St. Jude
PREDM
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PREDM: AN OPEN-LABEL PILOT INTERVENTION TRIAL TO PREVENT DIABETES IN PREDIABETIC ADULT SURVIVORS OF CHILDHOOD CANCER

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Protocol Summary

PREDM: An Open-Label Pilot Intervention Trial to Prevent Diabetes in Prediabetic Adult Survivors of Childhood Cancer
Principal Investigator: Stephanie Dixon, MD, MPH
IND Holder: St. Jude Children's Research Hospital, # XXXX
Brief Overview: This is a first-in survivor, single-arm pilot study with the goal of establishing evidence of feasibility and safety of a combined pharmacologic (metformin) and lifestyle intervention (using an existing digital platform) to prevent diabetes in prediabetic adult survivors of childhood cancer. In addition, we will evaluate preliminary data for efficacy of the combined intervention to improve measures of glycemic control, insulin resistance, weight/anthropometric measures, physical activity and frailty. The metformin + lifestyle intervention will be administered for 24 weeks and measures of adherence, safety, glycemic control, insulin resistance and anthropometrics assessed. If successful, this pilot will provide the preliminary evidence needed for a phase 2, randomized controlled trial to establish efficacy. This proposal leverages the unique resource of the SJLIFE cohort of extensively phenotyped survivors available for longitudinal follow-up.
Intervention: 41 survivors age 18 to <45 years determined to have prediabetes based on American Diabetes Association diagnostic criteria will be enrolled and receive the combined metformin and lifestyle intervention (using a digitally delivered platform) for 6 months.
Brief Outline of Treatment Plan: Eligible subjects who meet inclusion criteria will receive metformin extended release daily and be enrolled in the digital lifestyle intervention program. Following a 2-week run-in period at lower dose (500 mg/day) to minimize gastrointestinal side effects (diarrhea, nausea, flatulence, bloating), participants will be escalated to a maximum dose of 1000 mg/day. The digitally delivered lifestyle change program will include a core curriculum focused on diet quality, food types, exercise and behavioral strategies for goal setting, and self-monitoring. The intervention includes interaction with a lifestyle coach as well as a virtual peer group, hosted by a second group coach. Study end points will include treatment adherence will be assessed by telephone-based pill count at week 2, 4, 8, 16 and 20, and in-person assessment at subsequent clinic visits (12 and 24 weeks). Adherence to the lifestyle program will be monitored by completion logs from the digital platform as well as self-reported physical activity (NHANES-PAQ) and accelerometer data. Safety will be assessed using the Global Rating of Side Effects Burden, which includes the Common Terminology Criteria for Adverse Events (CTCAE v5.0) grade. Glycemic control and insulin resistance will be assessed by change from baseline in fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), insulin resistance using the homestatic model assessment (HOMA-IR) and insulin-like growth factor-binding protein 1 (IGF-BP1). We will also assess change from baseline in weight, body fat percentage, waist circumference, physical activity (self-report and accelerometer data) and frailty measures.
Study Design: Single-arm (combined metformin + digitally delivered lifestyle intervention), open-label pilot intervention trial to determine: 1) feasibility and safety using measures of treatment adherence, safety and adverse event reporting and 2) preliminary evidence for efficacy using measures of glycemic control, insulin resistance,

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weight/anthropometric measures, physical activity and frailty in adult survivors of childhood cancer who have prediabetes. The objective of this study is to provide initial evidence for feasibility, safety and efficacy in a pilot, open-label setting. If successful, these results will provide necessary preliminary data for a randomized, multi-arm phase 2b trial of efficacy.
Sample Size: We anticipate enrolling approximately 41 participants.
Data Management: The study team consisting of the study PI, study coordinator, protocol nurse, and the study statistician will be responsible for data management and monitoring, including implementation of stopping rules for feasibility and safety. Statistical analyses will be performed by the Department of Epidemiology and Cancer Control and the Biostatistics Department at St. Jude Children's Research Hospital.
Human Subjects: The risk to subjects will be related to the toxicity of metformin extended release. Metformin is a biguanide class oral hypoglycemic agent that is FDA-approved to improve glycemic control in adults and pediatric patients 10 years of age and older with type 2 diabetes mellitus. It has been widely utilized with safety and efficacy data in prediabetic adults, outside of it's FDA-approved indication. The expected side effects of metformin are gastrointestinal symptoms (diarrhea, nausea, flatulence, bloating). Participants will be informed of this during informed consent discussion and adverse events will be monitored, reported and managed according to good medical practice. Commercially available metformin extended release will be purchased and supplied as 500 mg tables at a dose of 500 mg on days 1-14, escalated to 1000 mg day 15 through study end (week 24). Metformin extended release is associated with fewer gastrointestinal side effects, especially when the dose is titrated, as planned in our study. Metformin may cause lactic acidosis in extreme clinical scenarios including overdose and, therefore, patients with risk factors for lactic acidosis including severe chronic kidney disease, hepatic impairment or acute heart failure will be excluded. The primary features of the lifestyle change program include a curriculum focused on diet and exercise goals using behavioral strategies and led by a lifestyle coach. Unique physical activity limitations of survivors, including frailty, may be a barrier to incorporating activity goals to meet the recommended 150 min/week, however, as no specific exercise or dietary restrictions are prescribed we do not anticipate adverse events related to the lifestyle component of the study.

1.0 OBJECTIVES

1.1 Primary Objective

The primary aim of this proposal is to establish the feasibility and safety of a 24-week combined metformin + intensive lifestyle intervention among adult survivors with prediabetes.

Primary endpoints of this trial will be adherence to 1) daily metformin administration, assessed by telephone-based pill counts (Appendix I), and 2) completion of required core-curriculum of the lifestyle change intervention. Safety will be assessed using the Global Rating of Side Effects Burden (Appendix II), which includes the Common Terminology Criteria for Adverse Events (CTCAE v5.0) grade.

Hypothesis: Metformin will be safe and well-tolerated among adult survivors of childhood cancer with prediabetes. Metformin can be successfully used in combination with a digitally delivered intensive lifestyle intervention.

1.2 Secondary Objectives

The secondary aim is to assess preliminary evidence for efficacy of the combined metformin + intensive lifestyle intervention on glycemic control and insulin resistance. Glycemic control will be measured by fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) and insulin resistance measured by the homeostatic model assessment (HOMA-IR) and IGF-binding protein 1 (IGF-BP1; a measure of insulin sensitivity strongly correlated with euglycemic insulin clamp testing).[1]

Hypothesis: A combined metformin and lifestyle intervention will improve measures of glycemic control and insulin resistance among adult survivors of childhood cancer with prediabetes, comparing baseline to 12-week (interim) and 24-week (study-end) timepoints.

1.3 Exploratory Objectives

To assess preliminary evidence for efficacy of the combined metformin + intensive lifestyle intervention on weight, other anthropometric measures, blood pressure and lipid profile, physical activity (self-reported and as measured by accelerometer), frailty measures, and health-related quality of life (HRQOL). We will also assess diabetes development at future SJLIFE visits.

To assess measures of participation in the lifestyle change program as well as barriers to participation and medication adherence.

Hypothesis: A combined metformin and lifestyle intervention will improve measures of body composition (including weight loss among overweight or obese survivors) and physical activity among adult survivors of childhood cancer

with prediabetes, comparing baseline to 12-week (interim) and 24-week (study-end) timepoints. Survivors with higher participation/engagement will have improved efficacy endpoints.

2.0 BACKGROUND AND RATIONALE

2.1 Background

Childhood cancer survivors are at high risk for diabetes: Compared to siblings, adult survivors of childhood cancer have near twice the risk of diabetes.[2,3] Specific cancer treatment exposures such as corticosteroids, abdominal or pancreatic radiation therapy, cranial radiation therapy and total body irradiation (TBI) are known to increase risk for diabetes, likely through alterations in insulin resistance and/or pancreatic insulin producing capacity (**Figure 1**).[2,3] Compared to siblings, survivors who received abdominal radiation experience a 3.5-fold increase in risk of diabetes and those who received TBI a near 12-fold increase in risk.[2] Although no association between asparaginase and diabetes has yet been identified, it is plausible that direct pancreatic injury resulting from exposure to this agent or drug-induced pancreatitis (corticosteroids, asparaginase or novel agents) could lead to a reduced insulin producing capacity and increased diabetes risk.

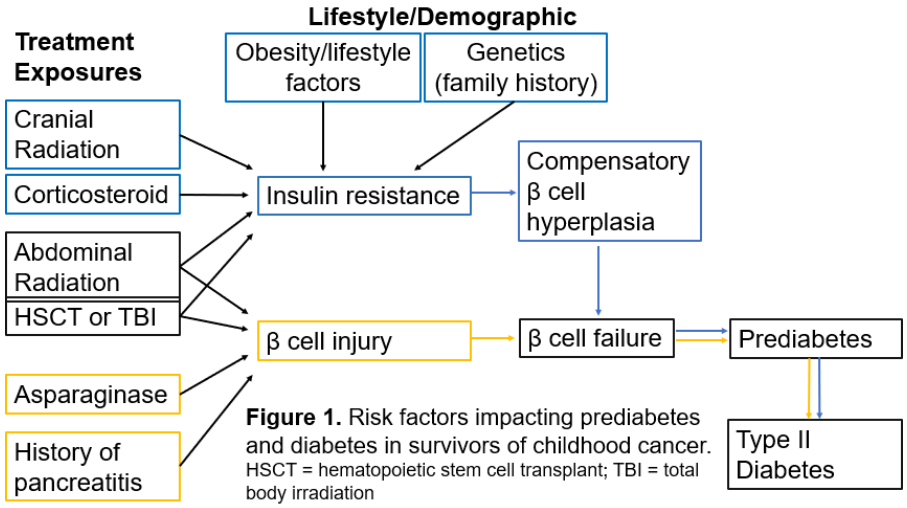


Figure 1. Risk factors impacting prediabetes and diabetes in survivors of childhood cancer. HSCT = hematopoietic stem cell transplant; TBI = total body irradiation

Survivors are at high risk for cardiac morbidity and mortality: Cardiac death is the leading non-cancer cause of late mortality in survivors of childhood cancer.[4] Survivors have a near 12-fold increase risk of cardiac death relative to similar age- and sex-matched US population.[4] Among long-term survivors exposed to cardiotoxic therapy the occurrence of modifiable cardiovascular risk factors, including diabetes, portends a near-multiplicative increase in risk for major cardiac events.[5] Thus, diabetes prevention could provide a significant risk

reduction impact on long-term cardiac morbidity and mortality in this high-risk population.

Diabetes prevention and control reduces cardiovascular risk in the general population: In the general adult population, diabetes is a well-established cardiovascular risk factor. Among adults with diabetes, cardiovascular disease is the leading cause of death and occurs up to 15 years earlier than in non-diabetics.[6] Improvement in glucose control decreases this risk and for every 1% reduction in hemoglobin A1c (HbA1c) towards a value of <6% there is an estimated 11-16% decrease in cardiovascular events including stroke, myocardial infarction and heart failure.[7] Additionally, adults with diabetes have a 60% increase in risk for all-cause mortality with an 80% increase in risk of death from vascular causes compared to those who do not have diabetes.[8] The specific impact of improved glucose control and diabetes prevention on mortality and cardiac morbidity in adult survivors is unknown and preliminary data generated from this pilot study would be used to design a randomized, large-scale trial of efficacy for diabetes prevention in survivors.

Diabetes prevention is effective in the general population: Prediabetes is defined as a fasting plasma glucose (FPG) of 100-125 mg/dl or hemoglobin A1c (HbA1c) 5.7-6.4% in the absence of overt diabetes. In the general population it is estimated that without intervention, 4-10% of prediabetics will become diabetic over one year.[9,10] Both pharmacologic therapy with metformin, a biguanide class oral hypoglycemic agent that reduces hepatic glucose production and impacts anaerobic glucose metabolism and uptake at the level of the intestine,[11] and intensive lifestyle intervention used in the Diabetes Prevention Program (DPP) have each been established to prevent progression to diabetes among prediabetic adults in the general population.[9,12] In this landmark trial, intensive lifestyle intervention included a 16-week core-curriculum led by a lifestyle coach and focused on diet, exercise and behavioral strategies targeting 7% weight loss and at least 150 minutes per week of moderate intensity physical activity (brisk walking or biking), and pharmacologic therapy was 850 mg metformin immediate release twice daily.[13] At study completion, with an average follow-up time of 2.8 years, lifestyle intervention reduced the incidence of diabetes by 58% and metformin by 31%, compared to placebo.[12] However, in the youngest subset of participants (25-44 years, the target age range for this application), metformin and lifestyle change had similar efficacy with the incidence of diabetes reduced by 44% in the metformin and 48% in the lifestyle group.[12] Despite this, metformin is not commonly used in prediabetic adults. Less than 1% reported metformin use in the National Health and Nutrition Examination Survey (NHANES).[14]

Whether treatment-related diabetes is preventable is unknown: Preliminary data from the St. Jude Lifetime Cohort (SJLIFE) suggests prediabetes prevalence in survivors is near twice that of similarly aged controls (**Table 1**). Still, it is unknown if interventions utilized in the general population are feasible or efficacious in this high-risk population.

Table 1. Prediabetes and Diabetes in SJLIFE Participants at Baseline by Age			Prediabetes		Diabetes	
		N	N	%	N	%
Survivors	18-24 yrs	1012	172	17.0	26	2.6
	25-34 yrs	1465	412	28.1	71	4.8
	35-44 yrs	792	328	41.4	89	11.2
	45-54 yrs	230	107	46.5	38	16.5
	55-64 yrs	30	13	43.3	5	16.7
Controls	18-24 yrs	85	8	9.4	1	1.2
	25-34 yrs	157	23	14.6	4	2.5
	35-44 yrs	136	31	22.8	9	6.6
	45-54 yrs	53	14	26.4	7	13.2
	55-64 yrs	17	5	29.4	0	0.0

2.2 Rationale

Type 2 diabetes has become an epidemic in the US, affecting 12% of the adult population.[15] Among survivors, our data in the SJLIFE cohort, consistent with prior studies, demonstrates an increased prevalence of diabetes among adult survivors; specifically, among those in middle adulthood (35-64 years), 12.5% were diabetic (Table 1). In the original Diabetes Prevention Program (DPP) trial performed in the overweight, general adult population with prediabetes, 72% of participants randomized to the metformin arm took 80% of prescribed metformin dose.[12] Additionally, in the DPP, 74% of lifestyle participants met the 150 min/week activity goal based on

Table 2. Potentially Eligible Participants from SJLIFE Age 18-<45 Known to be Prediabetic (N=603)		
Age at diagnosis, years (median, IQR)	6.55	2.9-12.7
	N	**%**
Age as of 12/1/2019		
18-24 years	27	4.5
25-34 years	237	39.3
35-<45 years	339	56.2
Exposure Type		
Pancreatic Radiation	234	38.8
Cranial Radiation	197	32.7
Total Body Irradiation	26	4.3
Corticosteroids	275	45.6
Asparaginase	189	31.3
Bone Marrow Transplant	54	9.0
Gender		
Male	385	63.8
Female	218	36.2
Race		
White, Non-Hispanic	476	78.9
Other	127	21.1
BMI Category (kg/m²)		
Underweight, <18.5	20	3.3
Healthy weight, 18.5-24.9	142	23.6
Overweight, 25.0-29.9	177	29.3
Obese, ≥30.0	264	43.8

participant logs and 50% achieved the goal 7% weight loss at 24 weeks. The 7% weight loss goal was based on prior studies suggesting behavioral weight loss strategies are able to achieve a 5-10% weight loss in 6 month study periods and that risk of developing diabetes increases with increasing BMI, therefore any decrease in BMI would be anticipated to decrease diabetes risk.[16] Unlike the DPP participants, some of the survivors in our study may have a BMI <25 kg/m^2 at study start, therefore we proposed a goal of 5% weight loss. Additionally, 74% of participants in the lifestyle arm of the DPP achieved the 150 minutes/wk activity goal at 24 weeks. For our feasibility aim, we chose to demonstrate adherence to the curriculum, not outcome based goals as over 25% of potentially eligible prediabetic survivors are not overweight (Table 2); therefore, although we will monitor change in weight, physical activity and diet, we have chosen adherence to the digitally-delivered curriculum to be defined as completion of at least 60% of core-curriculum during the 24 week study period. Finally, although 72% of participants in the DPP were able to be adherent to metformin and at least 74% met either a physical activity or weight loss goal, we anticipate that adherence to the combined intervention will be more difficult to achieve. Therefore, we have chosen to consider this intervention feasible if at least 60% of survivors are adherent to at least 80% of metformin doses and at least 60% of the core curricula.

Because lifestyle change and metformin demonstrate similar efficacy in adults aged 25-44 in the general population (a similar age to our target survivor population),[12] it is important to test both strategies in our pilot study. The etiology of prediabetes may differ in survivors due to prior therapy exposures and these interventions may work synergistically to improve glucose control and decrease insulin resistance. Each intervention is safe and tolerable in the general population, including those with heart failure and other chronic conditions.[17] We plan to pilot a combined metformin and lifestyle intervention to prevent diabetes in young adult survivors of childhood cancer with prediabetes. This will provide feasibility data on each approach and identify if one or both are feasible in an efficient manner.

The landmark DPP trial utilized a dose of metformin immediate release (IR) of 850 mg twice daily.[13] Metformin ER can be administered once daily and is associated with fewer gastrointestinal side effects,[17,18] with evidence for at least equivalent glycemic control.[19] Metformin may cause lactic acidosis in extreme clinical scenarios including overdose and, therefore, patients with risk factors for lactic acidosis including severe chronic kidney disease, hepatic impairment or acute heart failure are excluded.[17,20] The incidence of lactic acidosis in patients using metformin for diabetes has been estimated at between 3 and 9 cases per

100,000 person years of administration.[21-23] Given that most of these cases are in individuals with risk factors that will be excluded in our study, the potential risk of metformin associated lactic acidosis is extremely low. In many studies, including the landmark DPP trial, laboratory monitoring was performed no more frequently than every 3 months. Despite frequent gastrointestinal side-effects, most commonly diarrhea, metformin immediate release (IR) administered at doses up to 2.5 g/day was discontinued due to intolerable side effects in only 1.5-5% of participants over multiple studies.[18] Multiple studies have since demonstrated safety and efficacy of dosing up to and exceeding 1000 mg twice daily IR and 1000 mg daily ER in both diabetic and prediabetic populations.[19,24,25] Therefore, we expect our metformin discontinuation rate to be <5%.

Approximately 25% of potentially eligible survivors with prediabetes have a BMI <25 kg/m^2 (Table 2) and because eligibility criteria for entry into a DPP lifestyle change program includes a BMI of at least 25 kg/m^2, a DPP lifestyle change program will not be utilized. The digitally delivered, lifestyle change program used in our study features a core curriculum administered over the 24 week study period, similar to the set-up of the DPP. The focus is on dietary education and meal tracking, weight loss (for overweight and obese individuals) to a goal that can be tailored to each participant and physical activity through behavioral change using strategies based in cognitive behavioral therapy to promote self-efficacy. A lifestyle coach assigned to each participant by the digital lifestyle change platform virtually interacts with each participant and there is a second lifestyle coach from the digital lifestyle change platform that leads a peer group, both of these components are similar to the DPP digital programs. This program has demonstrated that the majority of regular users of the program achieve weight loss, with increased weight loss seen in individuals who demonstrate higher levels of engagement or adherence with self-monitoring in the application.[26,27] Among overweight and obese participants another study demonstrated the digital lifestyle change program resulted in 7.5% mean weight loss as well as a 5.7 mg/dL decrease in fasting plasma glucose levels over the first 15 weeks of the program, weight loss at 1 year was 5% demonstrating maintenance.[28] In a sub-analysis of DPP participants randomized to intensive lifestyle intervention, researchers identified that, for this group, weight loss was the primary predictor of decreased diabetes incidence and for every kilogram of weight loss the risk of diabetes was reduced by 16% after adjustment for dietary and activity changes.[29] Prior studies of digitally delivered DPP lifestyle change programs have demonstrated an average weight loss of 5.0-6.5%,[30,31] as well as a significant increase in exercise frequency and decrease in work absenteeism for

participants in the general population with prediabetes over the 16-course core curriculum.[32]

Frailty is typically described in older adults and identifies individuals who are at risk for adverse health outcomes and early mortality.[33,34] However, Ness et al. identified that the prevalence of frailty (7.9%) and prefrailty (22.2%), defined by the Fried criteria, among survivors in the SJLIFE cohort at a mean age of 33 years was similar to the prevalence reported among adults over 65 years of age.[33,34] Observational studies among older adults have demonstrated that metformin reduces all-cause mortality and frailty-related diseases, including reduced cancer and cardiovascular disease compared to both non-diabetes and diabetics using non-metformin regimens.[35,36] These observations, as well as animal studies suggesting metformin has anti-aging effects, has led to research interest and there is at least one ongoing study of frailty prevention in prediabetic adults using metformin.[37]

3.0 PARTICIPANT ELIGIBILITY CRITERIA AND STUDY ENROLLMENT

3.1 Inclusion Criteria

We will recruit to enroll 41 survivors who are at least 18 but <45 years of age who participate in the St. Jude Lifetime Cohort Study (SJLIFE) and have been identified to have prediabetes defined as hemoglobin A1c (HbA1c) 5.7-6.4% or fasting plasma glucose (FPG) 100-125 mg/dl.

3.1.1 Participant in SJLIFE

3.1.2 ≥18 and <45 years of age

3.1.3 Prediabetic: fasting plasma glucose 100-125 mg/dL, hemoglobin A1c 5.7-6.4% (either or both criteria may be present)

According to institutional and NIH policy, the study will accession research participants regardless of sex and ethnic background. Institutional experience confirms broad representation in this regard.

3.2 Exclusion Criteria

3.2.1 Absence of treatment related diabetes risk. Survivors will be excluded if their cancer treatment required observation only, surgery alone not

involving the abdomen or brain, radiation alone not involving the chest (pancreatic risk), abdomen or brain (e.g. retinoblastoma treated with enucleation alone, melanoma of an extremity treated with excision alone, neuroblastoma in an infant requiring observation only)

3.2.2 Diabetes at baseline assessment: FPG ≥126 mg/dL, HbA1c ≥6.5% or previous diagnosis by a physician (except gestational diabetes that resolved post-partum)

3.2.3 BMI <19 kg/m^2

3.2.4 Current metformin use (including for any period ≥30 days in the past 1yr)

3.2.5 Known allergy to metformin

3.2.6 Current use of other oral glucose lowering medications, non-insulin injectable diabetes medications or insulin (Appendix)

3.2.7 Current participation in a lifestyle change program

3.2.8 Chronic kidney disease ≥ stage IIIb (eGFR < 45 mL/min)

3.2.9 Severe cardiovascular disease or recent intervention (NYHA class ≥2 or heart failure hospitalization in the past 6mo, Aortic stenosis, Heart block including LBBB or 3rd degree AV block, SBP >180 or DBP >105 mmHg, myocardial infarction or coronary revascularization in the past 1 month)

3.2.10 Severe hepatic dysfunction: cirrhosis or AST/ALT >3 times upper limit of normal

3.2.11 Pulmonary disease with dependence on oxygen or daily use of bronchodilators

3.2.12 Weight loss >10% in the past 6 months

3.2.13 Bariatric surgery in the past 2 years

3.2.14 Pregnant, within 3 months post-partum, nursing, or planning to become pregnant

3.2.15 Anemia: hematocrit <36% in males or <33% in females

3.2.16 Ongoing alcohol or substance abuse using criteria from the AUDIT and DAST questionnaires (Appendix)

3.2.17 Diagnosis of schizophrenia or other psychotic disorder

3.2.18 Vision impairment limiting ability to interface with the digital program

3.2.19 Unable to swallow medication

3.2.20 Non-English speaking

3.2.21 Cognitive impairment defined by IQ <80

3.2.22 Current active cancer or undergoing treatment for active cancer

Complete inclusion/exclusion criteria are listed in Table 3.

Table 3. Inclusion Criteria	**Rationale**
Participant in SJLIFE: ≥5 years from completion of therapy	Limits study to a population especially vulnerable due to young age at cancer therapy. Minimizes interference with cancer surveillance. Reflects eligibility for SJLIFE cohort participation.
≥18 and <45 years of age at study entry	≥18 years reflects eligibility of CDC-recognized lifestyle change programs. Prior studies suggest metformin and lifestyle change are equally efficacious in this age group. We expect a larger proportion of prediabetes in this group to be attributable to childhood cancer treatment and not only lifestyle and physiologic aging.
Prediabetic (FPG 100-125 mg/dl, HbA1c 5.7-6.4%)	Targets subset of survivors at highest risk of developing diabetes.
Exclusion Criteria	
Treated by: 1) observation alone or 2) surgical resection alone and resection did not include abdomen or brain or 3) radiation therapy alone and radiation field did not include chest (potential to pancreas), abdomen or brain	No known treatment related risk for diabetes.
Diabetes at baseline: FPG ≥126 mg/dl or HbA1c ≥6.5% or previous diagnosis by a physician (except gestational diabetes, resolved post-partum)	Requires additional medical management and monitoring which may include glucose lowering medications that would interfere with ability to conduct trial.
BMI < 19 kg/m^2	Concern that incidental weight loss using the lifestyle change program would be detrimental to underweight or near underweight survivors.
Current metformin use (including for any period of >30 days in the past 1 year)	Limits assessment of current glycemia control measures and impact on glucose homeostasis.
Known allergy to metformin	Unable to tolerate intervention
Current use of other oral glucose lowering medications, non-insulin injectable diabetes medications or insulin	Limits assessment of current glycemia control measures and impact on glucose homeostasis. Limits inclusion of participants who are unclear about their prior diabetes diagnosis/current treatment or those on glucose lowering medications for indications other than diabetes.

	Includes: sulfonylureas, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose transporter (SGLT) 2 inhibitors, thiazolidinediones, glucagon-like peptide-1 (GLP-1) receptor agonists, meglitinides, amylinomimetics, insulins (Appendix)
Current participant in a lifestyle change program* (including for any period of >30 days in the past 3 months)	Limits assessment of baseline weight and physical activity and impact of intervention on these measures and measures of change in glucose homeostasis. *Excludes participants of any CDC-recognized diabetes prevention program OR any lifestyle change program targeting weight loss and physical activity using *behavioral therapy/psychology-based interventions* (such as NOOM) but not traditional programs focused primarily on calories/points (such as Weight Watchers, myWW)
Renal dysfunction: ≥Stage IIIb chronic kidney disease (eGFR < 45mL/min)	Metformin may result in lactic acidosis if patient with renal insufficiency undergo unexpected surgery or imaging.
Cardiovascular disease: NYHA class ≥2 or heart failure hospitalization in the past 6mo, Aortic stenosis, Heart block (LBBB, 3rd degree AV block), SBP >180 or DBP >105 mmHg, Myocardial infarction or coronary revascularization in the past 1mo	Increases the risk of physical activity associated with lifestyle change program. Acute heart failure can increase theoretical risk for lactic acidosis.
Severe hepatic dysfunction: cirrhosis, AST/ALT >3 times upper limit of normal (ULN)	Theoretically increases the risk for lactic acidosis.
Pulmonary disease with dependence on oxygen or daily use of bronchodilators	Increases the risk of physical activity associated with lifestyle change program.
Ongoing alcohol or substance abuse	Increases the risk of lactic acidosis. Interfere with ability to conduct trial. Scores on AUDIT >=13 in women and >=15 in men for alcohol abuse and DAST scores >=3 for substance abuse (Appendix)
Weight loss >10% in past 6 months or bariatric surgery within the past 2 years	Interferes with ability to conduct trial, exception is postpartum weight loss.
Anemia: hematocrit <36% in males or <33% in females	Interferes with ability to adhere to intervention, potential increase of associated risk.
Pregnant, planning to become pregnant	Metformin is a category B drug; no identified risk in animal studies, absence of well-controlled human studies. However, pregnancy impacts glucose homeostasis.
Within 3 months post-partum or nursing	Weight loss and other physiologic changes immediately post-partum and associated with increased energy demands during nursing would interfere with ability to assess changes in glycemic control and weight.
Diagnosis of schizophrenia or other psychotic disorder	May interfere with ability to adhere to medications and participate in digital lifestyle change platform.
Non-English speaking or literate	Unable to participate in the digital lifestyle change platform.
Vision impairment	Unable to fully participate in the digital lifestyle change platform.
Cognitive impairment defined as IQ < 80	Unable to fully participate in the digital lifestyle change platform.
No access to electronic device compatible with the platform	Unable to participate in the digital diabetes prevention platform.

Unable to swallow medication	Unable to receive metformin ER.
Current active cancer or undergoing treatment for active cancer	Potential for other medication interactions with metformin. Potential for current cancer or treatment to limit ability to participant in intervention.

3.3 Research Participant Recruitment and Screening

Participants for this study will be recruited from our NIH and institutionally-supported St. Jude Lifetime Cohort Study (SJLIFE; U01 CA195547, M.M. Hudson, L.L. Robison, MPI).[38] SJLIFE is a retrospective cohort with prospective follow-up and ongoing accrual that aims to facilitate prospective evaluation of health outcomes in aging adults surviving pediatric cancer.[38] Eligibility criteria for participation in SJLIFE includes five-year survival following diagnosis of pediatric cancer treated or followed at St. Jude Children's Research Hospital (SJCRH) and now comprises over 5000 survivors diagnosed from the 1960s through 2000s who have completed comprehensive on-campus clinical assessments.

We have identified 603 adult survivors <45 years old who were prediabetic at their last assessment (**Table 2**); however, as prediabetes prevalence increases with age and more survivors have aged in to the 18-24 group since last assessment, we anticipate an additional 200-300 potentially eligible participants based on a prevalence of prediabetes of 28% among those 18-<45 years in the SJLIFE cohort (**Table 1**).

Potentially eligible survivors, based on age (18-<45 years), potential for cancer treatment related risk for diabetes, and prediabetes status at last assessment will be identified prior to campus visit for a scheduled, SJLIFE core assessment. After reviewing potential eligibility in a weekly meeting, survivors they will be contacted by the study team to explain the study, including potential benefits and risks and asked if they would be interested in participating. If they are interested they will be scheduled with study staff for a PREDM consent and screening visit. The potential participants will be consented to PREDM following their SJLIFE consent visit and once consented to PREDM, will have study specific IGF-BP1 and lactate labs drawn at the same time as their SJLIFE core labs. Screening upon campus visit will be included in the typical SJLIFE core assessment including glycemia measure to assess if the participant meets all eligibility criteria, including being prediabetic by lab assessment (FPG 100-125 mg/dL or HbA1c 5.7-6.4%), neither FPG or HbA1c in the range for diabetes and not on any medications for diabetes or affecting glucose levels as detailed in the eligibility criteria. If all eligibility criteria are met (**Table 3)**, they will be enrolled. We anticipate that 2/3 of survivors identified and consented will be eligible for study participation, therefore, in order to enroll 41 evaluable

survivors we will need to obtain baseline labs on a total of 60 SJLIFE participants.

3.4 Enrollment on Study at St. Jude

Eligibility will be reviewed for completeness and correctness by the study team. A research participant-specific consent form will be released for participant signature.

The Study Team will enter the Participant Eligibility checklist information into the central enrollment system and release the informed consent document. The signed consent form will be scanned and sent to the CTO at protocoleligibilityoffice@stjude.org in order to complete enrollment.

To assist with enrollments and consent release, the CTO staff is available Monday through Friday. After hours, weekends, and holidays, the study team is referred to the CTO webpage for additional resources and instructions, Link: https://home.stjude.org/cto/Pages/default.aspx.

3.5 Procedures for Identifying and Randomizing Research Participants

Prior to initiating the study, the study team will be trained at SJCRH. The background to the study, study procedures, conditional enrollment and consent processes after determination of eligibility, user enrollment in the digital diabetes prevention platform by the study team, and plans to monitor intervention integrity and data quality will be included in this training workshop.

Following completion of training, screening for potentially eligible research participants will begin with biweekly review of SJLIFE participants scheduled for core assessments at least 4 weeks from the planned SJLIFE visit. Potentially eligible participants will be confirmed during the weekly meeting with the PI (Dr. Dixon), co-investigator (Dr. Armstrong) and study team. The study team will contact potentially eligible subjects by phone at least 2 weeks prior to their scheduled on-campus assessment to screen for any obvious exclusion criteria (interim diagnosis of diabetes mellitus, chronic conditions or medications that would exclude participation detailed in Table 3, or pregnancy). If the research participant agrees, the study team will schedule the patient for a consent visit at their upcoming SJLIFE visit. Once consented they will have IGF-BP1 and lactate levels drawn with their SJLIFE labs. Study staff will provide them with an accelerometer and directions for use to provide 7 days of baseline physical activity data following their campus visit. Eligible subjects who meet inclusion criteria will receive metformin extended release 1000 mg daily (after an initial run-in period of 14 days at 500 mg daily to minimize gastrointestinal side-

effects) and be enrolled in a digitally delivered lifestyle intervention program through an existing digital partner, after informed consent has been obtained.

3.6 Compensation

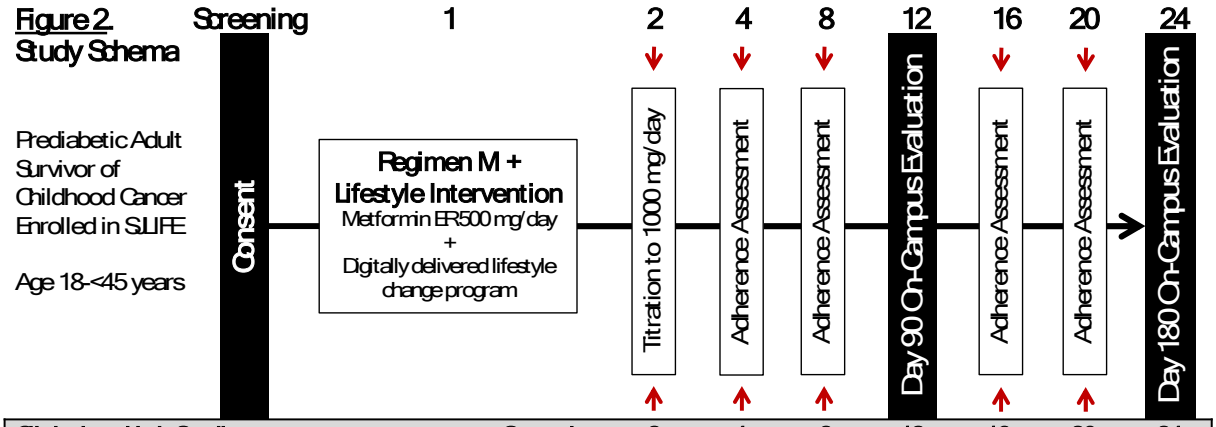
Participants will be compensated for their time and effort. They will receive $150 for completion of study visit 2 (week 12) and 3 (week 24). Study visit 1/Screening Visit (Day 0) will occur at the time of a regularly scheduled SJLIFE Core visit and include the regular SJLIFE visit compensation.

4.0 DESIGN AND METHODS

4.1 Design and Study Overview

This is a single-arm, open-label intervention pilot trial (Figure 2) to assess the primary endpoints of: 1) feasibility and safety of a combined metformin + digitally delivered lifestyle change program, and 2) effects on glycemic control, insulin resistance, weight and anthropometric measures and physical activity in survivors of childhood cancer, aged 18-<45 years, who are prediabetic. The objective of this study is to provide feasibility data and initial evidence for efficacy in an efficient pilot, open label setting. If successful, these results will provide necessary preliminary data for a randomized, phase 2b trial of efficacy. In the general population, metformin and lifestyle change have each demonstrated efficacy to reduce the incidence of diabetes by 40-50% among prediabetic adults aged 25-44 years.[12]

PREDM Study Schema



Clinical and Lab Studies	Screening	2	4	8	12	16	20	24
Cancer treatment history	X							
History and physical	X[e]				X			X
Anthropometrics[a]	X[e]				X			X
Frailty measures[b]	X[e]							X
Fasting blood work[c]	X[e]				X			X
Physical activity by 7-day accelerometer data	X				X			X
Self-Administered Questionnaires								
Demographic, medical & family history	X[e]				X[f]			X[f]
SF-36 for HRQOL	X[e]				X			X
DAST and AUDIT	X							X
Motivation to change	X							
Barriers to participation								X
Treatment Management and Adherence Monitoring								
Lifestyle change enrollment	X							
Metformin ER 500mg test dose	X							
Study tablets dispensed	X	X	X	X	X	X	X	
Follow-up phone call[d]		X	X	X		X	X	
Symptom log	X	X	X	X	X	X	X	X
Medication adherence log		X	X	X	X	X	X	X
Lifestyle change adherence log		X	X	X	X	X	X	X

Week 1 will be when the participant begins metformin 500 mg/day and the lifestyle change program and may occur up to 28 days after screening assessments. [a] Anthropometrics: BMI, body fat %, waist circumference [b] Frailty measures: walking speed, hand grip strength (body fat %) [c] Fasting blood work: glucose, insulin, hemoglobin A1c, IGF-BP1, complete metabolic panel (CMP), lactate, cystatin c, complete blood count, lipid panel. [d] Follow-up phone call: conduct pill count, confirm medication tolerance prior to titration, complete symptom log, arrange medication refill. [e] Repeat only if screening >30 days prior. [f] Limited interim medical history including medications.

*In the above schema, the 2 week visit will be conducted between +/- 4 days (between 10 and 18 days) and all monthly assessments including phone calls, labs and on-campus visits at weeks 4, 8, 12, 16, 20 and 24 will occur +/- 7 days from the planned date.

4.2 Definition and assessment of outcome measures

4.2.1 Primary Outcomes of PREDM

Adherence for feasibility: A participant will be considered adherent to the combined intervention if they are 80% adherent to metformin ER and complete 60% of the digitally-delivered core-curriculum. Metformin adherence will be monitored using virtual pill counts, the protocol will be adapted from Kalichman et

al.[39] and available in Appendix I. Participants will also be asked to bring all dispensed medication to campus at week 12 and 24 visits to perform in person pill-counts and any unused medication will be returned to pharmacy to be logged and discarded. Additionally, we will report on the proportion of days covered (PDC) where PDC= (number of days in period "covered"/number of days in period)*100% where "covered" refers to metformin being in the patients possession after a study visit or mail-out refill. Adherence to the digitally-delivered core curriculum will be assessed by completion of lessons on the app-based platform.

Safety and Adverse Events: Assessment of side effects and adverse events assessed using the Global Rating of Side Effects Burden (Appendix II), which includes the Common Terminology Criteria for Adverse Events (CTCAE v5.0) grade. The CTCAE grading criteria, published by the National Cancer Institute (NCI) is the accepted standard classification and grading scale for adverse events in cancer therapy clinical trials. These criteria will be assessed by phone or in person at weeks 2, 4, 8, 12, 16, 20 and 24. Additionally, study labs at week 12 and 24 study visits will assess for any safety concerns (CMP, lactate, cystatin C, complete blood count (CBC)). Pregnancy testing will be performed for female participants at week 12 and 24 study visits and, arranged as needed, based on symptoms and menstrual history.

4.2.2 Secondary Outcomes of PREDM

Glycemia will be measured using FPG and HbA1c. All fasting labs will be performed after a minimum of an 8 hour overnight fast (water is the only liquid that may be consumed during this period). Measures for an individual participant at weeks 12 and 24 will be compared to baseline. If at any study visit a participant meets American Diabetes Association (ADA) criteria for diabetes,[40] FPG is ≥126 mg/dL or HbA1c is ≥6.5% and the two tests are discordant (FPG is ≥126 mg/dL but HbA1c is <6.5% or FPG is <126 mg/dL but HbA1c is ≥6.5%) then the test which was in the diabetic range will be repeated using a fresh blood sample. If both FPG and HbA1c meet criteria for diabetes, or the two separate tests are concordant (FPG ≥126 mg/dL or HbA1c ≥6.5% on two occasions), the participant will be recorded as developing diabetes and be notified. They will be referred to their primary care provider for management and will come off-study.

Insulin resistance will be measured using the homeostatic method assessment for insulin resistance (HOMA-IR; fasting insulin (microU/L) x FPG (nmol/L)/22.5) and IGFBP-1 (a measure of insulin sensitivity strongly correlated with euglycemic insulin clamp testing).[29] Measures for an individual participant at weeks 12 and 24 will be compared to baseline.

4.2.3 Exploratory Outcomes of PREDM

Diabetes development over time

Although we anticipate few, if any, survivors will develop diabetes during the 24-week trial period, we would like to follow over time. In order to do so, we will monitor PREDM participants at any SJLIFE core assessment or other return visit that includes a measurement of weight and fasting blood work (FPG and HbA1c) for development of diabetes. SJLIFE core assessments typically occur every 3-5 years, however some participants return for specific studies sooner. We acknowledge that this will not capture all events in real time as some survivors may not seek medical care regularly and diabetes may remain undiagnosed.

Anthropometrics

- Weight
- BMI
- Body fat % by skin calipers will be calculated from assessment of skinfold fat using the 3-site method from Jackson-Pollack for men[41] (measured at chest, abdomen and thigh) and women[42] (measured at triceps, suprailiac and thigh). This method has been found to be highly correlated with body fat percentage by dual-energy x-ray absorptiometry in childhood cancer survivors.[43]
- Abdominal circumference (cm): measured at the midpoint between the lowest rib and the upper border of the iliac crest
- Hip circumference (cm): measured at the level of the pubic symphysis and the greatest gluteal protuberance
- Waist-to-Hip Ratio

Physical activity and frailty measures

- Self-reported physical activity reported using National Health and Nutrition Survey Physical Activity Questionnaire,[44] administered as part of SJLIFE Core assessment on Day 0 (baseline) and then at study visits on week 12 and 24. Change from baseline for an individual participant will be assessed.

Physical activity: Physical activity will be monitored by accelerometer using an Actigraphy which will be sent to participants following screening assessments before starting study drug and prior to, week 12 and 24 campus visits. The accelerometer will collect 7 consecutive days of physical activity data while the participant is in their home/routine setting. They will receive an accelerometer with written instructions, programmed to begin recording 12:01 a.m.. We have successfully used this method to collect physical activity data on over 2000 members of the SJLIFE cohort in other studies (R01CA174851; R01CA132901); many participants will be familiar with this data collection strategy. Wearing

instructions are explained in writing and provided verbally over the phone. The device is programmed to detect and record magnitude of acceleration or "intensity" of movement. Data are stored in memory as "counts" per time interval. We will use a one minute time interval or "epoch." An elastic belt with an adjustable Velcro closure and/or a belt clip will be provided. Participants will be instructed to wear the monitor at the right hip during waking hours. The device is removed for swimming and bathing. Accelerometer data will be converted into kilocalories. Males with <383 kcal per week and females with <270 kcal per week will be classified as having low activity.[33] Change from baseline for an individual participant will be assessed.

Table 4. Gender and height specific cut-points for walking speed

Males		Females	
Height	Cut-point to walk 15 feet	Height	Cut-point to walk 15 feet
≤173 cm	≥7 seconds	≤159 cm	≥7 seconds
>173 cm	≥6seconds	>159 cm	≥6 seconds

- Walking speed: Participants will be asked to walk as fast as possible for 50 feet. The time to complete the distance will be recorded in feet per seconds. This will be measured at day 0 (baseline) and then at study end (week 24). Change from baseline for an individual participant will be assessed. An abnormal walking speed will be defined by gender- and height- specific cut points for time to walk 15 feet described by Fried in her aging cohort (Table 4).[33]

- Hand grip strength: Hand grip strength in kilograms will be measured using a Jamar hand held dynamometer (Sammons Preston Rolyan, Nottinghamshire, UK). Participants will be seated with the shoulder at 0-10 and the elbow in 90 degrees of flexion. The forearm will be positioned in neutral. Each participant will complete three trials, the average used for analysis.[45,46] BMI specific cut points for strength, described by Fried in her aging cohort (Table 4),[33] will be used to classify those with muscle weakness.

Table 5. BMI-specific cut points for muscle weakness

Males		Females	
BMI (kg/m^2)	Cut-point (kg)	BMI (kg/m^2)	Cut-point (kg)
≤24	≤29	≤23	≤17
24.1-26	≤30	23.1-26	≤17.3
26.1-28	≤30	26.1-29	≤18
>28	≤32	>29	≤21

- Exhaustion/fatigue: Self-reported exhaustion will be assessed by scoring the Vitality Subscale of the Medical Outcomes Survey Short Form-36 (SF-36), which is part of the SJLIFE Home Survey. The SF-36, Version 2,[47] a widely used generic health profile appropriate for use with adults of all ages, has extensive age- and gender-specific norms for the US. The SF-36 provides subscale scores for 8 domains of health-related quality of life, including Vitality. Individuals with scores ≤40 on the Vitality subscale will be classified as having exhaustion/fatigue.
- Low lean muscle mass: Determined using body fat % to calculate lean mass as (1-(body fat %/100))*total mass (kg). This value will then be used to determine the relative lean muscle mass: lean mass (kg)/height in meters squared. Individuals with a relative lean mass ≤ 1.5 standard deviations below age-, sex-, and race-specific values from the National Health and Nutrition Examination Study (NHANES) will be classified as low lean muscle mass.[48] Of note, the NHANES study utilized calculations based on Dual x-ray absorptiometry and height.

Cardiovascular risk factors

- Lipids: Total cholesterol, HDL, LDL, Triglycerides
- Blood pressure

Health-related quality of life (HRQOL)

- Assessed by Medical Outcomes Short Form 36, SF-36

Participations/Engagement with lifestyle change application

- We will also collect information from the app-based platform on user engagement/participation as proportion of days the app was accessed, time spent in the app, food-tracking, digital coach interaction, peer-to-peer interaction, activity logging and weight logging because engagement with a digitally-delivered diabetes prevention program, such as lesson completions, have been demonstrated to predict success.[30]

Motivation to change

- Motivation to change will be assessed at screening visit using a 4 question survey (Appendix V)

Barriers to medication adherence and lifestyle change participation

- Barriers and facilitators to medication adherence will be assessed at 24-week visit using a modified version of the PETiT questionnaire (Appendix VI)
- Barriers and facilitators to participation will be assessed at 24-week visit using a questionnaire developed from previously identified categories of barriers to participation in healthy behavior change (Appendix VI)

5.0 TREATMENT PLAN

5.1 Treatment

Eligible subjects who meet inclusion criteria will be enrolled on study at Screening/Day 0. Study assessments included in the SJLIFE Core visit and study specific laboratory assessments will be completed at the screening visit including body fat percentage using skin calipers, abdominal circumference, hip circumference, SF-36 vitality subscale, walking speed and hand grip strength. Participants will be given a test dose of metformin ER (500 mg) and monitored for any adverse effects of medication for 1 hour in clinic by the study team. The dose will be administered after a meal or snack. At the study visit they will be dispensed the study drug and enrolled on the digital lifestyle 5.2 change program. A username will be selected by the study participant with the option to choose from a number of study team generated user names to provide anonymity for the study participant during group sessions.

On Day 1, participants will begin their digital lifestyle intervention using their smart-phone application with their lifestyle coach and peer group. On the same day, they will also begin metformin ER 500 mg daily for 14 days, taken after the evening meal. The 14-day supply will include additional tablets to prevent days off medication while titration occurs. Day 1 will occur at least 7 days (to allow for baseline physical activity data collection) and up to 28 days after screening assessments and participants will be notified of the start date based on assignment to a lifestyle intervention group.

On day 14, participants will be contacted by phone (+/- 4 days, day 10 to 18) and adherence assessed using virtual pill counts via phone calls, the protocol will be adapted from Kalichman et al.[39], and symptoms assessed using the Global Rating of Side Effects Burden (Appendix II), which includes the CTCAE v5.0 grading of events. After this call, if there are no signs or symptoms of adverse events, metformin ER dose will be increased to 1000 mg daily and mailed to participant.

At weeks 4, 8, 16 and 20 a phone-based pill count for adherence and adverse event symptom log will be completed and study medication dispensed.

At week 12 (interim assessment) and 24 (study-end), the participant will return to St. Jude Children's Research Hospital (SJCRH) for an in-person assessment to include

history and physical examination (weight, BMI, blood pressure, anthropometric measures, walking speed (week 24 only), hand-grip strength (week 24 only)), fasting blood work (FPG, HbA1c, insulin, IGFBP-1, CMP, CBC, lactate, cystatin C, lipid panel, pregnancy test if appropriate), adherence assessment by pill-count (all medication dispensed from past 12 weeks will be assessed to monitor for adherence over the prior 4 weeks and verify virtual assessments), NHANES-PAQ for self-reported physical activity, SF-36 for HRQOL and frailty measure of exhaustion which uses the vitality subscale, and CTCAE for adverse event grading will be completed. Accelerometer will be mailed at least 10 days prior to the on campus visit for collection of physical activity data.

The digital lifestyle change program will complete at week 24. We will collect data on lesson completion, self-reported weight, food logging, activity logging, participation with coach messages, participation with peer groups, dates and frequency of app access, and time spent in application.

