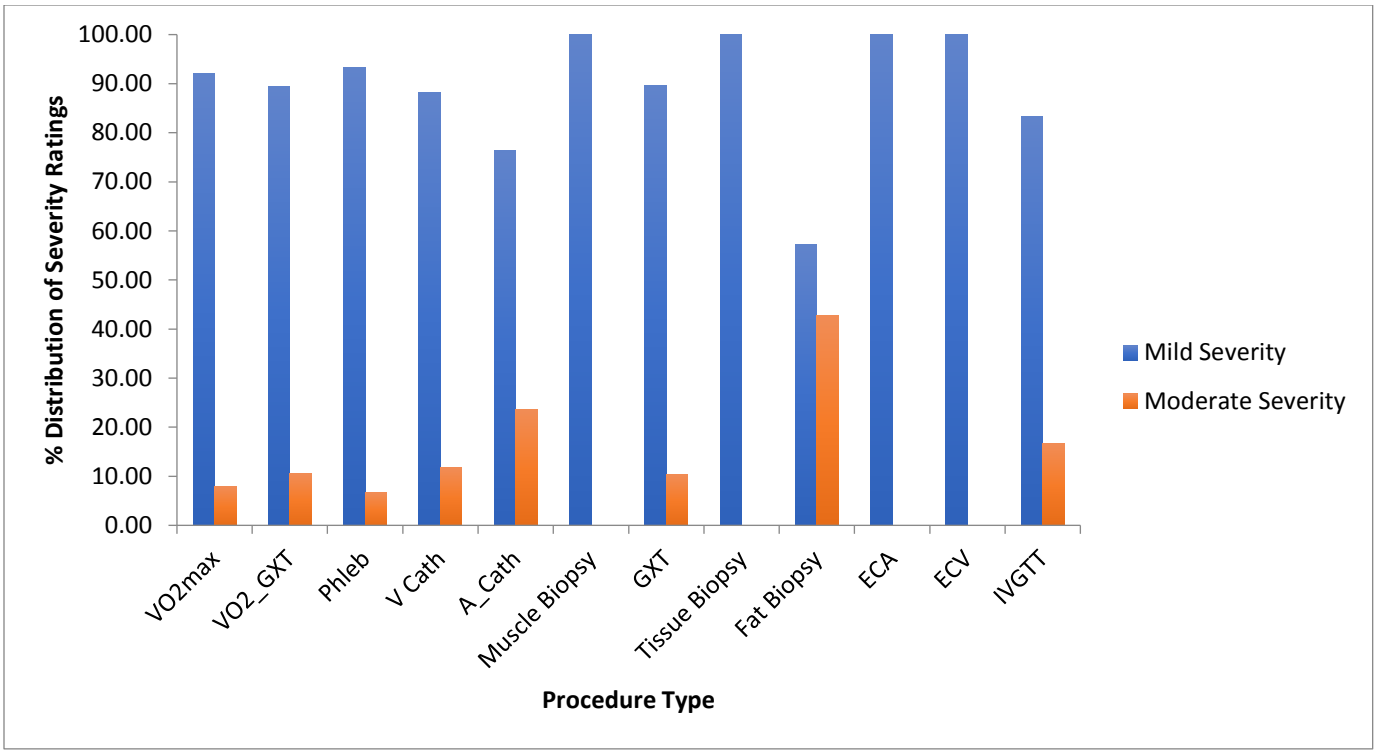

Figure 8. Percent distribution of severity-rankings based on procedure type. Fat biopsies had the highest percent of moderate-severity (42.9%). VO2max = maximal oxygen consumption test, GXT = graded exercise test, Phleb = phlebotomy, V Cath = venous catheter, A Cath = arterial catheter, ECA = arterial endothelial cell harvest, ECV = venous endothelial cell harvest, IVGTT = intravenous glucose tolerance test.

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Appendix

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UCB CTRC ADVERSE EVENT REPORTING FORM

PART I (Please complete both sides of the PART I)

Please provide the following basic information:			
Protocol Number:	Investigator Name:		
Date of Event:	Subject Gender:	Subject Age:	Subject Code:

Type of Adverse Event (circle the most applicable):

Anticipated **Unanticipated**

Circle the procedure associated with the adverse event:

GXT	VO_2max	BRS	Systemic Infusion	Phlebotomy	Venous Catheter
Venous Catheter - EC Harvest	Arterial Catheter	Arterial Catheter - EC Harvest	Non-Infusion Medication	Local Infusion Medication	Submaximal Exercise
DEXA	Nutrition	RMR	Fat Biopsy	Muscle Biopsy	Micro Neurography

Other_____

Please circle all that apply to the reported adverse event:

Pain/Discomfort	Numbness/Tingling	Vasovagal	Hematoma	Nausea
ST Depression	ST Elevation	Ventricular Ectopy	Chest Pain	
Headache	Vomiting	T Wave Inversion	Hypertension	

Other_____

Severity Rating of the Adverse Event (rate adverse event according to NCI Common Toxicity Criteria - circle the most appropriate response)

1	2	3	4	5
mild	moderate	severe & undesirable; requires hospital care or prolonged hospitalization	life-threatening or disabling;	death

Determine the attribution of the adverse event (circle the most appropriate response)		
Code	**Descriptor**	**Definition**
5	**Definite**	**The adverse event is clearly related to the investigational agent/procedure**
4	**Probable**	**The adverse event is likely related to the investigational agent/procedure**
3	**Possible**	**The adverse event is may be related to the investigational agent/procedure**
2	**Unlikely**	**The adverse event is doubtfully related to the investigational agent/procedure**
1	**Unrelated**	**The adverse event is clearly not related to the investigational agent/procedure**

Determine the ACUTE management outcome of the adverse event (circle the most appropriate response)		
optimal	**satisfactory**	**unsatisfactory**

Report prepared by: