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CANADIAN CANCER TRIALS GROUP (CCTG)

A PHASE III RANDOMIZED TRIAL OF METFORMIN VERSUS PLACEBO ON RECURRENCE AND SURVIVAL IN EARLY STAGE BREAST CANCER

NCIC CTG Protocol Number: MA.32
Participating NCTN Groups: The Alliance, ECOG-ACRIN, NRG, SWOG
Other Participating Groups: IBCSG, NCRI-BCSG - ICR- CTSU

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This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Institutions not aligned with CCTG will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix.

*The study protocol and all related forms and documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org

- Send completed site registration documents to the CTSU Regulatory Office. Refer to the CTSU Logistical Appendix for specific instructions and documents to be submitted.
- Patient enrollments will be done through the CCTG by means of a web-based Electronic Data Capture (EDC) System. Refer to the logistical appendix for specific instructions.
- Data management will be performed by the CCTG by means of a web-based Electronic Data Capture (EDC) System. Electronic case report forms must be submitted through the EDC system; clinical reports and supporting documentation may be submitted through the EDC system or sent by mail to CCTG unless otherwise directed by the protocol. Do not send study data or case report forms to the CTSU Data Operations.
- Data query and delinquency reports will be sent directly to the enrolling site by CCTG. Please send query response and delinquent data to CCTG and do not copy the CTSU Data Operations. Please note that data queries are both issued and should be responded to directly within the EDC system.
- Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP IAM Account contact information current. This will ensure timely communication between the clinical site and the CCTG data center.

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STUDY ACKNOWLEDGMENT/DISCLOSURE

I understand that this protocol contains information that is confidential and proprietary to CCTG.

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, and according to Good Clinical Practice and any applicable local regulations. I will make a reasonable effort to complete the study within the time designated. I confirm that I and study personnel participating under my supervision have adequate resource to fulfill their responsibilities as outlined in this protocol. I will maintain documentation of any investigator responsibilities assigned to participating study personnel.

I will provide copies of the protocol and access to all information furnished by CCTG to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational product and the study.

I will provide protocol information to my Research Ethics Board (REB), Institutional Review Board(s) [IRB(s)] or Independent Ethics Committee(s) [IEC(s)], subject to the following condition: The contents of this protocol may not be used in any other clinical trial and may not be disclosed to any other person or entity without the prior written permission of CCTG. The foregoing shall not apply to disclosure required by governmental regulations or laws; however, I will give prompt notice to CCTG of any such disclosure.

I understand that I may terminate or suspend enrolment of the study at any time if it becomes necessary to protect the best interests of the study subjects, however I will give prompt notice to CCTG. The study may be terminated at any time by CCTG with or without cause.

Any supplemental information that may be added to this document is also confidential and proprietary to CCTG and must be kept in confidence in the same manner as the contents of this protocol.

_____ _____

Investigator
(printed name and signature)

Date

Protocol Number: MA.32

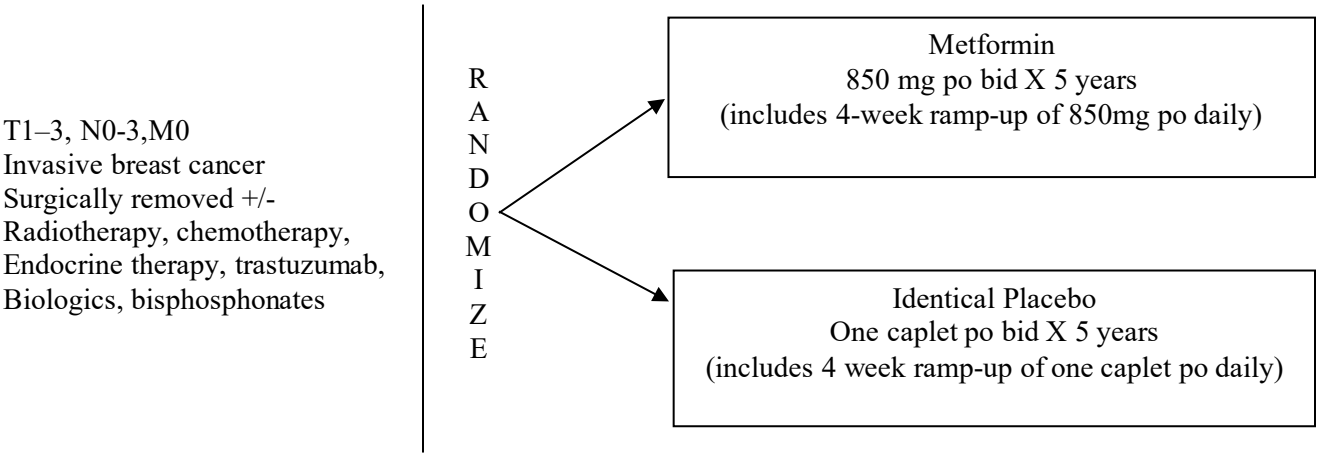
Centre: _____

TREATMENT SCHEMA

The study population will include subjects with invasive breast cancer who, within the previous 12 months, have received the first histologic diagnosis of invasive breast carcinoma and have undergone definitive surgical treatment for invasive breast cancer. Subjects may have received, at the discretion of their treating physician, standard adjuvant loco-regional radiation, adjuvant endocrine treatment, trastuzumab or other biologics or bisphosphonates prior to or during study treatment. Chemotherapy (adjuvant or neo-adjuvant), if given, must be completed prior to randomization.

Stratification:

1. ER and/or PgR positive versus both receptors negative
2. BMI $\leq$ 30 versus > 30 (kg/m^2)
3. HER2 positive versus HER2 negative
4. Chemotherapy – any versus none



Treatment is for 5 years or until primary endpoint is documented

Planned Sample Size: 3582 (80% power to detect HR 0.785 with 2-tail alpha=0.05)

Primary Endpoint: Invasive disease free survival

Secondary Endpoints:

- Overall survival
- Distant relapse free survival
- Breast cancer free interval
- Breast cancer specific mortality
- Incidence of contralateral invasive breast cancer
- Long-term clinical and laboratory safety
- Relevant Medical Endpoints (new diabetes; new cardiovascular hospitalizations)
- Health-Related Quality of Life, Physical Activity, Diet
- Change in BMI
- Correlative Science Outcomes

1.0 OBJECTIVES

Primary objective:

To compare invasive disease free survival (IDFS) between subjects treated with metformin (850 mg po bid for 5 years) versus placebo in addition to standard adjuvant therapy.

Secondary objective(s):

To compare the following endpoints between subjects treated with metformin (850 mg po bid for 5 years) versus placebo:

- overall survival
- distant disease-free survival
- breast cancer free interval
- breast cancer specific mortality
- incidence of contralateral invasive breast cancer
- invasive disease free survival in hormone receptor (ER and PgR) negative and positive (ER and/or PgR) sub-groups
- changes in body mass index (BMI = weight (kg)/height(m)^2)
- adverse events
- other medical endpoints – including a new diagnosis of diabetes mellitus or cardiovascular hospitalization or death (stroke, myocardial infarction)*
- health related quality of life, measured using the EORTC QLQ-C30, supplemented by a trial specific checklist; the Block Alive Screener; physical activity items from the Nurses Health Study Questionnaire II on a sub-set of MA.32 subjects (sub-set enrollment completed 2011NOV04)
- embedded correlative science outcomes including plasma insulin and molecular markers of metformin action
- metabolic parameters, including metabolic components of the insulin resistance syndrome as defined by the ATP III criteria, in a subset of subjects (and to be described in a separate protocol)

* "hospitalization" includes an emergency room visit or overnight stay(and cardiovascular hospitalizations include all ischemic and non-ischemic events)

2.0 BACKGROUND INFORMATION AND RATIONALE

Interest in metformin (an oral agent commonly used to treat diabetes) in the adjuvant setting in breast cancer reflects the recent convergence of several streams of research. In epidemiologic studies, metformin use in diabetics has been associated with reduced overall cancer risk and mortality *[Evans, 2005; Bowker, 2006; Monami 2008; Libby, 2009]*. Clinically, observational research has identified higher response rates to neoadjuvant systemic therapy in diabetic breast cancer patients receiving metformin for their diabetes compared to diabetic breast cancer patients who do not receive metformin or to non-diabetic breast cancer patients *[Jiralerspong 2009]*. Furthermore, obesity has been recognized as an adverse prognostic factor in breast cancer *[Chlebowski 2006; Goodwin, 2006]*. Variations in insulin levels within the normal range in breast cancer patients (reflecting varying degrees of underlying insulin resistance and strongly correlated with obesity) appear to be a likely mediator of this effect *[Goodwin, 2002; Pasanisi, 2006; Pollak, 2006; Irwin, 2009]*. Goodwin has shown that metformin reduces insulin levels in breast cancer patients, even in the absence of diabetes and when insulin levels are within the normal range *[Goodwin, 2008]*. The recent demonstration that metformin results in (1) initiation of an AMPK-dependent energy stress response which can adversely affect survival of BC cell lines and (2) inhibition of PI3K/Akt/mTOR signaling leading to reduced proliferation of breast cancer cell lines, has provided a molecular basis for additional, insulin independent, anti-tumour effects of metformin in breast cancer *[Zakikhani, 2006]*. Thus, metformin may exert anti-tumour effects through both insulin-dependent and insulin-independent mechanisms in women with a broad range of insulin levels commonly seen in newly diagnosed breast cancer. Because metformin is a generic, inexpensive, well known and generally well tolerated oral agent that is commonly used to treat diabetes (including breast cancer patients who have diabetes), its evaluation as a potential adjuvant treatment for breast cancer can take place in an accelerated fashion.

Clinical Evidence - Obesity, Insulin and Breast Cancer

Obesity is a recognized adverse prognostic factor in breast cancer - compared to normal weight women, overweight or obese women with breast cancer have a hazard ratio (HR) of distant recurrence of 1.7-1.9 and a HR of death of 1.6 *[Goodwin, 1995]*. Early postulated mechanisms for this effect, including underdosing of chemotherapy and elevated estradiol in obese women, do not explain obesity effects in women not receiving chemotherapy, in premenopausal women (in whom estrogen levels do not reflect obesity) or in estrogen receptor ER/PgR negative breast cancer. There is growing evidence that insulin is an important mediator of this adverse prognostic effect of obesity. We reported that insulin was strongly associated with obesity ($r=0.58$, $p<0.001$) and that it exerted an adverse prognostic effect in locoregional breast cancer that extended beyond the adverse prognostic effect of obesity *[Goodwin, 2002]*, despite the fact that the vast majority of insulin levels (>98%) were in the normal range *[Liu, 2006; Saxena, 2000]*. Women with insulin levels in the highest (vs lowest) quartile had a doubled risk of recurrence and tripled risk of death, effects that persisted after adjustment for tumour and treatment related factors. These prognostic effects were somewhat greater in women with ER/PgR negative tumours but they were also present in ER/PgR positive breast cancer (the difference between these groups was not significant). A quantitatively similar effect of insulin was subsequently reported by Pasanisi et al *[Pasanisi, 2006]*, who also found the insulin resistance syndrome, a clinical syndrome associated with high insulin levels, was associated with a tripled risk of recurrence *[Pollak, 2006]* and Irwin et al *[Irwin, 2009]* reported high C-peptide levels (released when insulin is cleaved from proinsulin) were significantly correlated with reduced disease-free survival (DFS) in ER/PgR positive breast cancer. In a final study; a high waist-hip ratio (a marker of insulin resistance) was associated with a tripled risk of breast cancer mortality *[Borugian, 2003]*.

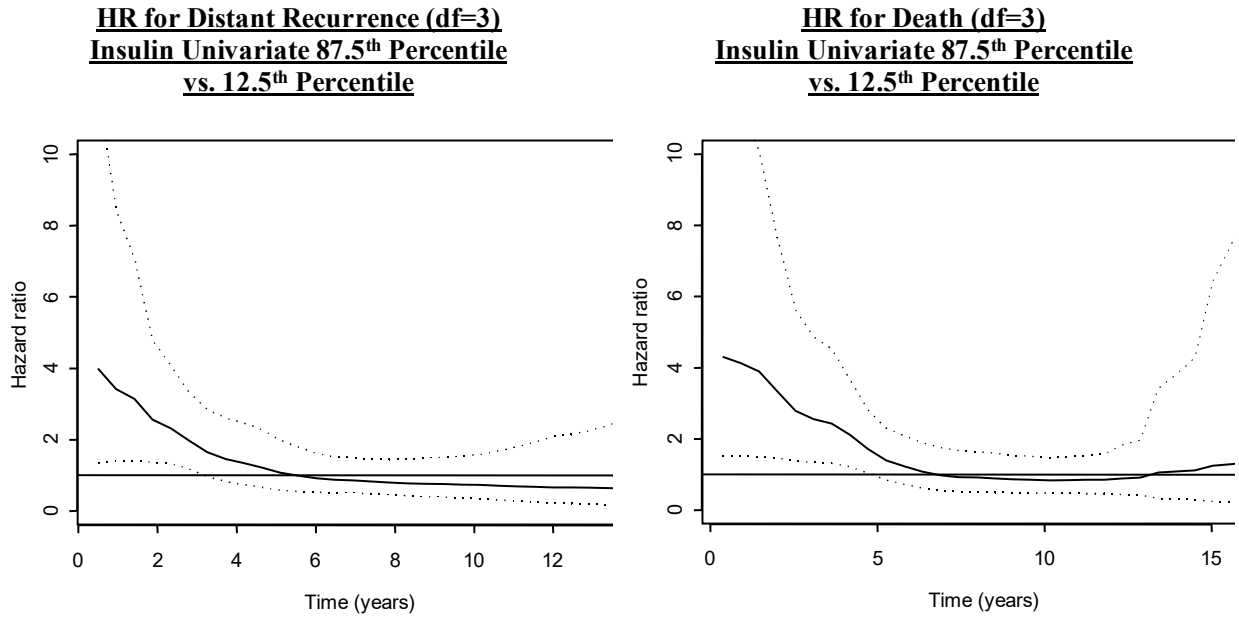
Table 1 Insulin and Related Factors and Breast Cancer Prognosis

		#	Factor Measured	Recurrence	Death
Goodwin	2002	512	Fasting Insulin	HR=2.0	HR=3.1
Pasanisi	2006	110	Fasting Insulin Insulin Resistance Syndrome	HR=2.42 HR=3.0	
Pollak	2006	667	Non-fasting C-peptide	p<0.05*	
Irwin	2007	689	Fasting C-peptide		HR=3.0
Borugian	2004	603	Waist/hip ratio**		HR=3.3 (post)

* HR not provided ** non-fasting insulin was not a significant prognostic factor
Abbreviations: post=postmenopausal, HR = hazard ratio

Recent analyses by our group have demonstrated that the increased risk of distant recurrence and death associated with higher versus lower insulin levels at breast cancer diagnosis persists for the first five years after diagnosis, but is no longer present after that time (see Figure 1, unpublished data). This pattern of recurrence is similar to that seen with ER/PgR negative breast cancer. This observation has contributed to our decision to administer metformin for 5 years in this trial.

Figure 1 HR Distant Recurrence and Death Over Time for Insulin at Diagnosis (midpoint of upper quartile vs. midpoint of lower quartile)



Insulin levels in the upper portion of the normal range in women with breast cancer appear to reflect the presence of the underlying Insulin Resistance Syndrome, a condition that is improved by metformin. The Insulin Resistance Syndrome includes central obesity, hypertension, an abnormal lipid profile, coronary artery disease, type 2 diabetes and a group of laboratory markers of inflammation *[Reaven, 2005; Bloomgarden, 2007]*. We have shown a high prevalence of these conditions in women with breast cancer who have higher insulin levels (even when these levels are in the normal range); we have also shown that these high insulin levels reflect underlying insulin resistance *[Goodwin, 2009]* as assessed using the Homeostasis Model Assessment (HOMA), a validated model of insulin resistance *[Vaccaro, 2004]*. Furthermore, women with early breast cancer have somewhat higher insulin levels than healthy controls [odds ratio (OR) for breast cancer = 2.83, highest vs. lowest quintile], consistent with the presence of insulin resistance prior to breast cancer diagnosis (possibly reflecting lifestyle factors such as obesity, physical inactivity and high fat diets that have been linked to breast cancer risk) *[Del Giudice, 1998]*. Similar observations have been reported by Pasanisi *[Pasanisi, 2006]*. In a recent study, Genarri et al *[Gennari, 2007]* identified a 15-gene set from 143 insulin resistance-related genes, that was predictive of DFS in both a training set (102 breast cancer patients) and a validation set (57 breast cancer patients) – they saw 91% 8 year DFS for expression scores above the median vs. 51% for scores below the median ($p<0.001$) in the training set [97% vs. 54% ($p=0.009$) in the validation set].

Insulin levels vary widely in relation to nutrient intake and health status (particularly the presence of diabetes). A normal reference range for fasting insulin has been defined variably from $\leq$ 20 microunits/ml ($\leq$ 139 pmol/L) *[Liu, 2006]* to $\leq$ 30 microunits/ml ($\leq$ 209 pmol/L) *[Saxena, 2000]*. In our population based cohort study of non-diabetic breast cancer patients, *[Goodwin, 2002]* the mean fasting insulin was 44.6 pmol/L and the range was 8.1 to 339.8 pmol/L; < 2% of our subjects had fasting insulin levels 140 pmol/L or higher. We expect a similar range of insulin levels, mainly in the normal range, in MA.32 subjects. There is evidence that the use of metformin in individuals with "normal" insulin levels appears to be safe and it reduces insulin levels. For example, in our Phase II study of 6 months of metformin (1500 mg/day) in breast cancer patients, the mean baseline fasting insulin level was in the "normal" range (75.7 pmol/L) and only one woman had an insulin level above 140 pmol/L (the level was 150 pmol/L). Insulin levels were reduced by 22% without the occurrence of hypoglycemia *[Goodwin, 2008]*, proportional reductions in insulin were constant across the range of baseline insulin studied. Similar safety and insulin-lowering effects of metformin have been reported in non-diabetic, non-breast cancer subjects with normal insulin levels. In a recent study of polycystic ovary syndrome (PCOS) *[Goldenberg, 2005]*, metformin (2250 mg/day) lowered fasting insulin levels by 18% from a mean baseline insulin of 64.5 pmol/L in women in the lowest quartile of baseline insulin (greater reductions were seen in women with insulin levels markedly above normal). Similar results in PCOS subjects were reported by Roumaldi *[Romualdi, 2008]* (mean baseline fasting insulin 47.0 pmol/L, 15% reduction after metformin at a low dose of 1000 mg/day for 6 months) and others *[Baillargeon, 2004]*. In another study, metformin use (2250 mg per day) in sedentary (non-diabetic) subjects having a mean baseline fasting insulin of 64.9 pmol/L led to a 17% reduction in insulin levels *[Ou, 2006]*. Finally, metformin (1700 to 2550 mg/day) safely reduced insulin levels by 18.5% (from 161.5 pmol/L to 131.4 pmol/L) in obese subjects with normal glucose tolerance *[Tankova, 2003]*. No episodes of hypoglycemia were reported in these studies. Thus, at doses similar to those we plan to use, metformin safely reduces insulin levels in the normal range, by about 20%. Based on these observations, we anticipate that metformin will safely lower insulin levels to a similar degree in subjects enrolled onto MA.32.

The insulin receptor (IR) is commonly expressed in human breast cancer *[Mulligan, 2007]* (see Table below), thereby providing a biologic mechanism for a prognostic effect of insulin. IGF-1R is less commonly expressed. In our dataset involving 150 women with sporadic breast cancer treated at a single institution, IR expression on breast tumour tissue was not correlated with circulating insulin levels (r=-0.02), indicating absence of downregulation by insulin. Similar to ER, we found that high IR expression predicted good breast cancer outcome. If this parallel extends to treatment, reduction in insulin (for example by the administration of metformin) may improve breast cancer outcomes, similar to improvements seen with reduction in estrogen by aromatase inhibitors (AIs) in ER/PgR positive breast cancer *[Baum, 2002]*.

Table 2 Insulin, IGF Receptors in Sporadic Locoregional Breast Cancer n=150

			IR	IGF-1R
Immunohistochemical (IHC) (Allred Score)				
Negative	(0-2)		1.1%	25.3%
Weak	(3-5)		11.2%	63.5%
Strong	(6-8)		87.6%	11.2%
Spearman r				
Insulin			-0.02	-0.10
IGF-1			-0.11	-0.02

There have been no randomized trials targeting insulin reduction as a means of improving breast cancer outcomes. However, the Women's Intervention Nutrition Study (WINS) *[Chlebowski, 2006]* randomized 2437 postmenopausal women to a low fat diet that was associated with a 2.3 kg weight loss (versus usual diet without weight loss). The diet improved 5 year DFS [HR 0.76, 95% Confidence Interval (CI) 0.60-0.98], with the largest effect in ER/PgR negative breast cancer (HR 0.58, 95% CI 0.37-0.91 vs HR 0.85, 95% CI 0.63-1.14 in ER + breast cancer). In contrast, the Women's Healthy Eating and Living Trial *[Pierce, 2007]*, involving 3088 breast cancer patients, found no 5 year DFS or overall survival (OS) effects of a high fruit and vegetable, low fat diet that was not associated with weight loss. It is possible these divergent results occurred because weight loss (typically associated with reduced insulin levels) was critical in influencing DFS in WINS; if correct, the larger effect in ER/PgR negative breast cancer may reflect enhanced importance of insulin signaling in that breast cancer subset. Ligibel et al *[Ligibel, 2008]*, have reported that exercise (a mixed strength and endurance intervention) promoted insulin reduction in women with breast cancer, providing evidence that lifestyle interventions targeting conditions such as physical inactivity that have been associated with poor breast cancer outcomes in observational studies can modify insulin in the breast cancer population.

There is a large body of work examining insulin-like growth factors (IGFs) and related binding proteins (BPs) in breast cancer *[Sachdev, 2007; Ibrahim, 2005]*. Although circulating IGFs have been associated with BC risk in some studies *[Hankinson, 1998; Schernhammer, 2005]*, evidence of a direct prognostic role is weak and inconsistent. Expression of these factors in tumour or stroma have been more consistently linked with prognosis and/or prognostic features of tumours, notably IGF1 expression with favourable *[Toropainen, 1995; Haffner, 2007]* and insulin-like growth factor binding protein 3 (IGFBP3) expression with unfavourable *[Rocha, 1996; Holdaway, 2003]* features. The IGF pathway is being evaluated as a target for breast cancer therapy in separate research *[Sachdev, 2006]*.

An IGF-1 gene expression profile has recently been reported in breast cancer *[Creighton, 2008]* – this profile involved over 800 genes that were up or down regulated by IGF-1 – these genes (which were enriched for transcriptional targets of ER, Ras/extracellular signal-related kinase1/2 and PI3K, mTOR pathways) were involved in cell proliferation, metabolism and DNA repair. The expression profile was correlated with adverse clinical and pathologic markers (ER/PgR negativity, luminal B subtype) and it was independently associated with poor outcomes. As noted above, a similar profile exists for insulin *[Gennari, 2007]*. The key issue may be which ligand (IGF-1, insulin, or both) is binding to receptors – clinical and epidemiologic evidence (reviewed above) provides strong support for a clinically relevant role for insulin, the target of our proposed intervention.

Clinical and Epidemiological Evidence – Metformin and Cancer

A recent observational study *[Jiralerspong, 2009]* examined response rates to neoadjuvant systemic therapy in breast cancer patients, some of whom were diabetic receiving metformin (n=68), some diabetic not receiving metformin (n=87) and some non-diabetic (n=2374). Pathologic complete response (pCR) was 24%, 8% and 16% in these three groups, respectively (p=0.03). Corresponding 39 month overall survival rates were 80.9%, 77.6% and 85.9%, respectively (p=0.02). That is, the use of metformin to treat diabetes was associated with higher pCR rates to neoadjuvant systemic therapy in early stage breast cancer patients (although the best survival was seen in non-diabetic patients).

In observational epidemiologic work, Evans et al. *[Evans, 2005]* reported the risk of subsequent cancer diagnosis (all cancer types, including BC) was reduced in type 2 diabetics who received metformin (OR 0.85 for any vs. no metformin exposure). The protective effect increased with greater metformin exposure (measured as total dose prescribed or total duration of use). Additionally, Bowker et al. *[Bowker, 2006]* reported cancer mortality was lower in diabetics receiving metformin (vs. sulfonylureas or insulin, HR 0.50-0.77), but they did not study diabetics not receiving any drug therapy. Furthermore, while confirming lower cancer risk in diabetics receiving metformin (versus those not receiving metformin), Monami et al. *[Monami, 2008]* did not find similar beneficial effects in diabetics receiving thiazolidenediones; effects of sulfonylureas (another class or oral anti-diabetic agents) were drug specific rather than a class effect. Libby et al. *[Libby, 2009]* have reported a significantly reduced risk of incident cancers (HR 0.63, 95% CI 0.53-0.75) in diabetics receiving metformin (versus those not receiving metformin); they recommended a randomized trial be conducted to "assess whether metformin is protective in a population at high risk for cancer". Finally, Currie et al *[Currie, 2009]* reported that diabetics receiving insulin or sulfonylureas had a significantly higher risk of subsequent cancer (HR 1.42 95% CI 1.27-1.60 and HR 1.36 (95% CI 1.27-1.60 respectively) compared to those receiving metformin alone.

Several reports recently published in Diabetologia (2009) have addressed a concern that an insulin analog (glargine) that is associated with increased mitogenic effects in vitro may be associated with increased risk of cancer in diabetic patients receiving this agent *[Hemkens, Jonasson, Colhoun, Currie, Home, 2009]*. The concern was first raised by Hemkens et al (Germany) who reported a dose dependent increased overall cancer risk in those receiving 50 IU/day og glargine (HR 1.31, 95% CI 1.20-1.42 compared to those receiving human insulin). Colhoun et al *[Colhoun, 2009]* identified a modest increased overall cancer risk in diabetics receiving glargine insulin (HR 1.55, 95% CI 1.01-2.37), and they found a significantly increased breast cancer risk in this group (adjusted HR 3.65, 95% CI 1.05-12.68). Jonasson et al *[Jonasson, 2009]* failed to identify an increase in overll cancer incidence in those receiving glargine insulin but they identified an increased risk of breast cancer (adjusted HR 1.97, 95% CI 1.29-3.00). Finally, Currie et al *[Currie, 2009]* failed to find an association of glargine insulin use with cancer incidence, but reported that diabetics receiving metformin had the lowest cancer risk (see preceding paragraph). In a meta-analysis of glargine insulin trials sponsored by Sanofi-Aventis, Home et al *[Home, 2009]* failed to identify an increased frequency of cancer reported as a serious event in diabetics receiving glargine (vs human) insulin. These results must for interpreted with caution for several reasons. First, it must be noted that these reports involved very short follow-up periods (less than 2.5 years in the observational studies and it was less than 1 year in all but one of the trials included in the meta-analysis). As a result, any effect of glargine insulin (or other insulins) on cancer risk see in these studies likely reflected an effect on progression of undiagnosed cancers rather than initiation of new cancers. Additionally, baseline imbalances between those receiving glargine and those not receiving galrgine (such as more obesity in the glargine group seen in some studies) may have accounted for effects on cancer incidence (representing confounding by indication. Furthermore, metformin (which may lower cancer incidence) was used concurrently with insulin in some studies, often to a differential extent in those receiving glargine versus other insulins. As a result, firm conclusions cannot be drawn regarding the effect of glargine insulin on cancer risk. Nonetheless, these observations are consistent with an adverse effect of insulin on cancer, possibly cancer progression and they strengthen the rationale for MA.32.

Evidence from Animal Models and Cell Culture

Insulin and Metformin in Laboratory Models of Breast Cancer

Studies in rodent models and cell culture support the concept that insulin stimulates mammary tumour growth. Early experiments revealed that N-nitroso-N-methylurea- induced mammary carcinomas grew more slowly in insulin-deficient diabetic rats; this was reversed with insulin treatment *[Cocca, 2003]*. Furthermore, chronic administration of a human insulin analogue, Asp B10, caused breast cancer in normal rats *[Ish-Shalom, 1997; Milazzo, 1997]*. Since this analogue has higher affinity than native insulin for IGF-1R, it was not clear whether one or both of IGF-1R and IR were responsible. Work by others has shown that IR is expressed in normal mammary epithelial cells and is upregulated in breast cancer cells *[Frittitta, 1997]*. In cell culture, insulin stimulates mitogenesis in breast cancer cells at concentrations which do not bind or stimulate IGF-1R and in the presence of IGF-IR specific blocking antibodies *[Papa, 1996]*, consistent with a direct role of insulin. Additional data supporting a direct role for insulin in mammary tumour growth stems from experiments examining insulin receptor substrate 1 (IRS-1) and insulin receptor substrate 2 (IRS-2), major signaling proteins and substrates of the IR tyrosine kinase. Cells expressing a dominant-negative IRS-1 molecule with all 18 Tyr phosphorylation sites mutated to phenylalanine had reduced cancer cell growth *[Chang, 2002]*. Breast tumours induced in IRS-$2^{-/-}$ mice expressing the polyanna middle T antigen in mammary gland grew as expected, but had a significantly reduced metastatic behaviour, even when the IRS-2 lacking tumours were transplanted into wild-type mice *[Nagle, 2004]*. These observations are consistent with a direct effect of insulin on tumour growth.

Recent studies have evaluated rodent models of insulin resistance (in which endogenous insulin levels are elevated) to provide in vivo data relevant to humans. In one diet induced model of obesity, two transplanted tumour cell lines (Lewis lung carcinoma and mouse colon 38-adenocarcinoma) showed increased tumour growth with increased obesity and insulin resistance *[Yakar, 2006]*. In another, more severely insulin resistant but non-obese "fatless" mouse model, breeding with a transgenic mouse mammary gland tumour model, C3(1)/T-Ag, showed a higher tumour incidence and multiplicity as well as decreased tumour latency in insulin resistant mice. Since these "fatless" mice lacked adipose tissue-derived hormones, including leptin, the role of insulin and/or IGF-1 (as opposed to adipocytokines such as leptin) was supported *[Nunez, 2006]*. Our own unpublished preliminary data show that a high fat diet in the HER2 overexpressing breast cancer mouse model leads to earlier and more frequent appearance of second and multiple tumours. Together, these observations strongly support a significant role of elevated insulin as an adverse effector of breast cancer growth.

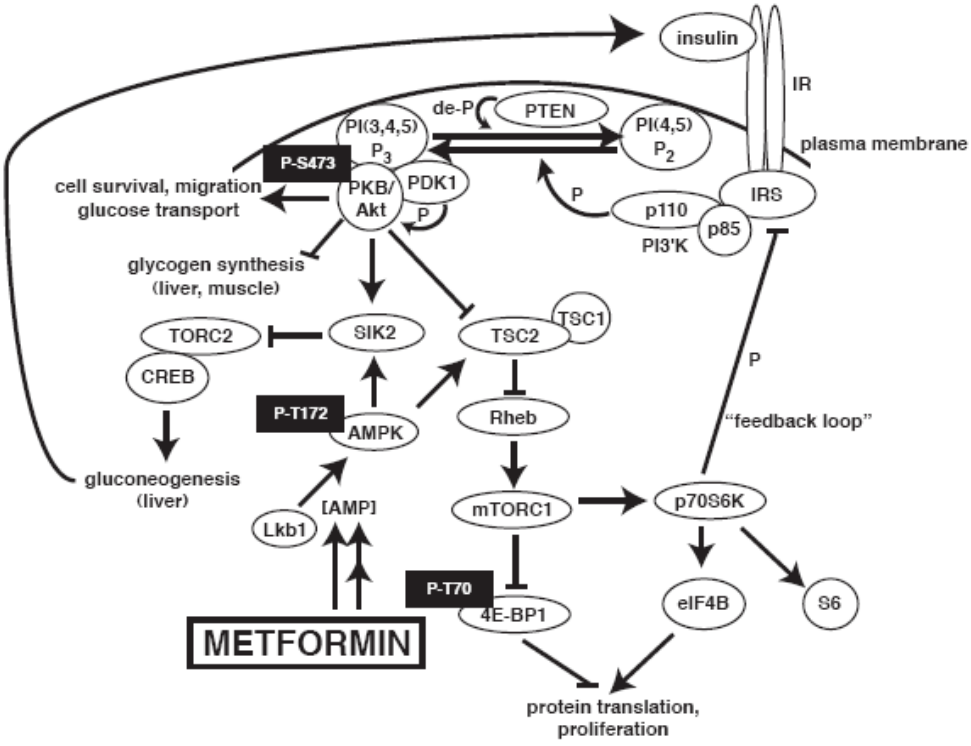
The effect of metformin in mouse mammary tumour models has also been explored. Anisimov et al *[Anisimov, 2005]* have reported that metformin significantly increases latency for mammary tumour development, significantly reduces mammary tumour size and significantly increases both mean and maximal life span in a HER2 overexpressing breast cancer mouse model. These effects were associated with a non-significant reduction in insulin levels. Similar results have recently been reported by Huang et al *[Huang, 2008]* in a PTEN deficient breast cancer mouse model – metformin suppressed tumourigenesis via the LKB1-AMPK pathway (described below). These two studies investigated metformin in doses that approximated the dose/plasma levels in humans (i.e: metformin 1500-2250 mg per day) – ranging from approximately 0.5 to 18 times the human dose. In contrast, another recent study *[Phoenix, 2009]* suggested metformin use in a mouse xenograft model was associated with an increase in VEGF production which led to augmented angiogenesis and mammary tumour growth. This study has been criticized because the cell line studied was actually derived from melanoma (not breast cancer) *[Hadad, 2009]* and the doses of metformin used in this study were 45 times (or more) that used in humans and plasma metformin levels were 300 times the recommended levels in humans *[Stambolic, 2009]*. Stimulation of angiogenesis occurs with other mTOR inhibitors and does not appear to be clinically relevant. In the case of metformin, VEGF effects appear to be dose and/or model related – large doses may provide excess metabolic stress leading to enhanced compensatory VEGF response. At present, there is no evidence to suggest that metformin in doses as high as 18 times the standard clinical dose exerts similar effects on VEGF or stimulates tumour growth in animal model systems.

Molecular Mechanism of Metformin Action (see Figure 2 below)

By inhibiting transcription of key gluconeogenesis genes in the liver and increasing glucose uptake in skeletal muscle, metformin reduces levels of circulating glucose, increases insulin sensitivity and reduces hyperinsulinemia *[Cusi, 1998; Witters, 2001]*. Activation of AMPK plays a prominent role in mediating the effects of this drug *[Zhou, 2001; Vazquez-Martin, 2009; Santomauro Junior, 2009]*. AMPK is a central cellular energy sensor whose activation leads to suppression of many of the processes highly dependent on ample cellular ATP supply, including gluconeogenesis, protein and fatty acid synthesis and cholesterol biosynthesis, while promoting catabolic processes such as fatty acid beta-oxidation and glycolysis *[reviewed in Hardie, 2007; Towler, 2007]*. Metformin directly inhibits complex I of the respiratory chain leading to decreased ATP synthesis and a rise in the cellular AMP:ATP ratio, effectively mimicking conditions of cellular energy stress *[El-Mir, 2000; Owen, 2000]*. Increased association of AMPK with AMP under such conditions facilitates its phosphorylation and activation by the upstream kinase LKB1, the protein product of the tumour suppressor gene mutated in the Peutz Jeghers cancer predisposition syndrome *[Lizcano, 2004; Shaw, 2004]*.

While most research into metformin action has focused on insulin-responsive tissues, emerging evidence suggests that other cell types, including cancer cells, initiate an AMPK-dependent energy stress response to metformin. Metformin-induced AMPK activation directly impacts the adaptive response of certain cancer cells to nutrient limitation and affects their survival, in part via a p53-dependent mechanism in colon cancer cell lines *[Buzzai, 2005; Buzzai,2007]*. This p53 dependence has not been seen in breast cancer cell lines *[Zhuang, 2008]*. In BC cell lines, metformin causes a strong growth suppressive response *[Irwin, 2009]*. This effect is independent of HER2 status and it has been found in a variety of cell lines having characteristics of the spectrum of molecular subtypes of breast cancer (e.g. luminal A and B, HER2, basal) *[Zhuang, 2008; Alimova, 2009]*. In human glioma and pancreatic cancer cell lines metformin exhibits an antiproliferative, antimigratory and proapoptotic effect *[Wang, 2008; Beckner, 2005; Isakovik, 2007]*. Recent data suggest there may be differential effects of metformin in hormone receptor and/or Her-2 positive versus triple negative breast cancer cell lines, with potential therapeutic activity being seen in all cell lines but a potential unique additional effect that includes enhanced apoptosis occurring in triple negative breast cancer cell lines and reduced expression of HER2 in HER2 positive cell lines *[Alimova, 2009; Liu, 2006]*. Because of these observations, and because a greater effect of dietary fat reduction (associated with weight loss) was reported in ER/PgR negative versus ER/PgR positive breast cancer in WINS (discussed above), we plan to conduct a formal subset analysis in the ER/PgR negative breast cancer subset enrolled onto MA.32.

Figure 2 Simplified schematic of the molecular mechanism of metformin action. See text for details. Phospho-specific antibody epitopes relevant to key molecular markers are highlighted within the black boxes. An additional marker, stathmin 1 (STMN 1), is a recently discovered surrogate marker for the signaling throughput via the PI3K/PTEN signaling pathway that can be monitored by immunohistochemistry *[Saal, 2007]*



In addition to the effects of metformin and AMPK on metabolic processes, activation of AMPK results in rapid inhibition of cellular protein synthesis and growth. Mechanistically, AMPK achieves this by phosphorylation and stabilization of the protein product of the tuberous sclerosis complex 2 (TSC2) tumour suppressor gene *[Corradetti, 2004; Inoki, 2003]*, which serves as an integrator of various regulatory inputs implicated in cell growth. TSC2 activity negatively regulates a small GTPase Rheb which serves as a binary switch for the master regulator of eukaryotic protein synthesis, the mTOR protein *[reviewed in Manning, 2003; Sarbassov, 2005]*. In addition to mediating the inhibitory effects of AMPK on protein synthesis, TSC2 integrates several activating inputs that impact cellular protein translation, notably signals emanating from the availability of amino acids and oxygen and growth factor-dependent stimulation of PI3K/Akt signaling. Activation of mTOR-dependent protein translation, as judged by phosphorylation of its downstream targets, p70S6K and 4E binding protein 1 (4E-BP1), is often found in BC specimens and has been shown to correlate with malignant progression and an adverse prognosis *[Armengol, 2007; Rojo, 2007]*.

Recent work indicates that increased mTOR-dependent protein translation and cell growth are hallmarks of tumourigenesis downstream of activated PI3K/Akt signaling. This cellular cascade is one of the most frequently deregulated oncogene/tumour suppressor gene networks in human breast cancer. Mutations in one of the genes encoding the PI3K catalytic subunit, PIK3CA, have been found in 20-35% primary breast cancer specimens and been associated with greater tumour size, lymph node metastasis and poor prognosis *[Bachman, 2004; Lee, 2005; Li, 2006; Saal, 2005; Wu, 2005]*. Mutations and loss of expression of the critical negative regulator of this pathway, the PTEN tumour suppressor, have been found in up to 40% of human breast cancers *[Rojo, 2007; Bachman, 2004, Lee, 2005; Li, 2006, Saal, 2005; Wu, 2005; Perez, 2007; Sansal, 2004; Vivanco, 2002]*, while up to 30% overexpress ErbB2, a potent activator of the PI3K cascade *[Yu, 2000]*. Notably, PI3K/Akt/mTOR signaling throughput correlates with hyperplastic changes in breast epithelium, increasing from normal epithelium to hyperplasia and atypia, to invasive lesions *[Zhou, 2004]* and contributes to resistance of breast cancer cells to chemotherapy, trastuzumab and tamoxifen *[Morgensztern, 2005]*.

Clinical Experience with Metformin

Metformin is a well known, readily available oral agent that is commonly used to treat Type 2 diabetes and, more recently, insulin resistance. It is inexpensive and, in general, it is well-tolerated. Its most potentially dangerous toxicity is lactic acidosis (estimated incidence: 3 cases per 100,000 patient years); when lactic acidosis occurs it is fatal in 50% of cases *[Kirpichnikov, 2002].* There is considerable debate as to whether the lactic acidosis that occurs in diabetics receiving metformin is due to the use of metformin or to the presence of diabetes *[Fantus, 2005; McCormack, 2005]*. This controversy arises from results of a meta-analysis that showed comparable rates of lactic acidosis in diabetics who did, and who did not, receive metformin *[Salpeter, 2003]*, by failure to demonstrate an association between lactic acidosis and metformin levels in diabetics *[Lalau, 1995; Jones, 2003]* and by the failure to observe increased lactic acidosis rates after the introduction of metformin in the United States *[Brown, 1998]*. Regardless, risk of lactic acidosis is increased in those over 80 years of age, in those with current or past congestive heart failure, renal insufficiency or hepatic insufficiency (including individuals with habitual excess alcohol intake), and in those with a prior history of metabolic acidosis. Risk of lactic acidosis is believed to be increased after surgery and use of radiologic contrast material – metformin should be temporarily discontinued for approximately 48 hours in these situations. Lactic acidosis is extremely rare if metformin use is restricted to individuals without any of these predisposing conditions. Additional toxicities include: gastrointestinal (> 1/10 - diarrhea, nausea, vomiting, abdominal bloating, flatulence, anorexia, metallic taste – usually transient when treatment is started and resolving spontaneously with continued treatment), rash (< 1/10,000), subnormal vitamin B12 (9% after 6 months – it is suggested that Vitamin B and/or hemoglobin levels be monitored at 6-12 months), hepatic dysfunction (<1/10,000), elevations in TSH (< 1/10,000). Modest weight loss (up to five pounds) is common.

Hypoglycemia does not normally occur when metformin is administered – extreme caloric restriction or excessive physical activity without adequate caloric intake may rarely lead to hypoglycemia. Metformin is commonly used for many years in diabetics without cumulative adverse effects. It also lowers risk of subsequent diabetes, and complications of the IRS (Insulin Resistance Syndrome) in individuals with IRS *[Knowler, 2002; Orchard, 2005]*.

Quality of Life in Placebo Controlled Metformin Trials

In this trial, metformin will be compared to a placebo. Clinical experience with metformin shows it is mainly associated with gastro-intestinal side effects. A literature review found six trials *[DeFronzo, 1995; Grant, 1996; Hoffman, 1997; Horton, 2000; Chiasson, 2001; Mather, 2001]* comparing metformin to a placebo that provided information about the frequency and magnitude of the main side effects and the contribution of GI symptoms to dropout rates. Although these trials reported toxicity, they did not formally evaluate QOL. Other trials that have not reported toxicity to date have not been included here.

Clinical Trials Comparing Metformin to Placebo

Study	Intervention	# of Pts	Side-effects		# of drop-outs due to GI symptoms/total drop outs
DeFronzo RA et al.1995	Protocol 1:				
	Metformin titrated up to 2250 mg/day	n=143	Severe diarrhea Severe nausea	8% 4%	11/31 pts
	Placebo	n=146			0/41 pts
	All for 29 weeks				
Grant PJ 1996	Metformin 3g/day	n=27	GI symptoms, not defined		13/13 pts
	Metformin 1.5g/day	n=25			8/12 pts
	Placebo	n=23			2/6 pts
	All for 6 months				
Hoffman U et al. 1997	Acarbose 100 mg TID	n=31	Flatulence or bloating (mild to moderate; ↓ with time)	16 pts	3 pts
			GI complaints:		
	Metformin 850 mg BID	n=31	Nausea, emesis, diarrhea	1 pt	1 pt
			Flatulence	1 pt	1 pt
	Placebo	n=32			
	All for 24 weeks				
Horton ES et al. 2000	Nateglinide 120 mg a.c.	n=172	Diarrhea	19.7%	1/5 pts
	Metformin 500 mg TID	n=178	Diarrhea	14.5%	6/12 pts
	Combination	n=172			6/16 pts
	Placebo				3/9 pts
	All for 24 weeks		Other side effects (comparable between groups):		
			URTI	14.3%	
			Headache	7.1%	
			Abdominal Pain	6.3%	
			Nausea	5.7%	
			Fatigue	5.1%	
			Sinusitis	5.0%	

Table continued on next page …

Study	Intervention	# of Pts	Side-effects		# of drop-outs due to GI symptoms/total drop outs
Chiasson J-L 2001	Miglitol 100 mg TID	n=82	Flatulence Diarrhea Constipation Nausea Dyspepsia Abdominal Cramps	63.2% 53.3% 9.2% 17.1% 14.5% 7.9%	11/11 pts*
	Metformin 500 mg TID	n=83	Flatulence Diarrhea Constipation Nausea Dyspepsia Abdominal Cramps	14.5% 10.8% 6.0% 2.4% 2.4% 2.4%	5/5 pts* 19/19*
	Combination Placebo All for 36 weeks	n=6 n=83			2/2 pts
Mather KJ et al. 2001	Metformin 500 mg BID	n=29	GI symptoms (mild GI discomfort)	4 pts	1/2 pts
	Placebo All for 12 weeks	n=15	GI symptoms (mild GI discomfort)	2 pts	1/2 pts

** It is assumed all drop-outs were due to GI tocicity*

It can be seen that gastrointestinal toxicity occurred more frequently in patients receiving metformin but, at doses comparable to those we plan to use in this study (we plan to give 1700 mg/day), it infrequently led to dropout from the study (0 to 6% dropout rate at doses ≤ 2000mg/day).

In other studies of metformin in diabetes patients, QOL has been measured. However, the questionnaires used are not relevant for our study. For example, the "Diabetes Specific Quality of Life Scale" *[Bott, 1998]* and the "Diabetes Treatment Satisfaction Questionnaire" *[Bradley, 1994]* deal with the impact of being diabetic on social functioning or glycemic control. Metformin has been used also in polycystic ovary syndrome. A Cochrane review found no study of metformin vs. placebo where QOL was an outcome *[Costello, 2007]*.

Even though it is unlikely that a decision to implement metformin as an adjuvant treatment in early stage breast cancer will depend on QOL results, we have elected to include HRQOL measurement in a subset of the population of MA.32 because metformin is associated with side-effects that may lead to discontinuation of the treatment and may impact QOL (e.g. diarrhea, flatulence). Furthermore, its effects on QOL in breast cancer patients receiving standard breast cancer therapy (.e.g. aromatase inhibitors, tamoxifen, herceptin) are not known. We will use the EORTC QLQ C-30 (Aaronson NK, 1993) supplemented by additional items from the CCTG item bank/new items. QOL assessments will be conducted at baseline, 6 and 12 months and then annually until 5 years. There is little evidence to suggest there are major differences in overall HRQOL according to adjuvant hormone therapy use (tamoxifen, aromatase inhibitors, none), however, there may be small but important differences in endocrine symptoms and bone pain similar to those that have been reported in adjuvant randomized trials of aromatase inhibitors compared to tamoxifen or placebo. In the CCTG MA.17 randomized trial comparing an aromatase inhibitor (letrozole) to a placebo in the extended adjuvant setting, there were small differences in favor of the placebo for bodily pain, general health, vasomotor and physical symptoms using the SF-36 and the Menopause Specific Quality of Life Questionnaire *[Whelan, 2005]*.

In the ATAC trial which compared anastrozole to tamoxifen, there was no difference in QOL between the two arms, but there were small differences in endocrine symptoms assessed with the FACT-B (less cold sweats and vaginal discharge but more vaginal dryness, painful intercourse and loss of sexual interest with anastrozole) *[Fallowfield, 2004]*. In the International Exemestane Study (exemestane versus tamoxifen after 2-3 years of tamoxifen), there was more vaginal discharge in those receiving tamoxifen when symptoms were assessed using the FACT-B *[Fallowfield, 2006]*.

Because endocrine symptoms and bodily pain may differ with different adjuvant endocrine therapies, we plan to enroll equal numbers of patients in the HRQOL sub-study in each of the following groups defined by adjuvant hormone therapy at randomization: no hormone therapy, tamoxifen or aromatase inhibitor.

We will also assess patterns of diet and physical activity in women who participate in the Quality of Life sub-study in order to evaluate changes in these behaviours over time in the group as a whole and in the participants randomized to Metformin as compared to those randomized to placebo. Dietary intakes will be assessed using the Block Alive Screener. In validation testing, the questionnaire was demonstrated to have good reliability (Pearson Correlation Coefficients [PCC] 0.65 – 0.8) construct validity (PCC 0.56 – 0.92) and predictive validity as compared to the full Block Food Frequency Questionnaire (PCC 0.44 – 0.56). The instrument was designed to focus on intake of saturated fat, trans- fats, total sugar, added sugars, fruit and fruit juices and vegetables along with estimates of Glycemic Load and Glycemic Index. Secondary estimates can be made for kcal, protein, total fat, carbohydrate and dietary fibre. Physical Activity patterns will be assessed through the Nurses Health Study II Questionnaire which asks participants to indicate the frequency with which they participate in a number of common recreational activities. This information will be utilized to generate a weekly Metabolic Task Equivalent (MET- hour score) which will provide a measure of both duration and intensity of physical activity. The Physical Activity Questionnaire has been validated on a number of populations and has been shown to correlate well with 7-day activity diaries and seasonal past 4-week questionnaires (Wolf, A. 1994). It has been widely used in observational studies to quantify physical activity patterns in breast cancer and other populations *[Holmes, M 2005; Meyerhardt J, 2006: Meyerhardt J, 2006]*.

Correlative Studies

Correlative studies will be an integrated component of the MA.32 clinical trial. Investigations of fasting glucose and insulin levels at baseline, 6 months post randomization and at the end of study treatment will be mandatory and will explore the indirect insulin-mediated effect of metformin on protocol defined outcomes. Tumour related factors at baseline, serum and plasma biomarkers will be evaluated and sample collection for this component will be strongly encouraged but remains optional. Proposed studies are outlined in section 13 of the protocol.

Summary

There is strong clinical evidence that fasting insulin levels are associated with poor BC outcomes across the normal range of insulin levels that is typically seen in women with early stage breast cancer, without evidence of a floor or ceiling effect. At the dose we plan to use in MA.32, metformin safely lowers insulin levels by about 20% in non-diabetic BC and non-cancer subjects who have baseline fasting insulin levels in the normal range. Observational evidence suggests that metformin use in diabetics may reduce cancer risk and mortality and may be associated with enhanced responses to neoadjuvant systemic therapy in diabetic women with BC. We hypothesize that metformin will reduce BC growth through its effect on insulin levels and we believe there is no justification for selecting subjects by insulin levels based on an insulin dependent action of metformin. Growing molecular evidence that metformin may also exert an insulin independent effect on breast cancer via activation of an insulin independent, AMPK-dependent energy stress response and/or inhibition of PI3K/Akt/mTOR signaling strengthens the rationale for studying metformin in BC. The existence of this direct (non-insulin dependent) metformin effect on AMPK/mTOR provides additional justification for inclusion of women with a broad range of insulin levels in MA.32 rather than limiting enrolment to those with insulin levels above an arbitrarily chosen cutpoint. Because metformin is a readily available, inexpensive oral agent, with known (and easily manageable) toxicities, we believe evaluation of its therapeutic effects in early stage BC can proceed at an accelerated pace.

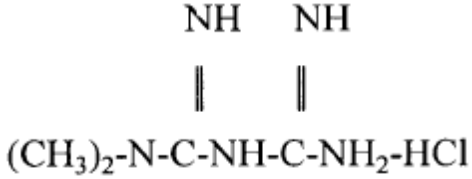
3.0 BACKGROUND THERAPEUTIC INFORMATION

(For a complete summary, please consult your current Metformin Product Monograph.)

3.1 Name and Chemical Information

N,N – dimethyl biguanide hydrochloride

3.2 Chemical Structure



Molecular mass = 165.6

Metformin HCl is a white crystalline powder soluble in water and 95% ethyl alcohol. It is practically insoluble in ether and in chloroform.

Melting Point: 218-220º C

3.3 Mechanism of Action

Metformin HCl is a biguanide derivative producing an antihyperglycemic effect which can only be observed in man or in the diabetic animal and only when there is insulin secretion. Metformin, at therapeutic doses, does not cause hypoglycemia when used alone in man or in the non-diabetic animal, except when using a near lethal dose. Metformin has no effects on the pancreatic beta cells. The mode of action of metformin is not fully understood. It has been postulated that metformin might potentiate the effect of insulin or reduce hepatic gluconeogenesis.

- Metformin absorption is relatively slow and may extend over about 6 hours. The drug is excreted in urine at high renal clearance rate of about 450 mL/min. The initial elimination of metformin is rapid with a half-life varying between 1.7 and 3 hours. The terminal elimination phase accounting for about 4 to 5 % of the absorbed dose is slow with a halflife between 9 and 17 hours. Metformin is not metabolized. Its main sites of concentration are the intestinal mucosa and the salivary glands. The plasma concentration at steady-state ranges about 1 to 2 mcg/mL.

Certain drugs may potentiate the effect of metformin HCl, particularly sulfonylurea type of drugs in the treatment of diabetes. The simultaneous administration of these two types of drugs could produce a hypoglycemic reaction, especially if they are given in patients already receiving other drugs which, themselves, can potentiate the effect of sulfonylureas. These drugs can be: long-acting sulfonamides, tubercolostatics, phenylbutazone, clofibrate, monoamine oxidase inhibitors, salicylates, probenecid and propanolol.

In healthy volunteers, the pharmacokinetics of propranolol and ibuprofen were not affected by metformin when co-administered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to sulfonylureas, which are extensively bound to serum proteins.

3.4 Toxicology

3.4.1 *Human Toxicity*

In man, no adverse effect has been reported on liver or kidney function, the hematopoietic system or on the blood vessels.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases / 1000 patient/years with approximately 0.015 fatal cases / 1000 patient/years).

The consecutive administration of both phenformin and metformin to the same patient has allowed for the demonstration of a fundamental difference between these two biguanides in relation to lactacidemia. In some instances, patients developed hyperlactacidemia with phenformin when the same patients were presenting normal lactic acid levels while being treated with metformin. In other instances, hyperlactacidemia observed during a treatment with phenformin did regress when metformin was substituted for phenformin. Metformin may increase lactacidemia but to a degree that is clinically less significant than the elevation seen after phenformin.

3.4.2 *Teratology*

Teratological studies were carried out in albino rats divided in three groups:

No abnormalities were found, even when high doses were administered. The number of animals was the same in each group.

Death rate in the three groups of treated animals and controls was approximately the same. However, the number of living animals in each group treated was slightly lower than in the control group. Also, the frequency of litters exceeding 10 live animals was slightly higher in the control group. A loss of weight at the time of weaning has been observed when compared to the control group.

Nevertheless, on a statistical basis, differences were shown to be non-significant. There is no difference between the groups of treated animals and the control group regarding the number of stillborn. The number of deaths after birth was slightly higher in metformin treated groups than in the control group, but the comparison of average death rates is not significant ($p \geq 0.05$).

3.5 Phase I & II Trials

Goodwin studied physiologic and quality of life effects of metformin (500 mg po three times daily for 6 months) in a single arm Phase II study involving 32 women with early BC who had completed their primary therapy; > 95% had baseline insulin levels in the normal range (see table below) *[Goodwin PJ, 2008]*. Insulin levels fell by 22.4% and insulin sensitivity [evidenced by the Homeostasis Model Assessment (HOMA)] *[Vaccaro, 2004]* improved by 25% after 6 months of metformin. Because participants were disease-free, effects on tumour proliferation could not be assessed. In general, metformin was well tolerated. There were no significant changes in HRQOL as measured using the EORTC QLQ C-30 (overall physical condition, global health, overall QOL, physical functioning, social functioning) or specific symptoms (nausea, appetite, diarrhea, constipation, pain) during the study. Mild to moderate GI toxicity led to discontinuation of the drug in 4 (12%) of the women. This compares to an aromatase inhibitor discontinuation rate of 22% in a recent clinic-based study *[Ohsako, 2006]*. An additional 6 (19%) did not complete the study for other reasons – vacation (2), development of diabetes requiring withdrawal from the study (1), pneumonia (1), family physician preference (1), scheduling problems (one woman completed six months of metformin but did not attend for final study measurements). Non-completion of the study was significantly associated with lower baseline HRQOL (global health, overall physical condition, overall QOL, physical or social functioning, pain). We believe non-completion rates will be lower in the phase III trial proposed here because we will gradually ramp up the metformin dose (850 mg po daily for 4 weeks, then 850 mg bid for the remainder of the 5 year intervention) and because we will explain to participants that we are hypothesizing metformin may influence breast cancer outcomes (no such claims were made in the Phase II study), thereby enhancing motivation to continue though intercurrent illnesses and vacations.

Phase II – Metformin in Locoregional Breast Cancer (post surgery, chemotherapy) n=32

	Baseline	6 months	% Change	p
Insulin (pmol/L)	70.7	54.9	-22.4	0.02
Glucose (mmol/L)	5.0	4.9	-2.3	0.29
HOMA	2.24	1.67	-25.6	0.02
Weight (kg)	75.4	73.5	-2.5	0.01
BMI (kg/m2)	28.1	27.4	-2.5	0.007

3.6 Adverse Effects

Please refer to protocol section 2, heading "Clinical Experience with Metformin" for a summary of adverse effects.

3.7 Pharmaceutical Data

Metformin

Supplied: 850 mg caplet, white to off-white, capsule-shaped, biconvex, film-coated. Engraved APO 850 on one side, plain on the other side

Stability: 2 year expiration

Storage: Store at room temperature (15° to 30°C) in well-closed containers

Route of Administration: Metformin is administered orally, with food

Placebo

Supplied: caplet, white to off-white, capsule-shaped, biconvex, film coated. Engraved APO 850 on one side, plain on other side

Stability: 3 year expiration

Storage: Store at room temperature (15° to 30° C) in well-closed containers

Route of Administration: Placebo is administered orally, with food

4.0 TRIAL DESIGN

The trial population will consist of subjects with invasive breast cancer who, within the previous 12 months, have received the first histologic diagnosis of invasive breast carcinoma and have undergone definitive surgical treatment for invasive breast cancer. Subjects may have received, at the discretion of their treating physician, standard adjuvant loco-regional radiation, adjuvant endocrine treatment, trastuzumab or other biologics or bisphosphonates prior to or during study treatment. Chemotherapy (adjuvant or neoadjuvant), if given, must be completed at least 4 weeks prior to randomization.

The first 888 eligible English/French -speaking MA.32 subjects will complete questionnaires dealing with Quality of Life. English-speaking subjects from the Quality of Life sub-study will also complete the Physical Activity and Diet Questionnaires. (Appendices VI and VII).

All subjects (regardless of randomization) will be given basic information on healthy lifestyle (diet, physical activity) developed by the American Cancer Society (www.cancer.org). The information to be provided is included as Appendix XII.

4.1 Stratification

Patients will be stratified by:
- Receptor Status (ER and/or PgR positive versus both negative*)
- BMI ($\leq$ 30 versus >30 kg/m^2)
- HER2 Status (positive versus negative**)
- Chemotherapy (any versus none)

* It is recommended that ER and PgR assays be considered positive if there are at least 1% positive tumour nuclei in the sample on testing in the presence of expected reactivity of internal [normal epithelial elements] and external control*[Hammond 2010]*.

** Positive = 3+ over-expression by IHC in > 30% of invasive tumour cells

OR HER2 gene amplification by FISH/CISH > 6 HER2 gene copies per nucleus

OR a FISH/CISH ratio: HER2 gene copies to chromosome 17 signals of $\geq$ 2.2

All other results will be considered negative.

4.2 Randomization

Subjects will be randomized (in a 1:1 ratio) to receive one of the following treatments:

Metformin or placebo, to a planned sample size of 3582.

Patients will be randomized to one of the following two arms:

Arm	Agent(s)	Dose	Route	Duration
1	Metformin	850 mg	p.o (with food)	b.i.d. X 5 years (includes 4 week ramp-up*)
2	Placebo	One caplet	p.o. (with food)	b.i.d. X 5 years (includes 4 week ramp-up*)

*The "ramp-up" to protocol dose and schedule will occur as follows:
- 1 caplet po daily for 4 weeks, then
- 1 caplet po bid for the balance of 5 years

4.3 Inclusion of Women and Minorities

There are no exclusions based on race or ethnicity in this trial. In the Canadian Cancer Trials Group as a whole, 60% of patients have been female and 40% have been male. The female preponderance reflects the number of studies performed in breast cancer. Insufficient data has been collected to test whether recruitment to breast cancer trials reflects race/ethnicity incidence in the Canadian population. This study, however, will be presented to patients through the major cancer-treatment institutions of the Canadian provinces, to which all racial/ethnic groups have equal access. The intention, therefore, is to recruit subjects from racial/ethnic groups in close approximation to the incidence of the disease in these groups. It will also be presented to patients of any race or ethnicity through participating centres of major American Cooperative Groups. Patients at participating American sites will have equal access to this study regardless of race or ethnicity; furthermore, Minority Outreach is a component of all CTEP-sponsored trials.

Within the United States, lower breast cancer incidence rates have been reported for blacks, Asians, American Indians, and Hispanics in comparison to non-Hispanic whites. Yet, blacks tend to have lower breast cancer survival rates. Several factors are thought to explain this difference. Among them are age at diagnosis, delay between onset of symptoms and diagnosis/treatment, stage, hormone receptor levels and socio-economic levels. During 1996, the racial composition of the women enrolled on NCCTG breast cancer protocols was non-Hispanic white (95%), black (4%) and Hispanic (1%).

Although there is some evidence that obesity and/or insulin resistance may occur more frequently in African Americans than in Caucasians, and that breast cancer outcomes may be poorer in African Americans *[Rose, 2007]*, there is insufficient evidence to conclude that these are causally linked, nor is there evidence that metformin has different biologic effects or efficacy in different racial groups. As a result, we will recruit subjects of all ethnic and racial groups to approximate the racial distribution of breast cancer seen at participating centers.

<table>
<tr><td colspan="6">Accrual Targets</td></tr>
<tr><td rowspan="2">Ethnic Category</td><td colspan="5">Sex/Gender</td></tr>
<tr><td>Females</td><td></td><td>Males</td><td></td><td>Total</td></tr>
<tr><td>Hispanic or Latino</td><td>358</td><td>+</td><td>1</td><td>=</td><td>359</td></tr>
<tr><td>Not Hispanic or Latino</td><td>3188</td><td>+</td><td>35</td><td>=</td><td>3223</td></tr>
<tr><td>Ethnic Category: Total of all subjects</td><td>3546 (A1)</td><td>+</td><td>36 (B1)</td><td>=</td><td>3582(C1)</td></tr>
<tr><td>Racial Category</td><td colspan="5"></td></tr>
<tr><td>American Indian or Alaskan Native</td><td>36</td><td>+</td><td rowspan="4">1</td><td>=</td><td>36.25</td></tr>
<tr><td>Asian</td><td>107</td><td>+</td><td>=</td><td>107.25</td></tr>
<tr><td>Black or African American</td><td>180</td><td>+</td><td>=</td><td>180.25</td></tr>
<tr><td>Native Hawaiian or other Pacific Islander</td><td>107</td><td>+</td><td>=</td><td>107.25</td></tr>
<tr><td>White</td><td>3116</td><td>+</td><td>35</td><td>=</td><td>3151</td></tr>
<tr><td>Racial Category: Total of all subjects</td><td>3546 (A2)</td><td>+</td><td>36 (B2)</td><td>=</td><td>3582(C2)</td></tr>
<tr><td></td><td>(A1 = A2)</td><td></td><td>(B1 = B2)</td><td></td><td>(C1 = C2)</td></tr>
</table>

Total Expected Accrual: 358 Min 358 Max

Accrual Rate: 100 pts/month

Projected Start Date of Study: Q1 2010

5.0 STUDY POPULATION

The study population will consist of subjects with invasive breast cancer who, within the previous 12 months, have received the first histologic diagnosis of invasive breast carcinoma and have undergone definitive surgical treatment for invasive breast cancer. Subjects may have received, at the discretion of their treating physician, standard adjuvant loco-regional radiation, adjuvant endocrine treatment, trastuzumab or other biologics or bisphosphonates prior to or during study treatment. Chemotherapy (adjuvant or neoadjuvant), if given, must be completed at least 4 weeks prior to randomization.

5.1 Eligibility Criteria

There will be NO EXCEPTIONS to eligibility requirements at the time of randomization. Questions about eligibility criteria should be addressed PRIOR to calling for randomization.

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to ensure that subjects who enter this study are medically appropriate candidates for this therapy. For the safety of the subjects, as well as to ensure that the results of this study can be useful for making treatment decisions regarding other patients with similar diseases, it is important that no exceptions be made to these criteria for admission to the study.

5.1.1 Subjects must have histologically confirmed invasive breast cancer and be enrolled in the trial within 12 months after the first histologic diagnosis of invasive breast cancer. A core biopsy interpreted as invasive cancer meets this criterion; otherwise, the date of first histologic diagnosis will be the date of first surgical procedure that identifies invasive cancer (biopsy, lumpectomy or mastectomy). TNM Stage (AJCC Version7) must be one of the combinations presented in Section 5.1.4. Neoadjuvant subjects should have no evidence of clinical T4 disease prior to chemotherapy and surgery. Please refer to 5.1.4 for eligible cTNM classifications. Bilateral breast carcinoma is allowed provided diagnoses are synchronous – that is, within 3 months of one another – and at least one of the two breast carcinomas meet the eligibility criteria and neither violates the eligibility criteria.

5.1.2 All subjects (both adjuvant and neo-adjuvant) must have sentinel lymph node biopsy and/or axillary lymph node dissection.

Sentinel lymph node biopsy alone is allowed in the following instances:

a) sentinel lymph node biopsy is negative: pN0

b) sentinel lymph node biopsy is positive for isolated tumour cells only: pN0 (i+)

c)* clinically node negative, T1-2 tumours with sentinel lymph node biopsy positive in $\leq$ 2 lymph nodes without extra-capsular extension or matted nodes and undergoing breast conserving surgery and tangential whole breast irradiation

(* excludes subjects treated with neo-adjuvant systemic therapy)

5.1.3 Definitive surgery and/or chemotherapy have been completed at least 4 weeks prior to randomization. Surgical margins must be clear of invasive carcinoma. If there is microscopic residual ductal in situ disease present at lumpectomy or total mastectomy margins, further excision is highly recommended. If further excision is not undertaken, the subject may still be entered on study, provided that in addition to breast or chest wall irradiation, a boost to the tumour bed is delivered. In situ lobular disease at the margin is acceptable.