The lifestyle change program includes dietary change with a goal to target 5% weight loss (among participants with a BMI $\geq$22 kg/m^2) and at least 150 min/wk. moderate intensity physical activity (brisk walking, biking, swimming, etc.) using a digital, app-based platform that includes a lifestyle coach who helps facilitate a core-curriculum focused on diet, exercise and behavioral strategies for goal setting and self-monitoring. Weight loss in this pilot would be a goal for participants with BMI $\geq$22 kg/m^2; however, dietary change, increased lean muscle mass and increased physical activity are desirable for all survivors. Participants will complete the remote, digitally-delivered core-curriculum, over 24 weeks with adherence measured by completion logs as well as monitoring of physical activity both by self-report (NHANES-PAQ) and accelerometer data.

5.2 Dose Modifications

All patients will be assessed throughout the 24 weeks of the study with assessment at weeks 2, 4, 8, 12, 16, 20 and 24 time-points. If a severe adverse event occurs at any time, a formal review will occur.

It is the responsibility of the Principal Investigator to oversee the safety of the study. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted below, as well as implementation of data and safety-monitoring. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

Renal dysfunction

Consideration to hold metformin should be made if a research participant's serum creatinine and cystatin C indicates a decline in renal function to an eGFR < 45mL/min due to possible increase in risk for lactic acidosis in the setting of severe renal impairment. Metformin peak and systemic exposure was 27% and 61% greater, respectively in mild renal impaired and 74% and 2.36-fold greater in moderate renal impaired patients as compared to healthy subjects. (from Highlights of prescribing information PDF)

Hepatic dysfunction

Consideration to hold metformin should be made if a research participant develops severe hepatic dysfunction (AST/ALT >3 times ULN, cirrhosis or other signs of synthetic dysfunction).

Lactic acidosis

Metformin will be held and best medical supportive care advised if lactic acidosis (serum lactate >4 mmol/L) or hyperlactatemia with elevation in lactate of ≥2 mmol/L from baseline values.

Gastrointestinal symptoms

Gastrointestinal AE including diarrhea, nausea, vomiting, flatulence and bloating are common with metformin. Diarrhea is the most common AE followed by nausea. If participants report CTCAE grade 2 diarrhea or nausea, consider reducing metformin ER to 500 mg daily (reassess titration of metformin to 1000 mg daily in 14 days). If at any time a participant develops grade 2 vomiting or grade 3 diarrhea or nausea (requires hydration or hospitalization to treat or maintain nutrition), metformin should be temporarily held, and, if felt to be due to metformin (no alternative explanation such as gastroenteritis etc.) metformin should be descalated (to 500 mg daily if currently at 1000 mg daily) upon resolution of symptoms or discontinued if dose is at 500 mg daily. See Deescalation and Rechallenge below.

Imaging or surgical procedures utilizing iodinated contrast

Due to the possibility of iodinated contrast to impair renal function, participants will be advised to stop metformin the day prior to any imaging procedure requiring iodinated controls if eGFR at baseline is <60 mL/min or they have a history of stable heart failure or hepatic dysfunction that was not classified as severe. If intraarterial contrast is used, participants will be advised to stop metformin the day prior to procedure regardless of other organ system function. If procedure is uncomplicated and the does not require admission, the patient can resume metformin 48 hours after procedure completion, otherwise they will remain off metformin until their case is reviewed by the study team and they are contacted.

Hospitalization

Due to the increased likelihood of acute onset renal dysfunction, need for imaging requiring iodinated contrast materials, and/or initiation of new medications, participants will be instructed to contact study staff with any hospitalization and that metformin should be discontinued during any hospitalization. Fortunately, as a large portion of the adult population admitted to US hospitals take metformin or other glucose reducing medications, it is common practice for physicians to review and often discontinue these medications at the time of hospitalization.

Excessive alcohol intake

Participants will be ineligible if they report alcohol abuse. Alcohol abuse will be defined as a score ≥13 in women and ≥15 in men (Appendix). Alcohol potentiates the effect of metformin on lactate metabolism. Participants will be warned against excessive alcohol intake while receiving metformin. Consider discontinuation of metformin, during history if it becomes apparent that participants have increased alcohol intake during the study period.

De-escalation and Rechallenge: If at any time during the study the participant is determined to require metformin to be held for reasons of toxicity or side effects (see those documented above) the following plan for de-escalation and rechallenge will be followed. If metformin is held for severe gastroinstestinal toxicity (see above) and the dose is at 1000 mg ER daily and toxicity felt to be likely or possibly due to metformin, the participant will have metformin held until symptom resolution or for a minimum of 3 days and will then be re-challenged with 500 mg metformin ER daily. If a participant develops severe gastrointestinal toxicity at 500 mg metformin ER daily and it is felt to be likely or possibly due to metformin and metformin is held, they will not be rechallenged. If a participant develops moderate toxicity including gastrointestinal CTCAE grade 2 diarrhea or nausea, the participant will be encouraged to continue the current dose and symptoms will be closely monitored as the expectation is that they will develop tolerance to gastrointestinal side effects with continued, consistent dosing and symptoms will improve or resolve; however, if they require a dose de-escalation from 1000 mg, they will be taken to 500 mg. If after 2 weeks, they have no or mild gastrointestinal symptoms, they will be re-challenged at 1000 mg. If participants require de-escalation of dosing x 2, they will remain at the highest tolerated dose of 500 mg. For this study, we will not use an intermediate dose of 750 mg metformin ER, however, this is a consideration for a future, large scale study if we find that 1000 mg ER is not well tolerated in our population.

Missed doses: Participants will be asked to take a daily dose of metformin ER, as detailed above. The goal is to take this dose
Monitoring for toxicity: Safety will be evaluated in this study through the monitoring of all serious and non-serious AEs, defined and graded according to

NCI CTCAE v5.0. Participants will be assessed for safety (including laboratory values) according to the specified study evaluations and time points beginning week 1 and ending at the time of study completion (week 24). General safety assessments will include serial interval histories, physical examinations, and specific laboratory studies, including serum chemistries, lactate and blood counts. All adverse events and serious adverse events whether volunteered by the subject, discovered by study personnel during questioning, detected through physical examination, clinically significant laboratory test, or other means, will be recorded. Each recorded adverse event or serious adverse event will be described by its duration (i.e., start and end dates), severity, regulatory seriousness criteria suspected relationship to the investigational product(s), the event outcome, and any actions taken. All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself. Protocol specific data and adverse events will be documented in the medical record and entered into the SJCRH Trials Database.

The study team consisting of the study PI (Dixon), study coordinator, protocol nurse, and the study statistician (Srivastava) will be responsible for monitoring the data and safety of this study, including implementation of stopping rules (see section 12.2) for safety and feasibility. Any symptoms that occur while on study will be managed according to good medical practice. Participants will complete a symptom log at the time of each telephone-encounter with the study team (weeks 2, 4, 8, 16 and 20) and during in-person assessments (weeks 12 and 24), which will be reviewed by the study team.

Decreased B12 serum was observed in approximately 7% of patients with previously normal levels prior to participation in clinical trials of 29-week duration with metformin HCl tablets. However, this vitamin deficiency, can sometimes be a contributing factor in mild anemia, although typically rapidly reverse after stopping metformin. We will monitor participants' blood levels for anemia and will determine if they will need to come off study and be referred to their primary physician.

5.3 Definitions of Toxicity

Gastrointestinal side effects including diarrhea and nausea ≥ grade 3 or vomiting ≥ grade 2 would be unexpected with metformin and, if attributable to the study drug, would result in a decrease in dose or discontinuation of the drug.

Lactic acidosis with lactate >4 mmol/L will result in discontinuation of metformin. If lactic acidosis is determined to have resulted from an alternate cause, resumption of metformin may be considered after the acute event resolves.

We know metformin adherence can be associated with gastrointestinal symptoms, however, this rarely results in medication discontinuation in prior studies (~5%), therefore discontinuation of metformin in 10% or more of participants due to gastrointestinal symptoms will be considered unacceptable. Therefore, the trial will

be stopped if 5 or more among the first 20 survivors or 8 or more among the total 41 discontinue metformin due to toxicity. These stopping rules are based on exact 95% lower confidence bounds for the probability of failure.

5.4 Concomitant Therapy

Drugs Affecting Glycemic Control:

A number of drugs are known to be associated with impaired glucose tolerance and may impact efficacy of metformin. Although risk of adverse events following concomitant administration has not been demonstrated in clinical trials, the impact of metformin on glucose control may be modified if these medications are initiated during the course of the study. These medications include: thiazides and other diuretics, calcium channel blockers, beta blockers, proton pump inhibitors, tyrosine kinase inhibitors, corticosteroids, thyroid products, phenothiazines, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics (including beta blockers), isoniazid and iodinated contrast materials. Although many anti-hypertensive medications and HMG-CoA reductase inhibitors (statins) may potentiate the risk for diabetes, their coadministration is not a contraindication to trial initiation. Rather, new medications prescribed during the study that may impact blood glucose control must be carefully documented and evaluated prior to outcome reporting.[49-51]

Iodinated Contrast Materials:

Iodinated contrast materials are widely used for a variety of imaging procedures. However, they carry a risk for contrast induced nephropathy (CIN), which could significantly impair renal function. In this scenario, the risk of metformin accumulation, due to ineffective renal clearance, and subsequent lactic acidosis is increased. This is particularly relevant for individuals on metformin with baseline mild- to moderate- renal dysfunction.[50] Therefore, metformin will be held on the day of any imaging procedure requiring iodinated contrast and will not be resumed for at least 48 hours after administration and after a serum creatinine level demonstrates an eGFR of at least 30 mL/min/m^2.

Drugs that Reduce Metformin Clearance including Cationic Drugs:

Caution should be used with coadministration of drugs that interfere with common renal tubular transport systems (organic cationic transporter-2, OCT-2, and multidrug and toxin extrusion, MATE, inhibitors) that are involved with renal elimination of metformin as there is a potential increase in risk for lactic acidosis due to increased exposure to metformin. However, this risk has not been demonstrated in clinical trials, and there will be no effort to exclude concurrent therapy with these drugs. These include cationic drugs eliminated by renal tubular secretion (amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, vancomycin), which have a theoretical potential to compete with metformin for common transport systems. Risk increases

with higher doses of metformin (maximum dose of metformin ER is 2000 mg) or decreased renal function, however, the specific dosage level these effects may begin to be observed has not been determined or was not available. These risks are theoretical, however, in patients with renal dysfunction, consultation with a pharmacist regarding risk and need for reduced dosing of metformin will occur for any potentially eligible participants taking one of the following medications: Cimetidine, Ranitidine, Proton Pump Inhibitors (PPIs), Trimethoprim, Cephalexin, Dolutegravir, Pyrimethamine, Ranolazine, Vandetanib, Imatinib, Nilotinib, Gefitinib, Erlotinib, Atenolol, or other cationic drugs including but not limited to (amiloride, digoxin, morphine, procainamide, quinidine, quinine, triamterene, vancomyocin).[50,51]
Carbonic Anhydrase Inhibitors:
Caution should be used with concurrent use of topiramate, zonisamide, acetazolamide or dichlorphenamide as these medications often cause a decrease in serum bicarbonate and subsequent non-anion gap, hyperchloremic metabolic acidosis. Therefore, concomitant use may increase the risk for lactic acidosis. Consider increased monitoring if participant is using these agents and has low serum bicarbonate at baseline.[52,53]

Insulin Secretagogues or Insulin:

Co-administration of metformin with other agents used for diabetes control that lower blood glucose levels increases the risk for clinically significant hypoglycemia. Participants with diabetes at baseline are ineligible to participate and those who develop diabetes will be removed from the study. As a result, no participants should be co-administered other hypoglycemic agents used in diabetes management while enrolled on this protocol. Appendix contains disallowed drugs list and drugs that will be tracked on study.

5.5 Supportive Care

All participants will be advised regarding the risk of metformin use in the setting of new onset renal dysfunction, heart failure, liver failure, excessive alcohol use and at the time of studies utilizing iodinated contrast. Participants will be advised to contact the study team if they are hospitalized for any reason or if they are notified of new changes to their health status. However, these relative contraindications to metformin use are well known in the medical community and all participants should receive care as per best medical practice. As metformin is a commonly used medication for the treatment of diabetes and its prevention, and participants are not blinded to their receipt of metformin, they should notify any medical provider responsible for their care of their metformin use at the time of any routine or emergent healthcare encounter.

6.0 DRUG INFORMATION

METFORMIN (Brand Name™ D-Care DM2 [DSC]; Fortamet; Glucophage; Glucophage XR; Glumetza; Riomet; Riomet ER)

Source and Pharmacology: Metformin hydrochloride tablets, USP contain the antihyperglycemic agent Metformin, which is a biguanide, in the form of monohydrochloride. The chemical name of Metformin hydrochloride is N,Ndimethylimidodicarbonimidic diamide hydrochloride. Metformin hydrochloride, USP is a white to off-white crystalline compound with a molecular formula of C H N • HCl and a molecular weight of 165.63. Metformin hydrochloride is freely soluble in water, slightly 4 11 5 soluble in alcohol, practically insoluble in acetone and in methylene chloride. The pKa of Metformin is 12.4. The pH of a 1% aqueous solution of Metformin hydrochloride is 6.68. Metformin hydrochloride tablets, USP contain 500 mg, 850 mg, or 1000 mg of Metformin hydrochloride, which is equivalent to 389.93 mg, 662.88 mg, 779.86 mg Metformin base, respectively. Each tablet contains the inactive ingredients povidone (K-30), povidone (K-90), pregelatinized starch, and magnesium stearate. In addition, the coating for the tablets contains artificial blackberry flavor, hypromellose, macrogol and titanium dioxide.

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes mellitus, lowering both basal and postprandial plasma glucose. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. With Metformin therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may decrease.

Formulation and Stability: Metformin is available as an oral immediate release solution (100mg/mL), an oral extended release suspension (100mg/mL), 500 mg, 850 mg and 1000 mg immediate release tablets, and 500 mg and 750 mg extended release tablets. The immediate release oral solution should be stored at 15^{o}C to 30^{o}C (59^{o}F to 86^{o}F). The extended release oral suspension should be stored at 20^{o}C to 25^{o}C (68^{o}F to 77^{o}F) with excursions permitted to 15^{o}C to 30^{o}C (59^{o}F to 86^{o}F). Any unused portion of the reconstituted extended release oral suspension should be discarded after 100 days. Tablet formulations should be stored protected from light and moisture at 20^{o}C to 25^{o}C (68^{o}F to 77^{o}F) with excursions permitted to 15^{o}C to 30^{o}C (59^{o}F to 86^{o}F).

Supplier: Commercially available

Toxicity: Toxicities include chest discomfort, flushing, palpitations, chills, dizziness, headache, taste disorder, diaphoresis, nail disease, skin rash, decreased

vitamin B12 serum concentrate, hypoglycemia, abdominal distention, abdominal distress, abdominal pain, abnormal stools, constipation, diarrhea, dyspepsia, flatulence, heartburn, nausea, nausea and vomiting, infection, myalgia, weakness, flu-like symptoms, rhinitis, upper respiratory tract infection, accidental injury. Rare but important or life-threatening toxicities include hepatic injury (cholestatic, hepatocellular, and mixed), and lactic acidosis.

Dosage and Route of Administration: 500 mg dose/day to be taken orally, increased to 1000 mg dose/day at day 14 throuhg week 24. The dose should be taken immediately following the evening meal and at approximately the same time daily (i.e. immediately following dinner each night). If a dose is forgotten, it should be taken within 4-6 hours of the originally planned dose; however, if the next dose is due to be administered in <12 hours from the current time, the forgotten dose should not be taken (i.e. a forgotten dinner dose may be taken later in the evening before bed but should not be taken the following morning with breakfast and then again that evening with dinner). If a dose is missed and cannot be made up (it is past bedtime/midnight on the night of the missed dose) this dose will be skipped. Participants should not take 2 doses within the same calendar day and should avoid taking 2 doses within a 12 hour period (ie 10 pm on Friday evening and then 7 am on Saturday morning).

6.1 Drug Distribution

Metformin extended release will be ordered by the study team at 500 mg daily (a 14 day supply) for each participant at the time of study enrollment and will be distributed to that participant by the St. Jude pharmacy during their time on campus. At the time of dose escalation (study day 14) and study visits conducted via phone (week 4, 8, 16 and 20), refills of metformin extended release 1000 mg daily (or reduced dose for gastrointestinal complications) will be dispensed in a 28 day supply and mailed by the St. Jude pharmacy. On week 12, metformin extended release 1000 mg daily for 28 day supply will be dispensed during the study visit. To prevent missed doses during any delay of study visits or mailing, 7 additional doses will be dispensed with each refill. Participants will be asked to bring all study drug with them at the time of return visits (weeks 12 and 24). After pill count, any remaining metformin extended release will be returned to St. Jude Pharmacy for destruction.