5.1.4 Adjuvant subjects with the following pT pN combinations are eligible:

- pT1c, pN0 *AND* negative estrogen and progesterone receptors *AND* HER2 negative

OR

- pT2N0 and at least one of the following tumour characteristics: histologic grade 3, lymphovascular invasion, negative estrogen and progesterone receptors, HER2 positive, Oncotype Dx recurrence score $\geq$ 25 (or if Oncotype Dx recurrence score is not available, Ki67 > 14%)

OR

- Subjects with pT3, pN0

OR

- Subjects with pT1-3, pN1-3

The eligibility of neo-adjuvant subjects is assessed on the basis of cTNM. The same eligible TNM combinations apply.

5.1.5 Estrogen and progesterone receptor status must be known. (*Receptor positive by immunohistochemistry: ERICA or PgRICA versus both receptors negative. It is recommended that ER and PgR assays be considered positive if there are at least 1% positive tumour nuclei in the sample on testing in the presence of expected reactivity of internal [normal epithelial elements] and external control. [Hammond 2010]*

5.1.6 HER2 status must be known. (*Positive = 3+ over-expression by IHC in > 30% of invasive tumour cells OR HER2 gene amplification by FISH/CISH > 6 HER2 gene copies per nucleus, OR a FISH/CISH ratio: HER2 gene copies to chromosome 17 signals of $\geq$ 2.2. All other results will be considered negative).*

5.1.7 Patients must have had a bilateral mammogram within 12 months prior to randomization, unless the initial surgery was a total mastectomy, in which case only a mammogram of the remaining breast is required. (Subjects with bilateral total mastectomies and no mammogram within 12 months prior to randomization must, instead, have a physical examination of the chest wall to ensure there is no residual or recurrent disease at the time of randomization. The date of this examination is used in place of the mammogram date on the eligibility checklist.)

5.1.8 Investigations, including chest X-ray or CT chest, bone scan (with radiographs of suspicious areas) and abdominal ultrasound or liver scan or CT abdomen have been performed between the first histologic diagnosis and the time of randomization.

- Chest X-Ray, 2 view (or Chest CT) is mandatory
- Bone scans (with x-rays of abnormal areas) are required only if there are signs or symptoms of metastatic disease
- Abdominal imaging is required only if there are signs or symptoms of metastatic disease

5.1.9 Hematology investigations (WBC, Granulocytes, Platelets, Hemoglobin) have been completed within 28 days prior to randomization and results are available.

5.1.10 Biochemistry investigations have been completed within 28 days prior to randomization and values are within the parameters required by the protocol.

AST < 1.8 X ULN
ALT < 1.8 X ULN
Alkaline Phosphatase < 2 X ULN
Serum Creatinine < 115 µmol/L (1.3mg/dL)
Serum Bilirubin < institution ULN (*except for subjects with Gilbert's Disease who are eligible despite elevated serum bilirubin level*)

5.1.11 ECOG Performance Status of 0,1 or 2 (at baseline evaluation visit within 28 days prior to randomization).

5.1.12 Age ≥ 18 and < 75 and life expectancy of at least 5 years (18 years of age was used as a cut-off due to the lack of data indicating that breast cancer is a health issue in the < 18 years age group and metformin safety in pediatric patients has not been confirmed. Age > 80 carries increased risk of lactic acidosis and study intervention is for 5 years).

5.1.13 Subjects must be accessible for treatment and follow-up. Investigators must assure themselves the subjects randomized on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.

5.1.14 In accordance with CCTG policy, protocol treatment is to begin within 10 working days of patient randomization.

5.1.15 Subject consent must be obtained according to local Institutional and/or University Human Experimentation Committee requirements. It will be the responsibility of the local participating investigators to obtain the necessary local clearance, and to indicate in writing to the CCTG Study Coordinator that such clearance has been obtained, before the trial can commence in that centre. Because of differing requirements, a standard consent form for the trial will not be provided but a sample form is given in Appendix XII. A copy of the initial full board REB approval and approved consent form must be sent to the central office. The patient must sign the consent form prior to randomization or registration. Please note that the consent form for this study must contain a statement which gives permission for the CCTG and monitoring agencies to review patient records (see Section 16 for further details).

For the first 888 eligible English or French-speaking subjects only (sub-set enrollment completed 2011NOV04):

5.1.16 Subject is able (i.e. sufficiently fluent) and willing to complete the Quality of Life (EORTC QLQ C-30 and Trial Specific Checklist) in English or French. The baseline assessment must already have been completed at the time of enrolment. Inability (illiteracy in English or French, loss of sight or other equivalent reason) to complete questionnaires will not make the patient ineligible for the study; however, ability but unwillingness to complete the questionnaires will make the patient ineligible. (Once the target number of 888 subjects is achieved, this criterion will no longer need to be fulfilled.) [See Appendix VI]. Sub-set enrollment completed 2011NOV04.

5.1.17 English-speaking subjects who have completed the Quality of Life Questionnaire who are able (i.e. sufficiently fluent) and willing to complete Nurses Health Study II Physical Activity Questionnaire and Block Alive Screener in English. The baseline assessment must already have been completed at the time of enrolment. Inability (illiteracy in English, loss of sight or other equivalent reason) to complete questionnaires will not make the patient ineligible for the study; however, ability but unwillingness to complete the questionnaires will make the patient ineligible. (This component of the study will close at the same time as the Quality Of Life sub-study.) [See Appendix VII]. Sub-set enrollment completed 2011NOV04.

5.2 Ineligibility Criteria

Subjects who fulfill any of the following criteria are not eligible for admission to the study.

5.2.1 Subjects with a history of other malignancies, except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumours curatively treated with no evidence of disease for $\geq$ 5 years.

5.2.2 Subjects with locally recurrent or metastatic breast carcinoma. (Subjects with prior invasive breast cancer at any time are not eligible. Subjects with prior DCIS only in either breast are eligible provided the DCIS has been curatively treated including surgery, radiotherapy and/or Tamoxifen).

5.2.3 Subjects whose axillary node status is unknown.

5.2.4 Known diabetes (type 1 or 2) or baseline fasting glucose > 7.0 mmol/L (126 mg/dL). (Sampled and assayed according to local institution's procedures.)

5.2.5 Known hypersensitivity or intolerance to metformin.

5.2.6 Any condition associated with increased risk of metformin-associated lactic acidosis (e.g. congestive heart failure defined as New York Heart Association {NYHA} Class III or IV functional status [see Appendix IX], history of acidosis of any type; habitual intake of 3 or more alcoholic beverages per day).

5.2.7 Currently taking metformin, sulfonylureas, thiazolidenediones or insulin for any reason.

5.2.8 Current or planned pregnancy or lactation in women of child-bearing potential. Men should not father a child. (An effective method of birth control should be used while on study treatment which could include abstinence, IUD, condoms or other barrier methods of birth control because the safety of metformin in pregnancy or in male fertility has not been established).

5.2.9 Concurrent or planned participation in randomized trials of weight loss or exercise interventions or trials targeting insulin, IGF-1 or their receptors, or involving P13K inhibitors (at the time of randomization)*.

* These interventions would interfere with the primary endpoint. (Also, in general, double randomizations in breast cancer trials for MA.32 patients are permitted only if the patient meets all the eligibility criteria for MA.32 and the sponsor of the previous trial has no objection to the patient also being enrolled in MA.32).

6.0 PRE-TREATMENT EVALUATION
(See Appendix I)

Investigations		Timing
History and Physical Exam including:	• Date of LMP, Menopausal status, Height, Weight , Waist and Hip Circumference, Blood Pressure, Performance Status (ECOG), BMI, smoking history, alcohol intake	Within 28 days prior to randomization
Pathology of Primary Tumour	• Histology, ER/PgR, HER2, pTNM, Histologic Grade	
Hematology	• WBC, Granulocytes, Platelets, Hemoglobin, MCV	Within 28 days prior to randomization
Biochemistry	• AST, ALT, Alkaline Phosphatase, Serum Creatinine, Serum Bilirubin, Serum Vitamin B12 • Fasting Glucose, Fasting Insulin *(same draw; Fasting Glucose measured locally; Fasting insulin measured centrally)*	Within 28 days prior to randomization
Radiology	• Bilateral mammogram (please note that MRI may not be substituted for mammogram but may be done in addition to a mammogram)	Within 12 months prior to randomization
	• Chest X-ray(2 view), chest CT (mandatory) • Bone scan (with x-rays of abnormal areas) if there are signs or symptoms of metastatic disease • Abdominal imaging if there are signs or symptoms of metastatic disease	Between the date of first histologic diagnosis and the date of randomization.
Other Investigations	• Women of child-bearing potential not pregnant	Within 7 days prior to randomization
	• Blood samples for correlative science (optional)	Within 28 days prior to randomization*
	• Tumour block submission (for subjects who consent)	When requested by Queen's University Department of Pathology
Concomitant Medications	• Current medications/Indications	Within 14 days prior to randomization
Adverse Event	• Baseline adverse event evaluation (to document residual adverse event from previous therapy and baseline symptoms) using CTC AE version 4	Within 14 days prior to randomization
Quality of Life (N = first eligible 888 English/French speaking subjects)	• EORTC QLQ-C30, Trial Specific Checklist,	Within 28 days prior to randomization *(sample size achieved by 2011NOV04)*
Physical Activity and Diet Questionnaires (English-speaking subjects of QoL sub-set)	• Physical Activity items (Nurses' Health Study II), Block Alive Screener	Within 28 days prior to randomization *(sample size achieved by 2011NOV04)*
* Optional correlative science samples going to the central lab and not required for eligibility may be drawn after randomization and prior to start of study treatment so that they can be labeled appropriately with patient ID#.		

7.0 ENTRY/RANDOMIZATION PROCEDURES
(CTSU sites please refer to the CTSU Logistical Appendix)

7.1 Randomization

All randomizations will be done through the CCTG web-based, password-operated Electronic Data Capture (EDC) system. Complete details regarding obtaining a password, accessing the system and carrying out randomizations will be provided at the time of study activation and will also be included in the CCTG EDC Generic Data Management Guidebook, posted on the MA.32 trial specific web-site. If sites experience difficulties accessing the system and/or randomizing subjects please contact the help desk (link in EDC) or the MA.32 Study Coordinator.

All eligible subjects enrolled on the study by the participating treatment centre will be assigned a serial number which must be used on all documentation and correspondence with CCTG.

The following information will be required:
- trial code (CCTG MA.32)
- treatment centre and investigator
- date of REB approval* for study at participating centre
- version of the informed consent that the patient signed
- patient's initials, hospital number (if permitted by the local REB) and CCTG serial number
- confirmation of the requirements listed in Section 5.0, including dates of essential questionnaires and tests and actual values
- completed eligibility checklist
- stratification parameters

* Initial approval of all studies must be Full Board.

Randomization will be performed electronically. Randomization will be given by the EDC system and confirmed by e-mail.

Note: The validity of results of the trial depends on the authenticity of and the follow-up of all subjects entered into the trial. Under no circumstances, therefore, may an allocated patient's data be withdrawn prior to final analysis unless the subject withdraws participation from the trial and requests that data collection/submission cease from the point in time of withdrawal.

All eligible subjects admitted to the trial will be followed by the coordinating centre. It is the responsibility of the physician in charge to satisfy him/herself that the patient is indeed eligible before requesting randomization.

All randomized subjects are to be followed until death or until sites are informed by CCTG that further follow-up is no longer required. The follow-up requirements for ineligible subjects who have received no study treatment whatsoever are submission of the Baseline Report plus an annual Short Follow-up Report. Ineligible subjects who have had study treatment should also be followed with the Short Follow-up Report to allow for treatment and adverse events assessment.

7.2 Stratification

Subjects will be stratified by:
- Receptor Status (ER and/or PgR positive versus both negative)
- BMI (< 30 versus >30 kg/m^2)
- HER2 Status (positive versus negative)
- Chemotherapy (any versus none)

CTSU sites should refer to Appendix XI for CTSU-specific procedures.
ICR-CTSU sites should refer to the ICR-CTSU specific appendix for Group-specific procedures.
IBCSG sites should refer to the IBCSG-specific appendix for Group-specific procedures.

8.0 TREATMENT PLAN

Although the Canadian Cancer Trials Group acts as the coordinating agency for the trial, the responsibility for treatment of subjects rests with the individual investigator.

8.1 Study Treatment Plan

Breast cancers must have been completely resected by lumpectomy (resection margins must be clear of invasive cancer) or mastectomy. If there is microscopic residual in situ disease present at lumpectomy or total mastectomy margins, further excision is highly recommended. If further excision is not undertaken, the patient may still be entered on study, provided that in addition to breast or chest wall irradiation, a boost to the tumour bed is delivered.

Radiation is to be administered according to pre-specified institutional guidelines either prior to or during protocol treatment. Either neo-adjuvant and/or adjuvant chemotherapy is allowed providing the last dose was administered at least 4 weeks prior to randomization. Other adjuvant therapies (including endocrine, biologic agents such as trastuzumab or lapatinib or bevacizumab, radiation, bisphosphonates) may be given before, during or after randomization and study treatment with metformin or placebo.

All subjects (both adjuvant and neo-adjuvant) must have sentinel lymph node biopsy and/or axillary lymph node dissection.

Sentinel lymph node biopsy alone is allowed in the following instances:

a) sentinel lymph node biopsy is negative: pN0

b) sentinel lymph node biopsy is positive for isolated tumour cells only: pN0 (i+)

c)* clinically node negative, T1-2 tumours with sentinel lymph node biopsy positive in $\leq$ 2 lymph nodes without extra-capsular extension or matted nodes and undergoing breast conserving surgery and tangential whole breast irradiation

(* excludes subjects treated with neo-adjuvant systemic therapy)

All subjects (regardless of randomization) will be given basic information on healthy lifestyle (diet, physical activity) developed by the American Cancer Society (www.cancer.org). The information to be provided is included as Appendix XII.

8.1.1 *Drug Administration*

Arm	Agent(s)	Strength	Route	Duration	Schedule
1	Metformin	850 mg	p.o	5 years or until primary endpoint	850 mg p.o. b.i.d with food (includes 4 week ramp-up*)
2	Placebo	One caplet	p.o.	5 years or until primary endpoint	One caplet p.o. b.i.d with food (includes 4 week ramp-up*)

In accordance with CCTG policy, protocol treatment is to begin within 10 working days of patient randomization.

* The "ramp-up" to protocol dose and schedule will occur as follows:
  - 1 caplet po daily for 4 weeks, then
  - 1 caplet po bid for the balance of 5 years

Please see protocol section 12.1 for a complete list of criteria for stopping protocol treatment.

8.1.2 *Patient Monitoring*

A calendar schedule will be provided for each patient for the ramp-up period and telephone contact will be made with the patient one month after enrolment to assess compliance, toxicity and to ensure the patient has increased medication to twice daily. (The calendar is intended only as a tool to assist subjects in adjusting to full dose at the correct time after starting study treatment.) A record of the telephone contact will be made, by the CRA, on the Telephone Follow-up report. (Please see Appendix IV.) Any problems identified by the CRA will be communicated to the responsible Investigator.

8.1.3 *Dose Adjustments*

The major toxic effects of metformin which limit dose are gastrointestinal (nausea, abdominal bloating, diarrhea). During the ramp-up period, subjects experiencing gastrointestinal symptoms should be encouraged to take tablets with food. If no improvement, subjects should try taking study medication every other day for two weeks, once per day for two weeks and then twice per day thereafter. Subjects not tolerating study medication after this approach may go off study treatment but Investigators are urged to re-challenge willing subjects 3 months later. Dose adjustments, for reasons of toxicity, will be as in the tables below. (Please note that none of the recommended dose adjustments require splitting of study medication pills. Pills are not to be split or crushed, prior to taking, for any reason.) Breaks of up to 4 weeks consecutively or 8 weeks overall are allowed to ascertain the cause of unpleasant symptoms. Beyond this, treatment is at the discretion of the Investigator.

Gastrointestinal Toxicity

Toxicity / Adverse Event	Grade	Investigator Action
Gastrointestinal Toxicity of any type	Grade 1	Patient should be encouraged to remain on full dose. If patient is unwilling, stop study treatment for one week. For subjects who were unwilling to remain on full dose, after one week without study drug, follow the ramp-up procedure. If Grade 1 symptoms persist or recur during the ramp-up or at full dose and the patient is unwilling to continue, follow instructions for Grade 2 toxicity.
From the Gastrointestinal Category of CTC AE Nausea Distension/Bloating Diarrhea Gastrointestinal - Other	Grade 2 (or higher)	Reduce to one tablet per day for one week. If symptoms resolve or are Grade 1 only, after one week, resume full dose (2 tablets per day). If symptoms persist or recur at Grade 2 or higher, stop study treatment for 4 weeks, then resume study treatment as follows: Re-start study drug according to original ramp-up schedule (one tablet per day for 4 weeks then 2 tablets per day if tolerated). If toxicity persists or recurs, the study drug should be adjusted to the maximum dose that is tolerated with Grade 1 toxicity or lower. A second attempt to increase to full dose should be made 3 months later and if the full dose is not tolerated at that time, the maximum tolerated dose should be used for the remainder of the 5-year intervention.

Other Toxicities / Events

Toxicity / Event	Grade	Investigator Action
Hepatic dysfunction* (bilirubin > ULN except for Gilbert's Disease)	Grade 1 (or greater)	Hold study drug for up to 4 weeks. If bilirubin returns to normal within that time frame, begin one tablet per day for 4 weeks, then 2 tablets per day.
Hepatic dysfunction* AST or ALT=1.8- 3.0 X ULN	Please consult CTC AE for precise grading	Repeat AST & ALT in 2 weeks. If either AST or ALT > 1.8 X ULN, continue at discretion of Investigator, monitoring AST & ALT every two weeks until both < 1.8 X ULN – then resume annual testing. If Investigator decides to stop medication , resume once AST &ALT < 1.8 X ULN, starting with one tablet per day for 4 weeks, then increasing to 2 tablets per day with annual AST & ALT assessments
Hepatic dysfunction* AST or ALT > 3.0 X ULN	Please consult CTC AE for precise grading	Hold study drug. Repeat LFTs in 2 weeks. If AST and ALT < 1.8 ULN, resume medication. Resumption involves 1 tablet per day for 4 weeks, then increase to 2 tablets per day, at the discretion of the Investigator, with resumption of protocol specified monitoring if both AST and ALT remain at < 1.8 x ULN. If repeat AST and ALT are 1.8-3.0 x ULN, follow steps as described in section above or resume study medication at the discretion of the Investigator. If AST and/or ALT > 3.0 x ULN, initiate workup for liver disease. If AST or ALT=1.8-3.0 resume medication at the discretion of the investigator.
Renal dysfunction Creatinine $\geq$ 115 µmol/L 1.3 mg/dL	Please consult your institution's ULN and CTC AE for precise grade	Hold study drug for up to 4 weeks. After resolution of event, using 4-week ramp-up schedule (one caplet per day for 4 weeks, then 2 caplet per day)
Clinical diagnosis of congestive heart failure	$\geq$ Grade 3 (Please consult CTC AE for precise grade)	Hold study drug for up to 4 weeks. Re-start may be considered if underlying condition (e.g. acute MI) has resolved. If Metformin is started after CHF, the ramp-up schedule (one caplet per day for 4 weeks then two caplets per day) should be used. Do not re-start if symptoms persist or ongoing treatment of CHF is required.
Acidosis (Lactate $\geq$ 5.0 mM) (pH < 7.3)	Grade 3	Stop study drug and do not re-start. Report as a serious adverse event. Please consult protocol section 11.
Anemia Hgb < 110 or MCV > 105	$\geq$ Grade 1	Perform CBC and serum B_{12} level. Initiate anemia workup if cause of anemia not apparent. Continue at full dose. *(Treatment is not held for anemia regardless of toxicity grade.)*
Skin Reactions Major – generalized urticaria, bullous rashes, exfoliative dermatitis	Generalized	Stop study drug. and do not re-start.

Continued on next page …

Other Toxicities / Events (*continued*)

Toxicity / Event	Grade	Investigator Action
Stevens Johnson Syndrome Localized	Localized	Hold study drug for up to 4 weeks if possibly, probably or definitely related to study drug. When rash clears, one caplet per day for 4 weeks, then 2 caplets per day – if rash recurs, and is thought to be possibly, probably or definitely related to study medication, discontinue study medication.
Hospitalization for any reason	As per grade of event causing hospitalization	Hold study drug for up to 4 weeks. The Investigator is to determine when it is safe to re-start. The drug should be re-started using a 4-week ramp-up schedule (one caplet per day for 4 weeks then two caplets per day) if the hospitalization resulted in discontinuation of the drug for 2 weeks or longer. If the discontinuation of the drug was less than 2 weeks, the drug should be re-started at full dose (two caplets per day) without a ramp-up.
* Be alert to signs of acidosis!: protocol specific biochemistry should be checked annually. If subject develops malaise, nausea, dark urine, jaundice or right upper quadrant pain, study medication should be stopped until biochemistry is performed. Medication should be resumed according to the algorithms above (if first biochemistry results are normal, resume immediately at full dose)		

Other Situations

Diagnostic Imaging:
If the subject is scheduled for any CT scans requiring intravenous contrast material, metformin should not be taken for 24 hours prior to the investigation nor for 48 hours after the procedure. (This does not include contrast used for MRI or nuclear medicine scans, including MUGA.) Study medication may then be resumed at full dose (without ramp-up) provided there is no concern about renal function. If there is concern about renal function, creatinine should be checked prior to resumption of study medication.

General Anaesthetic:
If general anaesthetic is required for surgery, study drug should not be taken on the morning of surgery nor for 48 hours after anaesthetic and surgery. Study medication may then be resumed at full dose (without ramp-up) provided there is no concern about renal function. The drug is restarted at full dose if the duration of interruption was less than 2 weeks. If the duration of drug interruption was more than 2 weeks, it should be restarted using a 4 week ramp-up schedule (one caplet per day for 4 weeks, then two caplets per day). If there is concern about renal function, creatinine should be checked prior to resumption of study medication.

Any Situation Considered Medically Necessary:
Study medication may be held in any situation which the Investigator considers it medically necessary, for up to 4 weeks, and may be resumed at Investigator discretion, using the 4-week ramp-up if re-starting.

Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events, version 4 (CTCAE). Only events of Grade 3, 4 and 5 will be collected. (Please consult Appendix V).

8.1.4 *Concomitant Therapy*

Permitted
Subjects may receive loco-regional radiation, adjuvant endocrine treatment, trastuzumab or other biologics or bisphosphonates, at the discretion of their treating physician, before during or after randomization and study treatment with metformin or placebo. Chemotherapy (or neoadjuvant chemotherapy), if given, must be completed at least 4 weeks prior to randomization.

Not permitted
Sulfonylureas, thiazolidenediones or insulin for any reason unless these drugs become necessary to treat a new diagnosis while on study therapy in which case the patient will discontinue study treatment. Subjects should avoid excessive alcohol intake (i.e. less than 3 alcoholic beverages on any given day).

8.1.5 *Duration of Therapy*

Subjects will take their allocated therapy orally, twice daily, with food.

The DSMC recommended, as an outcome of the second interim analysis, that all ER and PgR negative subjects discontinue study medication. Specifically, the results indicated that continuation of protocol therapy will not provide additional information about the benefit of metformin in this sub-population. Please see protocol section 14 for details.

Treatment will be continued for 5 years in receptor positive (ER and/or PgR positive) subjects unless unacceptable toxicity occurs or the subject has recurrent tumour, new invasive primary cancer (other than adequately treated basal cell carcinoma or squamous cell carcinoma of the skin), or concurrent illness that necessitates withdrawal or subject decides to withdraw from participation for any reason. (For details concerning toxicity and intercurrent illness, please consult protocol section 8. For a complete list of general criteria for stopping study treatment, please see protocol section 12.1.)

If the subject's immediate management for the new diagnosis is influenced by the knowledge of which treatment she/he was assigned, study medication will be unblinded upon the Investigator's request, by CCTG.

8.1.6 *Blinding/Unblinding*

Metformin and matching placebo are identical in appearance as are the bottles in which they are provided. Blinding is critical to the integrity of this clinical drug trial. However, in the event of a medical emergency in an individual subject, in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken by the treating physician. Before breaking the blind of an individual subject's blinded treatment, the Investigator should have determined that the information is necessary, i.e. that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not investigational product-related, the problem may be properly managed by assuming that the subject is receiving active product without the need for unblinding. The need to break the blind must first be discussed with the CCTG. For any treatment code unblinding, the reason and parties involved must be documented in the patient's medical record. Treatment identification information should be kept confidential and should be disseminated only to those individuals that must be informed for medical management of the patient. The CCTG must be notified as soon as possible of any emergency situation in which the drug code was broken.

To request an unblinding of patient treatment during regular office hours (8am to 6pm eastern time), please contact the MA.32 Study Coordinator, at 613-533-6430. For emergency after hours unblinding requests:
Toll Free number: 877-617-2810 (North America Only)
International Calls: 613-541-3280

The Investigator requesting the unblinding of a patient treatment must provide:
1) the trial code (MA.32);
2) the patient ID number;
3) patient initials;
4) reason for unblinding;
5) the last treatment kit number.

9.0 EVALUATION DURING AND AFTER PROTOCOL TREATMENT

All subjects entered on study must be evaluated according to the schedule outlined in Appendix I with documentation submitted according to the schedule in Appendix IV.

Subjects are to be followed every 6 months for the first year and then annually until 5 years from randomization while on study treatment. Treatment is for 5 years or until disease recurrence/progression, new invasive primary cancer (other than BCC or SCC of the skin that has been adequately treated), intolerable toxicity or subject withdrawal for whatever reason. After study treatment discontinuation, subjects should be followed annually for delayed/persistent toxicity and disease status.