7.0 REQUIRED EVALUATIONS, TESTS, AND OBSERVATIONS

7.1 Screening Evaluations

All entry/eligibility studies will be performed at the SJLIFE core visit including study-specific labs (lactate, IGFBP-1 level). Participants age 18-<45 years with prediabetes at last SJLIFE visit will be screened for potential eligibility by chart review performed by study team and potentially eligible participants will be contacted at least 2-3 weeks prior to their schedule SJLIFE core visit. If no exclusion criteria are identified at the PREDM consent visit and participants are willing, they will be consented. If eligibility is confirmed during SJLIFE visit based on examination and labs, the participant will be enrolled to receive study interventions. An accelerometer will be sent to them after their SJLIFE campus visit in order to monitor physical activity in their home environment for 7 days. If, due to split core visit or other reason, baseline data including labs have been performed >30 days participants will need to have studies repeated before starting on study drug/participating in digital lifestyle change program.

Table 6. Screening Evaluations	**prior to starting study drug**
History and physical exam with height (cm), weight (kg), and VS including resting blood pressure	X
Anthropometrics including body fat percetaage using skin fold calipers, abdominal circumference, hip circumference	X
Laboratory Studies, performed fasting: CBC, CMP (includes fasting plasma glucose), hemoglobin A1c, insulin level, IGFBP-1, lactate/lactic acid level, cystatin C, lipid panel	X
Walking speed	X
Hand grip strength	X
Accelerometer	X
*Pregnancy Test	X
HRQOL (SF-36) including Vitality subscale	X
NHANES-PAQ	X
Symptom Log: Global Rating of Side Effects Burden, includes CTCAE	X

Motivation to change assessment	X

*The St. Jude IRB requires that a female patient of childbearing potential must have a negative pregnancy test as a condition of clinical research eligibility.

7.2 Evaluations During Therapy

REQUIRED EVALUATIONS, TESTS, AND OBSERVATIONS

Table 7. Therapy Evaluations	**Week 2** +/- 4 days	**Week 4** +/- 7 days	**Week 8** +/- 7 days	**Week 12** +/- 7 days	**Week 16** +/- 7 days	**Week 20** +/- 7 days	**Week 24/ Off Study** +/- 7 days
History including medications				X			X
Physical Exam (Ht, Wt, VS)				X			X
Anthropometrics: body fat %, abdominal circumference, hip circumference				X			X
Fasting blood work: CBC, CMP, HbA1c, insulin, IGFBP-1, lactate, cystatin C, lipid panel				X			X
Walking speed							X
Hand grip strength							X
Accelerometer (mailed prior to visit)				X			X
*Pregnancy Test				X			X
HRQOL (SF-36)				X			X
NHANES-PAQ				X			X
Medication Adherence Assessment	X	X	X	X	X	X	X
Lifestyle Change Adherence Log	X	X	X	X	X	X	X
Symptom Log including CTCAE/Adverse Events	X	X	X	X	X	X	X
Barriers and facilitators to medication adherence and lifestyle change surveys							X

*The St. Jude IRB requires that a female patient of childbearing potential must have a negative pregnancy test as a condition of clinical research eligibility.

Obtain other studies as needed for good patient care.

Fasting labs must be obtained after an overnight fast (minimum of 8 hours). For all labs obtained as part of SJLIFE core assessment (CBC, CMP, cystatin C, insulin level, hemoglobin A1c, lipid panel), no changes in collection will be specified for this study. For IGFBP-1 level, this should be collected as a minimum of 1 mL whole blood in a red top tube. For lactate/lactic acid level, this should be collected as a minimum of 1 mL in a light green top tube. The sample will be placed on ice

and is stable for 2 hours. Samples will be collected at St. Jude and performed on site.

7.3 Response Evaluations

We will evaluate response at week 12, drawing fasting blood work including fasting glucose, HbA1c, IGFBP-1 and insulin, and measuring weight, anthropometrics, physical activity and HRQOL.

7.4 Off-Study Evaluations

Similar to response evaluations, we will evaluate response at study completion (week 24) by drawing fasting blood work including fasting glucose, HbA1c, IGFBP-1 and insulin, and measuring weight, anthropometrics, physical activity, HRQOL, walking speed and hand-grip strength.

7.5 Long-Term Follow-up Evaluations

We will monitor participants of PreDM at subsequent SJLIFE core assessments or any assessment including fasting labs (FPG and HbA1c) and weight for the development of diabetes. We will record this data, including diabetes diagnosis, date of diagnosis (either at SJLIFE assessment or validated diagnosis by medical records or lab reports at an outside site), FPG, HbA1c and weight. We will follow these participants for a period of up to 6 years to ensure all participants will have had the opportunity to return for another SJLIFE core assessment.

8.0 EVALUATION CRITERIA

8.1 Response Criteria

N/A

8.2 Toxicity Evaluation Criteria

The Global Rating of Side Effects Burden which includes the CTCAE v 5.0 grading of the National Cancer Institute will be utilized and can be found in Appendix II. Copies of the CTCAE versions can be downloaded from the CTEP home page (http://ctep.info.nih.gov) or from the St. Jude DocuShare home page.

8.3 Subject Compliance Monitoring

Participant adherence to metformin will be monitored by virtual pill counts conducted using a web-based meeting by the study team on week 2, 4, 8, 15 and 20, the protocol will be adapted from Kalichman et al.[39] In-person pill counts will be performed on weeks 12 and 24 to assess adherence for the prior 4 weeks and confirm virtual pill count assessments. Adherence to the lifestyle change program will primarily be assessed by review of the log of lesson completion at the time of study completion. We will also collect data on lesson completion, self-reported weight, food logging, activity logging, participation with coach messages, participation with peer groups, dates and frequency of app access, time spent in application.

9.0 OFF STUDY AND OFF THERAPY CRITERIA

9.1 Off study criteria

- Death
- Lost to follow-up
- Request of the Participant
- Discretion of the Study PI, such as the following:
  - The researcher decides that continuing in the study would be harmful
  - A treatment is needed that is not allowed on this study
  - The participant misses so many appointments that the data cannot be used in the study. Specifically, a participants data will not be evaluable for efficacy endpoints (secondary) if they are not assessed within 3 weeks of the end of therapy time point (24 week visit) and will not be evaluable for interim efficacy if they are not assessed within 3 weeks of the interim campus visit time point (12 week visit). However, because the primary aim of the study is feasibility, participants will not be taken off study for non-adherence or missed appointments, of course, drug will not be dispensed (and therefore they will be non-adherent to the metformin intervention) until contacted and adherence and adverse events assessed by the study coordinator.
  - The participant develops diabetes requiring additional treatment (if FPG ≥ 126 mg/dl but < 140 mg/dL or HbA1c ≥ 6.5% but <7.0% and the patient's PCP does not feel alternate therapy would benefit the patient they may remain on study as metformin + lifestyle change are typical first line diabetes management strategies)
  - New information is learned that a better treatment is available, or that the study is not in the participant's best interest
  - Completion of week 24 evaluations

9.2 Off therapy criteria

- Development of unacceptable toxicity during treatment
- Refusal of therapy
- Discretion of the Study PI, such as the following:
  - The researcher decides that continuing in the study would be harmful
  - A treatment is needed that is not allowed on this study
  - The participant misses so many appointments that the data cannot be used in the study. Specifically, drug will not be dispensed unless the participant is contacted and adherence assessed within the timepoints detailed in the study schema; however, participants will remain enrolled in the lifestyle change program throughout the duration of the study.
  - The participant develops diabetes requiring additional treatment (if FPG ≥ 126 mg/dl but < 140 mg/dL or HbA1c ≥ 6.5% but <7.0% and the patient's PCP does not feel alternate therapy would benefit the patient they may remain on study as metformin + lifestyle change are typical first line diabetes management strategies)
  - New information is learned that a better treatment is available, or that the study is not in the participant's best interest
  - Completion of week 24 evaluations

10.0 SAFETY AND ADVERSE EVENT REPORTING REQUIREMENTS

10.1 Adverse Events (AEs)

Adverse events will be monitored from the time of first study intervention or treatment. Participants will be instructed to report all AEs during the study and will be assessed for the occurrence of AEs throughout the study.

10.2 Definitions

Adverse Event (AE): Any untoward medical occurrence associated in a study participant after the first treatment or intervention on study. Adverse Events will be graded by the NCI CTCAE version 5.0.

Serious Adverse Event (SAE): Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or

- any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

10.3 Handling of Adverse Events (AEs) and Deaths

Recording of Adverse Events and Serious Adverse Events: Adverse events (AEs) will be evaluated and documented by the clinical staff and investigators through patient reports, phone-encounters and study visits. The study team will be responsible for reviewing documentation related to AEs and entering directly into the protocol specific database. The data to be recorded are 1) event description, 2) NCI CTCAE v5.0 code and grade, 3) onset date, 4) resolution date (or ongoing), 4) action taken for event, 5) patient outcome, 6) relationship of AE to protocol treatment and/or interventions, 7) if AE was expected (ie GI intolerance with metformin) or unexpected, and 8) any comments felt pertinent to AE.

Attribution of an adverse event
Not related – The lack of temporal relationship of the event to protocol treatment makes a causal relationship not reasonably possible, or other drugs/medications (prescribed or taken outside of this study), therapeutic interventions or underlying conditions provide a sufficient explanation.
Unlikely related – The temporal relationship of the event to the protocol treatment makes a causal relationship reasonably unlikely, and other drugs/medications (prescribed or taken outside of this study), therapeutic interventions or underlying conditions may not provide sufficient explanation for the event observed.
Possibly related – The temporal relationship of the event to the protocol treatment makes a causal relationship reasonably possible, and the event is more likely explained by exposure to the study drug or interventions than by other drugs/medications, therapeutic interventions or underlying conditions.

Reporting Adverse Events and Serious Adverse Events: The St. Jude PI, upon awareness of an event, will review adverse events to determine the seriousness of AEs (corrections will be made if applicable) and ensure that all SAEs and all Unanticipated Problems (UPs) are entered into the electronic submission system (iRIS) within 10 days. All AEs, serious or not, will be recorded in a log, spreadsheet, or report and submitted to the St. Jude IRB at the time of continuing review. The St. Jude Regulatory Affairs Office, upon receipt, reports SAEs on study to the FDA within mandated regulatory timelines per 21 CRF 312 or 812. For the purpose of safety analyses, all AE's that are classified as likely or possibly related will be considered treatment-related events.

Reporting of Unanticipated Problems (UPs): The St. Jude PI will refer to St. Jude Human Research Protection Program (HRPP) Policy 01.720 for specifics on

the reporting of unanticipated problems to the St. Jude IRB. The St. Jude IRB reports UPs to BIMO as per 21 CFR 56. The UP link follows: https://home.stjude.org/hrpp/Policies/01-720.pdf#search=unanticipated.

Deaths: All treatment related deaths and any unanticipated fatal or unanticipated life-threatening event judged by the study PI to be at least possibly due to the study treatment, will be reported to the FDA by telephone or fax as soon as possible but no later than seven calendar days after notification of the event and followed by a written safety report as complete as possible within eight additional days (ie. full report 15 calendar days total after notification of event). Unanticipated non-fatal and non-life-threatening adverse events that occur in on-study participants and that are considered due to or possibly due to the investigational agent, will be reported to the FDA by written safety report as soon as possible but no later than 15 calendar days of the notification of the occurrence of the event. Expected SAEs, even unexpected fatal SAEs, considered by the study PI to be not related to the study, will be reported to the FDA in the Annual Review Report along with non-serious AEs. All FDA correspondence and reporting will be conducted through the St. Jude Office of Regulatory Affairs. Copies of the correspondence to the St Jude IRB, including SAE reports, are provided to the St Jude Regulatory Affairs office by the St. Jude study team. FDA-related correspondence and reporting will be conducted through the Regulatory Affairs office.

10.4 Emergency Unblinding

N/A

11.0 DATA COLLECTION, STUDY MONITORING, AND CONFIDENTIALITY

11.1 Data Collection

St. Jude Clinical Research Associates or the site Study Coordinator will be responsible for data collection. Data from the participant's record will be entered directly into a secure study-specific database. Instructions for data entry are outlined in the database.
Data management will be supervised by the Principal Investigator (PI). Protocol-specific data and adverse events will be recorded in the electronic database within 2 weeks following the completion of a study visit (either by phone or on campus). All questions will be directed to the PI or designee and will be reviewed at regularly scheduled working meetings.

Regular summaries of toxicity and protocol events will be generated for the PI and the Department of Biostatistics to review.
The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial. All SAEs and protocol-defined events of special interest will be reported in an expedited fashion. Participants who have an ongoing study treatment−related adverse event upon study completion or at discontinuation from the study will be followed until the event has resolved to baseline grade, the event is assessed by the investigator as stable, new treatment is initiated, the patient is lost to follow-up, the patient withdraws consent, or until it has been determined that study treatment or participation is not the cause of the AE. All participants who receive any amount of study drug will be evaluable for toxicity. At each visit, a brief focused history will be obtained and any indication of treatment-related toxicity will be evaluated by appropriate examination and/or laboratory/radiographic studies. All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with their policies.

11.2 Study Monitoring

Moderate Risk

An application for IND exemption is being prepared for submission for the use of metformin in this study. In the event that the IND exemption is granted, monitoring of this protocol is considered to be Moderate Risk. However, if an IND exemption is not granted and this becomes a St. Jude sponsored, investigator-initiated IND pilot study, monitoring for this protocol would be considered in the High Risk 3 category. The risks of the products are still being explored, although the study drug has been widely utilized with an acceptable safety profile in diabetic and prediabetic adults, including those with comorbid conditions. Both monitoring for Moderate Risk and HR-3 studies are included below as the IND exemption has not yet been granted.

If an IND exemption is obtained, this study is considered moderate risk for monitoring purposes. Protocol and regulatory compliance, including essential regulatory documentation, will be assessed as well as the accuracy and completeness of data points related to the primary study objective semi- annually. If the study design has strata, accrual will be tracked continuously. The first two enrollees and then 10 % of participants will be monitored semi-annually.

The PI and study team are responsible for protocol and regulatory compliance, and for data accuracy and completeness. The study team will meet at appropriate intervals to review case histories or quality summaries on participants and retain copies of the minutes which are signed by the PI.

Clinical Trials Operations (CTO) will verify informed consent documentation of and eligibility status for 50% of trial participants within 5 days of enrollment. Additionally, A quality review will be performed by CTO personnel on 100% of St. Jude participants' informed consent forms to assure completeness.

Overall study conduct, compliance with primary objectives, age of majority consenting, safety assessments and reporting, and the timeliness and accuracy of database entries are monitored routinely. Study documents routinely monitored on selected participants include medical records, database entries, study worksheets, and case report forms. Study documents are monitored for participant status, demographics, staging, subgroup assignment, treatments, investigational drug accountability, evaluations, responses, participant protocol status, off-study and off-therapy criteria, and for all other specifics as detailed in a separate study-specific monitoring plan. The study-specific monitoring plan may be revised over time, to adapt monitoring frequency and/ or intensity to a changing environment when appropriate (for example: new safety signals; positive history of compliance; all participants are in long term follow-up; or the enrollment period has ended).

The recording and reporting of Adverse Events, Serious Adverse Events (SAEs), and Unanticipated Problems (UPs) to include type, grade, attribution, duration, timeliness and appropriateness will be reviewed by the Monitor/ CRM. The CRM will generate a formal report which is shared with the Principal Investigator (PI), study team and the Internal Monitoring Committee (IMC).

Continuing reviews by the Institutional Review Board (IRB) and Scientific Review Committee (CT-SRC) will occur at least annually. In addition, unanticipated problems are reviewed in a timely manner by the IRB.

High Risk 3 (HR-3)

If an IND is required and obtained, this study is considered high risk (HR-3) for monitoring purposes. Protocol and regulatory compliance, including essential regulatory documentation, will be assessed as well as the accuracy and completeness of all data points relating to the primary and secondary objectives semi-annually. If the study design has strata, accrual will be tracked continuously. The first two enrollees will be monitored and 15 % of the study enrollees thereafter, semi-annually.

The PI and study team are responsible for protocol and regulatory compliance, and for data accuracy and completeness. The study team will meet at appropriate intervals to review case histories or quality summaries on participants and retain copies of the minutes which are signed by the PI.

Clinical Trials Operations (CTO) will verify informed consent documentation and eligibility status on 100% of St. Jude participants within 5 working days of enrollment completion.

The Clinical Research Monitor (CRM) will perform a quality verification of select St. Jude participants during routine monitoring intervals (every 6 months). Overall study conduct, compliance with primary and secondary objectives, age of majority consenting, safety assessments and reporting, and the timeliness and accuracy of database entries are monitored routinely.

Study documents routinely monitored on selected participants include medical records, database entries, study worksheets, and case report forms. Study documents are monitored for participant status, demographics, staging, subgroup assignment, treatments, investigational drug accountability, evaluations, responses, participant protocol status, off-study and off-therapy criteria, and for all other specifics as detailed in a separate study-specific monitoring plan. The study-specific monitoring plan may be revised over time, to adapt monitoring frequency and/ or intensity to a changing environment when appropriate (for example: new safety signals; positive history of compliance; all participants are in long term follow-up; or the enrollment period has ended).

The recording and reporting of Adverse Events, Serious Adverse Events (SAEs), and Unanticipated Problems (UPs) to include type, grade, attribution, duration, timeliness and appropriateness will be reviewed by the Monitor/ CRM. The CRM will generate a formal report which is shared with the Principal Investigator (PI), study team and the Internal Monitoring Committee (IMC).

Continuing reviews by the Institutional Review Board (IRB) and Clinical Trials-Scientific Review Committee (CT-SRC) will occur at least annually. In addition, unanticipated problems are reviewed in a timely manner by the IRB.

11.3 Confidentiality

SJLife study numbers will be used in place of an identifier such as a medical record number. No research participant names will be recorded on the data collection forms. Information for this study will be collected during the evaluation at SJCRH, using physical measurements, lab assessments and standardized questionnaires in addition to by telephone or web-meeting encounters led by the study team. Information on cancer treatment has already been obtained from medical records abstracted as part of the SJLIFE study and will be linked to these new databases after participants have provided informed consent for this protocol. Data from the medical record abstraction, the physical and laboratory measurements and the questionnaires will be recorded by study personnel by participant identification number on optical recognition forms and downloaded daily into a dedicated study computer. All files will be password protected. Identifying information will be stored separately and the files linked by identification number. Study related data from participation in the digital lifestyle change program will be transferred weekly. Any paper forms will be stored in a locked file cabinet. Study personnel will have access to data only on a need to know basis. Data will be evaluated without identifiers for safety monitoring, process

evaluation and outcomes analysis, and linked to the identifying information only if necessary for participant safety.
The medical records of study participants may be reviewed by the St. Jude IRB, FDA, clinical research monitors, auditors, etc.

12.0 STATISTICAL CONSIDERATIONS

We will test our primary hypothesis, that a combined pharmacologic and lifestyle intervention using metformin extended release and a digitally-delivered, lifestyle change intervention program will be feasible and safe by our primary endpoints: adherence and the number of CTCAE v5.0 grade 1-4 adverse events. We will test our secondary hypothesis that a combined metformin and lifestyle intervention will improve measures of glycemic control and insulin resistance in prediabetic survivors by our secondary end points: change at week 24 from baseline of glycemic control (FPG and HbA1c) and insulin resistance (HOMA-IR using fasting insulin and IGFBP-1 level). In addition, we will assess the hypothesis that a combined metformin and lifestyle intervention will improve anthropometric measures, physical activity, and quality of life by our exploratory end points: change at week 24 from baseline of anthropometric measures, physical activity (self-reported and measured through walking speed and accelerometer data), cardiovascular risk factors (lipids and blood pressure) and HRQOL. The analyses of the secondary and exploratory outcomes will demonstrate preliminary efficacy data to move this study forward to a larger randomized trial.

Analytic plan:

Primary Objective - Establish the feasibility and safety of a combined metformin + intensive lifestyle intervention (using a digitally-delivered, lifestyle change program) among adult survivors with prediabetes.

Primary endpoints of this trial will be adherence to both the daily metformin administration, assessed by telephone-based (Appendix I) or in-person pill counts, and the lifestyle intervention, assessed by completion of required core-curriculum, and safety, assessed using the Global Rating of Side Effects Burden (Appendix II), which includes the Common Terminology Criteria for Adverse Events (CTCAE v5.0) grade. A single-arm pilot study was chosen as it would establish the necessary safety and feasibility data of the combined intervention to then move forward to a larger randomized clinical trial of comparative efficacy of the combined intervention vs either metformin or lifestyle intervention.

For this study, adult survivors age 18-<45 years with prediabetes will be the target population. There are two components to feasibility assessment using combined

adherence to metformin and the lifestyle change program. Adherence will be assessed on day 14 for metformin titration and then every 4 weeks (weeks 4, 8, 12, 16, 20 and 24. Metformin adherence will be monitored using telephone-based pill counts, the protocol will be adapted from Kalichman et al.[39] Adherence to the lifestyle change intervention will be assessed by completion of at least 60% of the educational lifestyle curriculum over the 24 week study period. Completion of each piece of educational content will be recorded within the digitally-delivered platform for each participant and then this data will be securely transferred and entered in the study specific database. A survivor would be considered to have met the combined adherence criteria if s/he takes 80% of the recommended drug and completes at least 60% of the digitally-delivered lifestyle change core curriculum.

Sample size and power: Because metformin has been demonstrated to be safe and well-tolerated in multiple population of adults with chronic health conditions,[17,20] as well as in non-obese diabetic populations,[54] and lifestyle change is the current recommended first line management for adults in the general population with prediabetes,[55] we do not anticipate significant safety concerns. Therefore, the sample size justification is based on the combined adherence to metformin and the intensive lifestyle change curriculum.

The study would be considered feasible if at least 60% of the survivors are adherent. However, adherence rates of less than 40% would be considered unacceptable. Note that, since survivors need to meet two criteria to be adherent, a slightly lower feasibility rate is acceptable.

Simon's two-stage design (1988) is used to test the null hypothesis $H_0: \pi =< 0.4$ vs. $H_1 : \pi \geq 0.6$. This design has a type I error rate of $\alpha = 0.05$ and power of 80%.

In the first stage, 21 survivors will be accrued. If there are 9 or fewer among these 21 who achieve at least 80% adherence to metformin and complete 60% of digital curriculum modules, the study will be stopped. Otherwise, 20 additional survivors will be accrued for a total of 41. The null hypothesis will be rejected if 22 or more survivors achieve at least 80% adherence to metformin and complete 60% of lifestyle change program among the total 41 survivors. This design yields a type I error rate of $\alpha=0.05$ and power of more than 80%.

Objective safety measures: The number of grade 1-4 toxicities (CTCAE v 5.0) will be tabulated. Any common gastrointestinal toxicity including diarrhea, nausea, flatulence, or bloating grade ≥3 or any other toxicity grade ≥2 will be considered abnormal. Discontinuation of metformin due to these side effects is rare and it is expected that less than 5% of the survivors will experience abnormal toxicity requiring medication discontinuation. Therefore, a rate of discontinuation >10% would be considered unacceptable. If among the first 20 survivors more than 5, and among 41 survivors, more

than 8 of them discontinue metformin due to toxicity, then the trial will be stopped. These stopping rules are based on the exact 95% lower confidence bounds for the probability of failure.

Secondary and Exploratory Objectives:

Assess preliminary evidence for efficacy of the combined metformin + intensive lifestyle intervention on glycemic control and insulin resistance. Glycemic control will be measured by fasting plasma glucose (FPG) and hemoglobin A1c (HbA1c) and insulin resistance measured by the homeostatic model assessment (HOMA-IR: fasting insulin (microU/L) x FPG (nmol/L)/22.5) and IGFBP-1.

Detectable difference of mean for paired data:

Data from the landmark Diabetes Prevention Program (DPP) study in the general adult population demonstrated that at 6 months after randomization, the change in fasting plasma glucose in the placebo group was <1mg/dL increase while that in the metformin and lifestyle groups were 4-5 mg/dL decrease. While the change in HbA1c from baseline was approximately a 0.06% increase in the placebo group and a 0.04-0.08% decrease in the metformin and lifestyle groups.[12] Based on preliminary date from prediabetic adults in the SJLIFE cohort, the mean and standard deviation of HbA1c%, FPG in mg/dL and HOMA-IR are known (Table 6). Based on sample size 41 with 80% power, standard deviation of the difference and additional assumptions of i) variability of hemoglobin A1c, fasting plasma glucose and HOMA-IR considered to be the same at the baseline and the 6-month follow-up at the end-of-study visit and ii) there is at least a 0.5 correlation between values at the baseline and the follow-up, this study would be powered to detect an approximately 4 mg/dL change in FPG, 0.2% change in HbA1c and 2 unit change in HOMA-IR. Detectable differences for key secondary outcomes are provided in the Table 6.

Table 8. Detectable differences for glycemia and insulin resistance

	Mean (SD) at baseline	Detectable difference of mean for paired data
HbA1c, %	5.59 (0.34)	0.15
Fasting plasma glucose, mg/dL	101.74 (8.62)	3.92
HOMA-IR	4.92 (4.41)	2.00

The measurements of glycemic control and insulin resistance will be collected at baseline, week 12 and week 24. The primary focus will be the change in these measures from baseline to study end (week 24). The measurements at baseline and 24 weeks are denoted by Y_1 and Y_2, respectively, then $D_i = (Y_{2i} - Y_{1i})$ for i=1,2,…,n denotes the differences for *n* survivors. We will test whether the mean difference is different from 0 (*i.e.* test the hypothesis $H_0:\mu_D=0$ vs. $H_1:\mu_D\neq0$), where μ_D denotes the population mean of

the differences. For each outcome measure (FPG, HbA1c, HOMA-IR, IGFBP-1), we will obtain the difference D_i for i=1,2, …,41 and then we will assess if the mean differences are significantly different from 0 using a one-sample t-test. We will also conduct analyses to determine whether the effect of the combined intervention is noticeable at week 12. In a similar manner, as discussed above, we will take the differences between week 12 and baseline observations.

In addition, since we will have observations at three time points, we will also use a Generalized Estimating Equations (GEE) approach to assess the pattern of change over time using PROC GENMOD in SAS 9.4 and using compound symmetry as the working covariance structure to account for correlation among repeated observations.

The exploratory outcomes of weight, body fat %, cholesterol and triglyceride measures, systolic blood pressure (SBP), diastolic blood pressure (DBP), physical activity (NHANES-PAQ score, measured activity by accelerometer data and walking speed) and HRQOL will also be assessed at baseline, week 12 and week 24 and, in the case of frailty measures (walking speed, hand grip strength, lean muscle mass, exhaustion and low activity) at baseline and week 24. Similar to the secondary outcomes above, the mean difference from baseline to week 24 (and then week 12) in the outcome measures will be assessed using a one sample t-test to determine if the mean difference for each outcome is significantly different from 0.

12.1 Anticipated Completion Dates

Anticipated Primary Completion Date: December 2022
Anticipated Study Completion Date December 2022

12.2 Summary of Primary and Secondary Objectives

Objective #	Objective Type	Analysis #	Resp Party	Stat	Safety	Analysis Measure	Analysis Title	Data Collection Time Frame	# of Participants
1.0	P	1	SBD	DK, SMS	N	Combined metformin and lifestyle adherence, proportion of metformin pills taken and proportion of lifestyle curriculum completed	Assess adherence to combined metformin and lifestyle change intervention	Weeks 2, 4, 8, 12, 16, 20, and 24	41
1.0	P	2	SBD	DK, SMS	Y	Safety of combined intervention, CTCAE graded adverse events	Assess safety of combined intervention		41
2.0	S	1	SBD	DK, SMS	N	Glycemic control (FPG, HbA1c), change in FPG, HbA1c from baseline	Effect of intervention on glycemic control	Baseline, weeks 12, 24	41
2.0	S	2	SBD	DK, SMS	N	Insulin resistance (HOMA-IR, IGF-BP1), change in HOMA-IR, IGF-BP1 from baseline	Effect of intervention on insulin resistance	Baseline, weeks 12, 24	41
3.0	S	1	SBD, KN	DK, SMS	N	Anthropometrics, change in weight, BMI, body fat % and waist-to-hip ratio from baseline	Effect of intervention on weight and other anthropometric measures	Baseline, weeks 12, 24	41
3.0	S	2	SBD, KN	DK, SMS	N	Physical activity, change in self-reported and accelerometer measures of physical activity from baseline	Effect of intervention on physical activity	Baseline, weeks 12, 24	41
3.0	S	3	SBD	DK, SMS	N	Blood pressure, change in SBP and DBP from baseline	Effect of intervention on blood pressure	Baseline, weeks 12, 24	41
3.0	S	4	SBD	DK, SMS	N	Lipid profile, change in lipid profile from baseline	Effect of intervention on lipid profile	Baseline, weeks 12, 24	41
3.0	S	5	SBD, KN	DK, SMS	N	Frailty, change in frailty measures from baseline	Effect of intervention on measures of frailty	Baseline, week 24	41
3.0	S	6	SBD	DK, SMS	N	Health-related quality of life, change in HRQOL by survey from baseline	Effect of intervention on HRQOL	Baseline, weeks 12, 24	41
3.0	S	7	SBD	DK, SMS	N	Future diabetes (GPG, HbA1c), proportion of participants who develop diabetes	Effect of intervention on diabetes long-term	All return SJLIFE core visits through 6 years	41
3.0	S	8	SBD, TB	DK, SMS	N	Participation in lifestyle program and barriers to participation and metformin adherence	Assess lifestyle program participation (logging, days accessed, etc) and relationship to efficacy, assess barriers to adherence and participation	Baseline, week 24	41

12.3 Stopping Rules

This ad hoc stopping rule is designed based on unacceptable toxicity of metformin. A rate of discontinuation of metformin >10% would be considered unacceptable. If among first 20 survivors more than 5, and among 41 survivors, more than 8 of them discontinue (stop taking for 7 or more days without intent to resume) metformin due to toxicity, then the trial will be stopped. These stopping rules are based on the exact 95% lower confidence bounds for the probability of failure.

13.0 OBTAINING INFORMED CONSENT

13.1 Informed Consent Prior to Research Interventions

Informed consent will be obtained prior to all study related observations, evaluations and interventions.

13.2 Consent at Age of Majority

N/A; Participants must be 18 years or older to enroll on the study.

13.3 Consent When English is Not the Primary Language

Due to current limitations of the digital lifestyle change platform, participants who are unable to participate in English will not be eligible for this study.

REFERENCES

1. Maddux BA, Chan A, Mandarino LJ, et al: IGF-Binding Protein-1 levels are related to insulin-mediated glucose disposal and are a potential serum marker of insulin resistance. Diabetes Care 29:1535-1537, 2006
2. Meacham LR, Sklar CA, Li S, et al: Diabetes mellitus in long-term survivors of childhood cancer. Increased risk associated with radiation therapy: a report for the childhood cancer survivor study. Arch Intern Med 169:1381-8, 2009
3. Mostoufi-Moab S, Seidel K, Leisenring WM, et al: Endocrine Abnormalities in Aging Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study. J Clin Oncol 34:3240-7, 2016
4. Armstrong GT, Chen Y, Yasui Y, et al: Reduction in late mortality among 5-year survivors of childhood cancer. N Engl J Med 374:833-42, 2016
5. Armstrong GT, Oeffinger KC, Chen Y, et al: Modifiable risk factors and major cardiac events among adult survivors of childhood cancer. J Clin Oncol 31:3673-80, 2013
6. Low Wang CC, Hess CN, Hiatt WR, et al: Clinical Update: Cardiovascular Disease in Diabetes Mellitus: Atherosclerotic Cardiovascular Disease and Heart Failure in Type 2 Diabetes Mellitus - Mechanisms, Management, and Clinical Considerations. Circulation 133:2459-2502, 2016
7. Stratton IM, Adler AI, Neil HA, et al: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ (Clinical research ed.) 321:405-412, 2000
8. Gregg EW, Cheng YJ, Srinivasan M, et al: Trends in cause-specific mortality among adults with and without diagnosed diabetes in the USA: an epidemiological analysis of linked national survey and vital statistics data. Lancet 391:2430-2440, 2018
9. Knowler WC, Fowler SE, Hamman RF, et al: 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet 374:1677-86, 2009
10. Morris DH, Khunti K, Achana F, et al: Progression rates from HbA1c 6.0–6.4% and other prediabetes definitions to type 2 diabetes: a meta-analysis. Diabetologia 56:1489-1493, 2013
11. Rena G, Hardie DG, Pearson ER: The mechanisms of action of metformin. Diabetologia 60:1577-1585, 2017
12. Knowler WC, Barrett-Connor E, Fowler SE, et al: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 346:393-403, 2002
13. The Diabetes Prevention Program. Design and methods for a clinical trial in the prevention of type 2 diabetes. Diabetes Care 22:623-34, 1999
14. Tseng E, Yeh HC, Maruthur NM: Metformin Use in Prediabetes Among U.S. Adults, 2005-2012. Diabetes Care 40:887-893, 2017
15. Menke A, Casagrande S, Geiss L, et al: Prevalence of and Trends in Diabetes Among Adults in the United States, 1988-2012. Jama 314:1021-9, 2015
16. The Diabetes Prevention Program (DPP): description of lifestyle intervention. Diabetes Care 25:2165-71, 2002
17. Flory J, Lipska K: Metformin in 2019: use of metformin for type 2 diabetes in 2019. JAMA 321:1926-1927, 2019
18. Bonnet F, Scheen A: Understanding and overcoming metformin gastrointestinal intolerance. Diabetes Obes Metab 19:473-481, 2017

19. Derosa G, D'Angelo A, Romano D, et al: Effects of metformin extended release compared to immediate release formula on glycemic control and glycemic variability in patients with type 2 diabetes. Drug Des Devel Ther 11:1481-1488, 2017
20. Crowley MJ, Diamantidis CJ, McDuffie JR, et al: Clinical outcomes of metformin use in populations with chronic kidney disease, congestive heart failure, or chronic liver disease: a systematic review. Ann Intern Med 166:191-200, 2017
21. Bodmer M, Meier C, Krähenbühl S, et al: Metformin, sulfonylureas, or other antidiabetes drugs and the risk of lactic acidosis or hypoglycemia: a nested case-control analysis. Diabetes care 31:2086-2091, 2008
22. Misbin RI, Green L, Stadel BV, et al: Lactic Acidosis in Patients with Diabetes Treated with Metformin. New England Journal of Medicine 338:265-266, 1998
23. Stang M, Wysowski DK, Butler-Jones D: Incidence of lactic acidosis in metformin users. Diabetes Care 22:925-927, 1999
24. Hostalek U, Gwilt M, Hildemann S: Therapeutic use of metformin in prediabetes and diabetes prevention. Drugs 75:1071-1094, 2015
25. Moin T, Schmittdiel JA, Flory JH, et al: Review of metformin use for type 2 diabetes prevention. Am J Prev Med 55:565-574, 2018
26. Jacobs S, Radnitz C, Hildebrandt T: Adherence as a predictor of weight loss in a commonly used smartphone application. Obes Res Clin Pract 11:206-214, 2017
27. Chin SO, Keum C, Woo J, et al: Successful weight reduction and maintenance by using a smartphone application in those with overweight and obesity. Sci Rep 6:34563, 2016
28. Toro-Ramos T, Lee DH, Kim Y, et al: Effectiveness of a Smartphone Application for the Management of Metabolic Syndrome Components Focusing on Weight Loss: A Preliminary Study. Metab Syndr Relat Disord 15:465-473, 2017
29. Hamman RF, Wing RR, Edelstein SL, et al: Effect of weight loss with lifestyle intervention on risk of diabetes. Diabetes Care 29:2102-7, 2006
30. Sepah SC, Jiang L, Peters AL: Translating the Diabetes Prevention Program into an Online Social Network: Validation against CDC Standards. The Diabetes Educator 40:435-443, 2014
31. Michaelides A, Raby C, Wood M, et al: Weight loss efficacy of a novel mobile Diabetes Prevention Program delivery platform with human coaching. BMJ Open Diabetes Research & Care 4:e000264, 2016
32. Alwashmi MF, Mugford G, Abu-Ashour W, et al: A Digital Diabetes Prevention Program (Transform) for Adults With Prediabetes: Secondary Analysis. JMIR diabetes 4:e13904-e13904, 2019
33. Fried LP, Tangen CM, Walston J, et al: Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 56:M146-56, 2001
34. Ness KK, Kirkland JL, Gramatges MM, et al: Premature Physiologic Aging as a Paradigm for Understanding Increased Risk of Adverse Health Across the Lifespan of Survivors of Childhood Cancer. J Clin Oncol 36:2206-2215, 2018
35. Campbell JM, Bellman SM, Stephenson MD, et al: Metformin reduces all-cause mortality and diseases of ageing independent of its effect on diabetes control: A systematic review and meta-analysis. Ageing Res Rev 40:31-44, 2017

36. Wang CP, Lorenzo C, Habib SL, et al: Differential effects of metformin on age related comorbidities in older men with type 2 diabetes. J Diabetes Complications 31:679-686, 2017
37. Espinoza SE, Jiwani R, Wang J, et al: Review of Interventions for the Frailty Syndrome and the Role of Metformin as a Potential Pharmacologic Agent for Frailty Prevention. Clin Ther 41:376-386, 2019
38. Hudson MM, Ness KK, Nolan VG, et al: Prospective medical assessment of adults surviving childhood cancer: study design, cohort characteristics, and feasibility of the St. Jude Lifetime Cohort study. Pediatr Blood Cancer 56:825-36, 2011
39. Kalichman SC, Amaral CM, Cherry C, et al: Monitoring medication adherence by unannounced pill counts conducted by telephone: reliability and criterion-related validity. HIV clinical trials 9:298-308, 2008
40. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes 2018. Diabetes Care, 2018
41. Jackson AS, Pollock ML: Generalized equations for predicting body density of men. Br J Nutr 40:497-504, 1978
42. Jackson AS, Pollock ML, Ward A: Generalized equations for predicting body density of women. Med Sci Sports Exerc 12:175-81, 1980
43. Karlage RE, Wilson CL, Zhang N, et al: Validity of anthropometric measurements for characterizing obesity among adult survivors of childhood cancer: A report from the St. Jude Lifetime Cohort Study. Cancer 121:2036-43, 2015
44. Survey UDoHaHSNHaNE: US Department of Health and Human Services: National Health and Nutrition Examination Survey. 2007-2008 Data Documentation, Codebook, and Frequencies. Physical Activity (PAQ_E), 2009
45. Mathiowetz V, Kashman N, Volland G, et al: Grip and pinch strength: normative data for adults. Arch Phys Med Rehabil 66:69-74, 1985
46. Mathiowetz V, Weber K, Volland G, et al: Reliability and validity of grip and pinch strength evaluations. J Hand Surg Am 9:222-6, 1984
47. Ware JE, Jr., Sherbourne CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 30:473-83, 1992
48. Kelly TL, Wilson KE, Heymsfield SB: Dual energy X-Ray absorptiometry body composition reference values from NHANES. PLoS One 4:e7038, 2009
49. Eleftheriadou I, Tsioufis C, Tsiachris D, et al: Choice of antihypertensive treatment in subjects with pre-diabetes. Is there a dream after the navigator. Curr Vasc Pharmacol 9:715-22, 2011
50. Pakkir Maideen NM, Jumale A, Balasubramaniam R: Drug Interactions of Metformin Involving Drug Transporter Proteins. Advanced pharmaceutical bulletin 7:501-505, 2017
51. Triplitt C: Drug Interactions of Medications Commonly Used in Diabetes. Diabetes Spectrum 19:202-211, 2006
52. Zaidi FH, Kinnear PE: Acetazolamide, alternate carbonic anhydrase inhibitors and hypoglycaemic agents: comparing enzymatic with diuresis induced metabolic acidosis following intraocular surgery in diabetes. The British journal of ophthalmology 88:714-715, 2004
53. Ismail IS: The Role of Carbonic Anhydrase in Hepatic Glucose Production. Curr Diabetes Rev 14:108-112, 2018

54. Ong CR, Molyneaux LM, Constantino MI, et al: Long-Term Efficacy of Metformin Therapy in Nonobese Individuals With Type 2 Diabetes. Diabetes Care 29:2361-2364, 2006

55. American Diabetes A: Prevention or Delay of Type 2 Diabetes: Standards of Medical Care in Diabetes-2019. Diabetes Care 42:S29-S33, 2019

APPENDIX I: MATRIX FOR METFORMIN PILL COUNT

Drug and Dose	Number of doses per day	Pills taken per dose	Previous number of pills counted	Pills dispensed since previous count	Total pills counted	Stop date	Start date
Metformin ER 500 mg	1						
Metformin ER 500 mg	1						
Metformin ER 500 mg	1						
Metformin ER 500 mg	1						
Metformin ER 500 mg	1						
Metformin ER 500 mg	1						
Metformin ER 500 mg	1						

APPENDIX II:

Adverse Event Monitoring Log
Global Rating of Side Effects Burden

MRN: _____Name: _____ Date: _____Timepoint: _____

Completed By: _____

Answer Yes or No if you have experienced any of these symptoms since the last time we spoke. We last spoke on (insert day) and it has been about (insert how many days since last symptom questionnaire). Answer "Yes" only if a symptom developed after starting the study drug or worsened while on the study drug. For any side effect marked "yes", complete the side effect detail on later pages.

Symptom	Present - Yes or No	Drug dose (mg)	CTCAE Score (1-5)
Muscle pain	Y___ No___		
Leg cramp	Y___ No___		
Muscle weakness	Y___ No___		
Joint pain	Y___ No___		
Headache	Y___ No___		
Abdominal pain	Y___ No___		
Diarrhea	Y___ No___		
Nausea	Y___ No___		
Other stomach problems	Y___ No___		
Attention/concentration problem	Y___ No___		
Memory problem	Y___ No___		
Sleep change/problem	Y___ No___		
Depression	Y___ No___		
Fatigue/Lack of energy	Y___ No___		
Dizziness	Y___ No___		
Irritability	Y___ No___		
Change in sexual function	Y___ No___		
Rash / skin problems	Y___ No___		
Extremity swelling	Y___ No___		
Numbness/tingling/burning	Y___ No___		
Urinary dysfunction	Y___ No___		
Any other	Y___ No___		
List other:	Y___ No___		
	Y___ No___		
	Y___ No___		
	Y___ No___		
	Y___ No___		
	Y___ No___		

Physician Reviewed by: _____ Review Date: _____

Collect details for all reported symptoms. Only collect side effects that occurred since the last contact with the participant. Check all relevant boxes.

Symptom 1:_____
Details:

a. Choose the response that best describes the frequency of the side effect of the metformin you have taken in the past (time interval since last monitoring) weeks. Do not rate side effects if you believe they are due to treatments that you are taking for other medical conditions.

No side effects	10% of the time	25%	50% of the time	75%	90%	All the time

b. Choose the response that best describes the intensity of the side effects that you believe are due to the metformin you have taken within the last (study interval) weeks. Rate the intensity of the side effect:

No side effect	Trivial	Mild	Moderate	Marked	Severe	Intolerable

c. Choose the response that best describes the degree to which this side effect has interfered with your day to day functions.

No impairment	Minimal impairment	Mild impairment	Moderate impairment	Marked impairment	Severe impairment	Unable to function due to side effects

d. Did you receive treatment for the side effect, details: _____

e. Did you go to the doctor or hospital for the side effect, details:_____

f. Is this side effect related to treatment:

Definitely Related	Possibly Related	Not Related

g. Is this a serious adverse event? Yes No

h. Is this expected or unexpected? Expected Unexpected

CTCAE Grade: _____

Symptom 2:_____
Details:

a. Choose the response that best describes the frequency of the side effect of the metformin you have taken in the past (time interval since last monitoring) weeks. Do not rate side effects if you believe they are due to treatments that you are taking for other medical conditions.

No side effects	10% of the time	25%	50% of the time	75%	90%	All the time

b. Choose the response that best describes the intensity of the side effects that you believe are due to the metformin you have taken within the last (study interval) weeks. Rate the intensity of the side effect:

No side effect	Trivial	Mild	Moderate	Marked	Severe	Intolerable

c. Choose the response that best describes the degree to which this side effect has interfered with your day to day functions.

No impairment	Minimal impairment	Mild impairment	Moderate impairment	Marked impairment	Severe impairment	Unable to function due to side effects

d. Did you receive treatment for the side effect, details: _____

e. Did you go to the doctor or hospital for the side effect, details:_____

f. Is this side effect related to treatment:

Definitely Related	Possibly Related	Not Related

g. Is this a serious adverse event? Yes No

h. Is this expected or unexpected? Expected Unexpected

CTCAE Grade: _____

Symptom 3:_____
Details:

a. Choose the response that best describes the frequency of the side effect of the metformin you have taken in the past (time interval since last monitoring) weeks. Do not rate side effects if you believe they are due to treatments that you are taking for other medical conditions.

No side effects	10% of the time	25%	50% of the time	75%	90%	All the time

b. Choose the response that best describes the intensity of the side effects that you believe are due to the metformin you have taken within the last (study interval) weeks. Rate the intensity of the side effect:

No side effect	Trivial	Mild	Moderate	Marked	Severe	Intolerable

c. Choose the response that best describes the degree to which this side effect has interfered with your day to day functions.

No impairment	Minimal impairment	Mild impairment	Moderate impairment	Marked impairment	Severe impairment	Unable to function due to side effects

d. Did you receive treatment for the side effect, details: _____

e. Did you go to the doctor or hospital for the side effect, details:_____

f. Is this side effect related to treatment:

Definitely Related	Possibly Related	Not Related

g. Is this a serious adverse event? Yes No

h. Is this expected or unexpected? Expected Unexpected

CTCAE Grade: _____

Symptom 4:_____
Details:

a. Choose the response that best describes the frequency of the side effect of the metformin you have taken in the past (time interval since last monitoring) weeks. Do not rate side effects if you believe they are due to treatments that you are taking for other medical conditions.

No side effects	10% of the time	25%	50% of the time	75%	90%	All the time

b. Choose the response that best describes the intensity of the side effects that you believe are due to the metformin you have taken within the last (study interval) weeks. Rate the intensity of the side effect:

No side effect	Trivial	Mild	Moderate	Marked	Severe	Intolerable

c. Choose the response that best describes the degree to which this side effect has interfered with your day to day functions.

No impairment	Minimal impairment	Mild impairment	Moderate impairment	Marked impairment	Severe impairment	Unable to function due to side effects

d. Did you receive treatment for the side effect, details: _____

e. Did you go to the doctor or hospital for the side effect, details:_____

f. Is this side effect related to treatment:

Definitely Related	Possibly Related	Not Related

g. Is this a serious adverse event? Yes No

h. Is this expected or unexpected? Expected Unexpected

CTCAE Grade: _____

APPENDIX III: SCHEDULE OF RESEARCH EVALUATIONS

REQUIRED EVALUATIONS, TESTS, AND OBSERVATIONS

STUDIES TO BE OBTAINED	**Pre-Study***	**Week 2** +/- 4 days	**Week 4** +/- 7 days	**Week 8** +/- 7 days	**Week 12** +/- 7 days	**Week 16** +/- 7 days	**Week 20** +/- 7 days	**Week 24** +/- 7 days
History including medications	X				X			X
Physical Exam (Ht, Wt, VS)	X				X			X
Anthropometrics: body fat %, abdominal circumference, waist-to-hip ratio	X				X			X
Fasting blood work: CBC, CMP, HbA1c, insulin, IGFBP-1, lactate, cystatin C, lipid panel	X				X			X
Walking speed and hand grip strength	X							X
Accelerometer (mailed prior to visit)	X				X			X
*Pregnancy Test	X				X			X
HRQOL (SF-36)	X				X			X
NHANES-PAQ	X				X			X
Medication Adherence Assessment		X	X	X	X	X	X	X
Lifestyle Change Adherence Log		X	X	X	X	X	X	X
Symptom Log including CTCAE/Adverse Events	X	X	X	X	X	X	X	X
Motivation to change	X							
Barriers to medication adherence and lifestyle change participation								X

* Pre-study evaluations may be completed up to 30 days prior to enrollment.

APPENDIX IV:DAST AND AUDIT QUESTIONNAIRES

DAST

Today's date: ☐☐ / ☐☐ / ☐☐☐☐ (m m / d d / y y y y)

MRN: ☐☐☐☐☐

The following questions concern information about your possible involvement with drugs *not including alcoholic beverages* during the past 12 months.

"Drug abuse" refers to (1) the use of prescribed or over-the-counter drugs in excess of the directions, and (2) any nonmedical use of drugs.

The various classes of drugs may include cannabis (marijuana, hashish), solvents (e.g ., paint thinner), tranquilizers (e .g., Valium), barbiturates, cocaine, stimulants (e.g., speed), hallucinogens (e.g ., LSD) or narcotics (e.g ., heroin). Remember that the questions ***do not*** include alcoholic beverages.

Please answer every question. If you have difficulty with a statement, then choose the response that is mostly right.

In the past 12 months ...	Yes	No
A1. Have you used drugs other than those required for medical reasons?	☐	☐
A2. Do you abuse more than one drug at a time?	☐	☐
A3. Are you unable to stop abusing drugs when you want to?	☐	☐
A4. Have you ever had blackouts or flashbacks as a result of drug use?	☐	☐
A5. Do you ever feel bad or guilty about your drug use?	☐	☐
A6. Does your spouse (or parents) ever complain about your involvement with drugs?	☐	☐
A7. Have you neglected your family because of your use of drugs?	☐	☐
A8. Have you engaged in illegal activities in order to obtain drugs?	☐	☐
A9. Have you ever experienced withdrawal symptoms (felt sick) when you stopped taking drugs?	☐	☐
A10. Have you had medical problems as a result of your drug use (e.g. memory loss, hepatitis, convulsions, bleeding)?	☐	☐

Thank you very much for completing this questionnaire.

Please! Do not mark below this line

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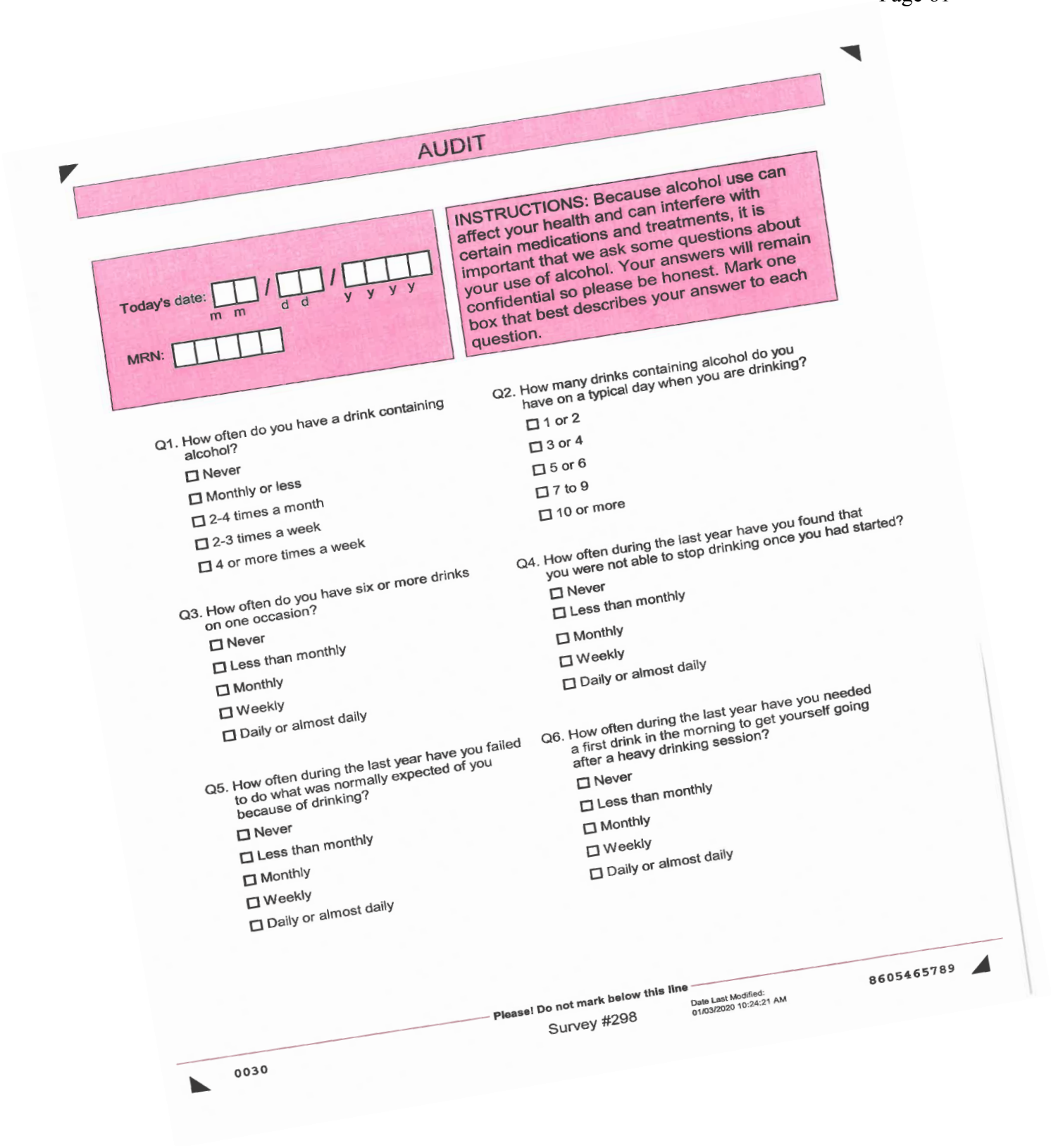

AUDIT

Today's date: m m / d d / y y y y

MRN:

INSTRUCTIONS: Because alcohol use can affect your health and can interfere with certain medications and treatments, it is important that we ask some questions about your use of alcohol. Your answers will remain confidential so please be honest. Mark one box that best describes your answer to each question.

Q1. How often do you have a drink containing alcohol?

- ☐ Never
- ☐ Monthly or less
- ☐ 2-4 times a month
- ☐ 2-3 times a week
- ☐ 4 or more times a week

Q2. How many drinks containing alcohol do you have on a typical day when you are drinking?

- ☐ 1 or 2
- ☐ 3 or 4
- ☐ 5 or 6
- ☐ 7 to 9
- ☐ 10 or more

Q3. How often do you have six or more drinks on one occasion?

- ☐ Never
- ☐ Less than monthly
- ☐ Monthly
- ☐ Weekly
- ☐ Daily or almost daily

Q4. How often during the last year have you found that you were not able to stop drinking once you had started?

- ☐ Never
- ☐ Less than monthly
- ☐ Monthly
- ☐ Weekly
- ☐ Daily or almost daily

Q5. How often during the last year have you failed to do what was normally expected of you because of drinking?

- ☐ Never
- ☐ Less than monthly
- ☐ Monthly
- ☐ Weekly
- ☐ Daily or almost daily

Q6. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?

- ☐ Never
- ☐ Less than monthly
- ☐ Monthly
- ☐ Weekly
- ☐ Daily or almost daily

Please! Do not mark below this line

Survey #298

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Q7. How often during the last year have you had a feeling of guilt or remorse after drinking?

- ☐ Never
- ☐ Less than monthly
- ☐ Monthly
- ☐ Weekly
- ☐ Daily or almost daily

Q8. How often during the last year have you been unable to remember what happened the night before because of your drinking?

- ☐ Never
- ☐ Less than monthly
- ☐ Monthly
- ☐ Weekly
- ☐ Daily or almost daily

Q9. Have you or someone else been injured because of drinking?

- ☐ No
- ☐ Yes, but not in the last year
- ☐ Yes, during the last year

Q10. Has a relative, friend, doctor, or other health care worker been concerned about your drinking or suggested you cut down?

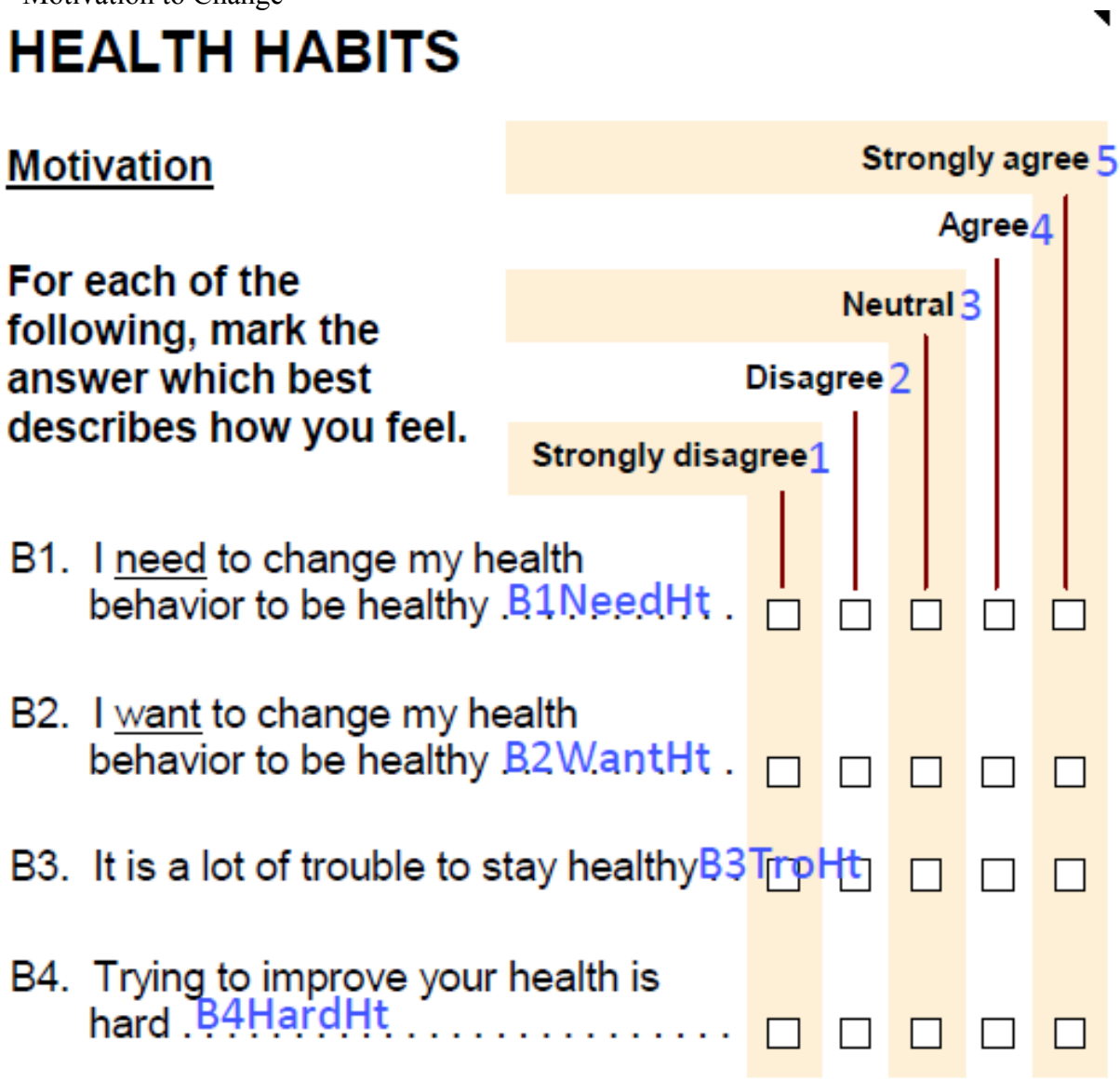
- ☐ No
- ☐ Yes, but not in the last year
- ☐ Yes, during the last year

Thank you very much for completing this questionnaire.

Please! Do not mark below this line

APPENDIX V:

Motivation to Change



APPENDIX VI:BARRIERS TO MEDICATION ADHERENCE

Please answer the following questions based on your feelings about the study drug over the past week.

		Often	Sometimes	Never
1.	I forget to take my medication			
2.	I am often too busy to take my medication			
3.	My medication is helping me			
4.	I dislike my current medication			
5	Friends and family believe that my current medication is good for me			
6.	Taking medication is unpleasant			
7.	Taking my medication interferes with my planned meal times			
8.	I feel that the good things about taking medication outweigh the bad			

Questions 1, 3, 4, 5, 6 and 8 were taken from the Personal Evaluations of Transitions in Treatment (PETiT) questionnaire developed by Voruganti and Awad in 2002.

Please answer the following questions based on your feelings about changing diet and physical activity and the digital lifestyle change program, referred to as “the app”.

		Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
1.	Healthy food options cost too much					
2.	It is too hard or time consuming to eat healthy					
3.	I don’t have time for physical activity					
4.	I don’t have access to exercise equipment or safe, outdoor spaces for walking					
5	Persistent side effects of my cancer treatment (neuropathy, pain, etc) limit my physical activity					
6.	I have more motivation to make healthy changes because I am a cancer survivor					
7.	I often (3 or more days per week) forgot to read the daily lessons in the app					
8.	It was too time consuming to log meals					
9.	It was too complicated to log meals					
10.	It was too time consuming to log physical activity					
11.	It was too complicated to log physical activity					
12.	I often (3 or more days per week) forgot to log meals					
13.	I often (3 or more days per week) forgot to log physical activity					

14.	I forgot to log my weight					
15.	I don’t have access to a scale					
16.	The tools in the app didn’t work for me					
17.	I liked having a health coach in the app					
18.	I liked having a peer group in the app					

APPENDIX VII:DISALLOWED DRUGS ON STUDY

Anti-hyperglycemic or diabetes medications
Insulins
(not allowed on study):
Regular insulin
Insulin aspart
Insulin Glulisine
Insulin lispro
Insulin isophane
Insulin degludec
Insulin detemir
Insulin glargine

Amylinomimetic drug
(not allowed on study):
Pramlintide

Alpha-glucosidase inhibitors
(not allowed on study):
Acarbose
Miglitol

Dopamine agonist
(not allowed on study):
Bromocriptine

Dipeptidyl peptidase-4 (DPP-4) inhibitors
(not allowed on study):
Alogliptin
Linagliptin
Saxagliptin
Sitagliptin

Glucagon-like peptide-1 (GLP-1) receptor agonists
(not allowed on study):
Albiglutide
Dulaglutide
Exenatide
Exenatide extended-release
Liraglutide
Semaglutide

Meglitinides
(not allowed on study):
Nateglinide
Repaglinide

Sodium-glucose transporter (SGLT) 2 inhibitors
(not allowed on study):
Dapagliflozin
Canafliglozin
Empagliflozin
Ertugliflozin

Sulfonylureas
(not allowed on study):
Glimepiride
Gliclazide
Glipizide
Glyburide
Chlorpropamide
Tolazamide
Tolbutamide

Thiazolidinediones
(not allowed on study):
Rosiglitazone
Pioglitazone

Monitored/Recorded Drugs on Study

Drugs Affecting Glycemic Control

Thiazide diuretics
(will be tracked on study):
Chlorothiazide
Chlorthalidone
Hydrochlorothiazide
Indapamide
Metolazone

Calcium channel blockers
(will be tracked on study):
Amlodipine
Diltiazem
Felodipine
Isradipine
Nicardipine
Nifedipine
Nisoldipine
Verapamil

Beta-blockers
(will be tracked on study):
Acebutolol
Atenolol
Bisoprolol
Carvedilol
Esmolol
Labetalol
Metoprolol
Nadolol
Nebivolol
Penbutolol
Pindolol
Propranolol
Sotalol
Timolol

Proton pump inhibitors (PPIs)
(will be tracked on study):
Esomeprazole
Dexlansoprazole
Lansoprazole
Omeprazole
Pantoprazole
Rabeprazole

Oral corticosteroids
(will be tracked on study):
Cortisone
Dexamethasone
Hydrocortisone
Methylprednisone
Methylprednisolone
Prednisone
Prednisolone

Thyroid replacement hormone
(will be tracked on study):
Levothyroxine sodium
Liothyronine sodium
Liotrix

Oral estrogens and oral contraceptives
(will be tracked on study):
Estrogen and/or progesterone containing oral medications

HMG-coA reductase inhibitors
(will be tracked on study):
Atorvastatin
Fluvastatin
Lovastatin
Pitavastatin
Pravastatin
Rosuvastatin
Simvastatin

Drugs with Potential to Reduce Metformin Clearance

Cationic drugs eliminated by renal tubular secretion (OCT-2 and MATE inhibitors) (will be tracked on study and consultation with pharmacy regarding need to dose adjustment if eGFR <90 ml/min/m^2):

Amiloride
Atenolol
Cephalexin
Cimetidine
Digoxin
Dolutegravir
Erlotinib
Gefitinib
Imatinib
Morphine
Nilotinib
Procainamide
Proton pump inhibitors (PPIs)
Pyrimethamine
Quinidine
Quinine
Ranitidine
Ranolazine
Triamterene
Trimethoprim
Vancomycin
Vandetanib

Other Drugs with Theoretical Increase in Risk for Lactic Acidosis

Carbonic Anhydrase Inhibitors (will be tracked on study):

Topiramate
Zonisamide
Acetazolamide
Dichlorphenamide