9.1 Evaluation During Protocol Treatment

Investigations		Timing
History and Physical Exam including:	• Weight, Waist and Hip Circumference, Blood pressure, BMI, Compliance (patient reported and pill count), Cardiovascular hospitalizations, New diagnosis of diabetes	• At each clinic visit
Hematology*	• WBC, Granulocytes, Platelets, Hemoglobin, MCV	• At 6, 12, 24, 36, 48 and 60 months while on study treatment
Biochemistry*	• ALT, AST, Alkaline Phosphatase, Serum Creatinine, Serum Bilirubin • Serum Vitamin B12* • Fasting Glucose, Fasting Insulin *(same draw; Fasting Glucose measured locally; Fasting insulin measured centrally))*	• At 6, 12, 24, 36, 48 and 60 months while on study treatment • At 12, 36 and 60 months while on study treatment • At 6 month visit & at 48 months (or just prior to end of study treatment if not at 48 months)***
Radiology	• Annual mammogram (*please note that MRI cannot be substituted for mammogram but may be done in addition to mammogram*)	• Annually from baseline mammogram
Other Investigations	• Serum, plasma, DNA (optional)	• At 6 month visit & at 48 months (or just prior to end of study treatment if not at 48 months)
	• As needed to assess for recurrence/progression	• As needed, at Investigator discretion
Adverse Events** *(Appendix V)*	• Subjects must be evaluated at each clinic visit for adverse events	• At each clinic visit
Quality of Life (888 patient subset)	• EORTC QLQ-C30, Trial Specific Checklist,	• At 6, 12, 24, 36, 48 and 60 months while on study treatment
Physical Activity and Diet (Quality of Life subset)	• Physical Activity Items (Nurses' Health Study II), Block Alive Screener	• At 6, 12, 24, 36, 48 and 60 months while on study treatment

* Vitamin B_{12} deficiency should be managed according to Investigator discretion.

** Adverse events will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events, version 4.

*** For subjects who discontinue study treatment anytime prior to 4 years, the mandatory fasting glucose and fasting insulin should be drawn just prior to study treatment discontinuation. For subjects who complete 4 years of therapy, a 4-year treatment should be done at the 48 month visit. Subjects who have passed the 48 month mark may have their samples drawn at the 60 month visit prior to treatment discontinuation.

9.2 Evaluation After Protocol Treatment

Subjects are seen annually, after cessation of study treatment

Prior to reaching primary endpoint

Investigations		Timing
History and Physical Exam including:	• Clinical assessment for recurrence/progression • Weight, BMI, Cardiovascular hospitalizations, New diabetes	At each clinic visit
Radiology	• Annual mammogram (*Please note that MRI may not be substituted for a mammogram but may be done in addition to mammogram*)	Annually from baseline mammogram
Other Investigations	• As necessary to assess for recurrence/progression, Contralateral breast carcinoma, DCIS alone, New invasive non-breast primary	At each clinic visit
Adverse Events	Adverse events (related to study treatment only) will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (Version 4 CTCAE - Appendix V).	At each clinic visit
There will be no QoL, Physical Activity or Diet Questionnaires after protocol treatment.		

After experiencing invasive local/regional recurrence (a primary endpoint) but no distant recurrence

Investigations		Timing
History and Physical Exam including:	• Clinical assessment for distant recurrence/progression, Contralateral breast carcinoma, New invasive non-breast primary	At each clinic visit
Radiology	• Annual mammogram (*Please note that MRI may not be substituted for a mammogram but may be done in addition to mammogram*) if there is breast tissue remaining	Annually from baseline mammogram
Other Investigations	• As necessary to assess for recurrence/progression, New primaries (breast or non-breast)	At each clinic visit
Adverse Events	Adverse events (related to study treatment only) will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (Version 4 CTCAE - Appendix V).	At each clinic visit
There will be no QoL, Physical Activity or Diet Questionnaires after local recurrence.		

After distant recurrence/progression (a primary endpoint)

Investigations		Timing
History and Physical Exam including:	• Clinical assessment	At each clinic visit
Other Investigations	• As necessary (& to assess for new invasive non-breast primary)	At each clinic visit
Adverse Events	Adverse events (related to study treatment only) will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (Version 4 CTCAE - Appendix V).	At each clinic visit
There will be no QoL, Physical Activity or Diet Questionnaires after distant recurrence.		

After Contralateral Invasive Breast Carcinoma (a primary endpoint)

Investigations		Timing
History and Physical Exam including:	• Clinical assessment for local/regional recurrence, distant recurrence	At each clinic visit
Other Investigations	• Annual mammogram (*Please note that MRI may not be substituted for a mammogram but may be done in addition to mammogram*) if there is breast tissue remaining • As necessary (& to assess for new invasive non-breast primary)	Annually from baseline mammogram
Adverse Events	Adverse events (related to study treatment only) will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (Version 4 CTCAE - Appendix V).	At each clinic visit
There will be no QoL, Physical Activity or Diet Questionnaires after distant recurrence.		

New invasive non-breast primary, treated with curative intent (a primary endpoint)

Investigations		Timing
History and Physical Exam including:	• Clinical assessment for breast recurrence/progression, contralateral breast carcinoma and DCIS alone	At each clinic visit
Other Investigations	• Annual mammogram (*Please note that MRI may not be substituted for a mammogram but may be done in addition to mammogram*) • Other investigations, as necessary	Annually from baseline mammogram
Adverse Events	Adverse events (related to study treatment only) will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (Version 4 CTCAE - Appendix V).	At each clinic visit
There will be no QoL, Physical Activity or Diet Questionnaires after a new invasive non-breast primary.		

Other new invasive non-breast primary, incurable (a primary endpoint)

Investigations		Timing
History and Physical Exam including:	• Clinical assessment	At each clinic visit
Other Investigations	• As necessary	At each clinic visit
Adverse Events	Adverse events (related to study treatment only) will be recorded and graded according to the NCI Common Terminology Criteria for Adverse Events (Version 4 CTCAE - Appendix V).	At each clinic visit
There will be no QoL, Physical Activity or Diet Questionnaires after a new invasive non-breast primary.		

10.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

10.1 Definitions of Evaluability

10.1.1 *Evaluable for Adverse Events*. All subjects will be evaluable for adverse event evaluation from the first date of their metformin/placebo.

10.1.2 *Evaluable for Quality of Life Assessment*. All subjects who have completed the quality of life questionnaires are evaluable for quality of life. The quality of life questionnaires are being done in a defined sub-set of MA.32 subjects. (Sub-set closed to accrual 2011NOV04; follow-up continues.)

10.1.3 *Evaluable for Physical Activity and Nutrition Assessment.* All subjects who have completed the Physical Activity and Nutrition Questionnaires are evaluable for these items. The Physical Activity and Nutrition Questionnaires are being done in a defined sub-set of MA.32 subjects.

10.2 Criteria for Measurement of Study Endpoints

As invasive disease free survival is an important endpoint in this study, it is vital that it be adequately and precisely documented. The definitions used are from the STEEP System *[Hudis, 2007]*.

10.2.1 *Definitions of Endpoints*

Primary Endpoint
Invasive Disease Free Survival is defined as the time from randomization to the time of any of the following events: ipsilateral and contralateral invasive breast tumour, local/regional invasive recurrence, distant recurrence, death from breast cancer, death from non-breast cancer cause, death from unknown cause, diagnosis of a second primary invasive non-breast cancer (except squamous cell carcinoma and basal cell carcinoma of skin, completely excised and presumed cured).

Secondary Endpoints
Overall Survival is defined as the time from randomization to the time of death from breast cancer, death from a non breast cancer cause or death from an unknown cause.

Distant Relapse Free Survival is defined as the time from randomization to the time of distant recurrence, death from breast cancer, death from a non breast cancer cause or death from an unknown cause.

Breast Cancer Free Interval is defined as the time from randomization to the time of diagnosis of invasive ipsilateral breast tumour recurrence, local/regional invasive recurrence, distant recurrence, death from breast cancer, invasive contralateral breast cancer, ipsilateral DCIS, contralateral DCIS.

Breast Cancer Specific Mortality is defined as the time from randomization to the time of death from breast cancer.

Contralateral Invasive Breast Cancer is defined as the diagnosis of a primary invasive breast cancer in the opposite breast after randomization.

Other Medical Endpoints – including one or more of:
1. Diabetes: initiation of new anti-diabetes medication (or confirmed MD diagnosis of diabetes)
2. Cardiovascular hospitalization or cardiovascular death (stroke, myocardial infarction)
3. Changes in BMI (Please see Appendix IX)

10.3 Evidence of Disease Recurrence/Progression

As defined below, *definite* evidence of disease recurrence is required to determine that disease has recurred.

Recurrence will be categorized as local, regional or distant.

Local (Breast) Recurrence is defined as recurrence within the breast, following partial mastectomy. See 10.5 for management.

Local (Chest Wall) Recurrence is defined as recurrent cutaneous or subcutaneous tumour occurring in an area bounded superiorly by the clavicle, inferiorly by a horizontal line at the level of the xiphisternum, medially by the midline and laterally by the posterior axillary line.

Regional (Nodal) Recurrence is defined as recurrent tumour in the lymph nodes in the homolateral axilla, homolateral supraclavicular fossa or ipsilateral internal mammary chain.

Distant Recurrence is defined as spread of disease beyond the limits specified in those above.

10.3.1 *Local - Regional Sites*

1. Definite - positive cytology, aspiration or biopsy
2. Suspicious - a visible or palpable lesion

10.3.2 *Distant Recurrence*

a) Bone Marrow
   1. Definite - positive cytology, aspiration or biopsy
   2. Suspicious - leukoerythroblastic blood picture
b) Lungs and Pleural
   1. Definite -
      i) Positive cytology, aspiration or biopsy, or
      ii) Presence of multiple pulmonary nodules which are felt to be consistent with pulmonary metastases

Note: If a solitary lung lesion is found and no other lesions are present on lung tomograms, further investigation, such as CT scan, biopsy or needle aspiration, or thoracic diseases consultation should be performed.

c) Skeletal
   1. Definite -
      i) X-ray evidence of lytic, blastic, or mixed lytic-blastic lesions on skeletal films with or without bone scan confirmation or
      ii) Biopsy proof of bone metastases or
      iii) Progressive bone scan changes over at least a four week period showing development of new lesions is necessary in asymptomatic subjects with only bone scan abnormalities

Note: In the absence of progressive disease by scan a biopsy is strongly recommended. Any positive bone scan in joints or in a recent area of trauma (surgical or otherwise) cannot be used as a criterion of treatment failure.

d) Ascites and Pleural Effusions
   1. Definite - positive cytology or
   2. Suspicious - roentgenographic or clinical evidence

e) Liver
   1. Definite -
      i) Liver enlargement, especially if the liver is nodular, with additional confirmation by an abnormal liver scan, ultrasound or CT scan demonstrating solid space occupying lesions or
      ii) Liver biopsy confirmation of metastatic disease

Note: If the liver scan, ultrasound or CT scan findings are not definitive a liver biopsy is mandatory.

f) Central Nervous System
   1. Definite -
      i) Positive CT scan or MRI, usually in a patient with neurological symptoms or
      ii) Biopsy or cytology (for a diagnosis of meningeal involvement)

10.4 Dating of First Recurrence

This should always be based on the onset of a sign but never on the onset of a symptom. The date of first detection of a palpable lesion is acceptable only when the diagnosis of tumour involvement is subsequently established.

The diagnosis of recurrent disease by radiographs or scans should be dated from the first positive record, even if this is determined in retrospect.

Initial recording of dates of first recurrence and death should be made as they occur by those who are responsible for the care of the patient. Dates that are based on suspicion alone will be reviewed by the CCTG coordinating office in order to establish their accuracy through subsequent behaviour. In addition, the case records of those subjects not reported as having recurrent disease will be scrutinized regularly to check that review is continuing and to ensure consistent recording.

10.5 Management Following Recurrence

Subject management following recurrence (breast, chest wall, regional and/or distant) is at the discretion of the Investigator but the subject must come off study treatment when recurrence is confirmed by the Investigator. (Subjects need not come off study treatment for new *in situ* breast carcinoma only).

10.6 Contralateral Breast Carcinoma – Invasive and *in situ*

A lesion in the opposite breast will be assumed to be a new primary malignancy unless obviously contiguous with recurrent chest wall disease or proven on cytology/biopsy to be of metastatic origin. Subjects must come off study treatment upon the diagnosis of invasive disease in the contralateral breast. (Subjects need not come off study treatment for new in situ breast carcinoma only).

10.7 Second Malignancy

Subjects developing any new non-breast primary malignancies, except for adequately treated superficial squamous or basal cell carcinoma of the skin or in situ carcinoma of the cervix will discontinue protocol treatment (the exceptions based on the assumption that disease has been completely surgically excised and presumed cured).

11.0 SERIOUS ADVERSE EVENT REPORTING

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 will be utilized for Adverse Event (AE) reporting. All appropriate treatment areas should have access to a copy of the CTCAE Version 4. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

All serious adverse events (SAE) defined as per ICH guidelines (see below) and other adverse events must be recorded on case report forms. In addition, all "reportable" serious adverse events are subject to expedited reporting using the CCTG SAE form. The term 'reportable SAE' is used in the definitions which follow to describe those SAEs which are subject to expedited reporting to CCTG.

11.1 Definition of a Reportable Serious Adverse Event
(Serious, Unexpected AND Related)

- All serious adverse events which are unexpected and related to protocol treatment must be reported in an expedited manner (see Section 11.2 for reporting instructions). These include events occurring during the treatment period (until 30 days after last protocol treatment administration) and at any time afterwards.
- Unexpected adverse events are those which are not consistent in either nature or severity with information contained in the Product Monograph.
- Adverse events considered related to protocol treatment are those for which a relationship to the protocol agent cannot reasonably be ruled out.
- A serious adverse event (SAE) is any adverse event that at any dose:
  - results in death
  - is life-threatening
  - requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospital admissions for study drug administration, transfusional support, scheduled elective surgery and admissions for palliative or terminal care)
  - results in persistent or significant disability or incapacity
  - is a congenital anomaly/birth defect

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the events listed above.

11.2 Serious Adverse Event Reporting Instructions

Please report only events that are serious, unexpected AND related to study treatment as serious adverse events. All reportable serious adverse events must be reported using a web-based Electronic Data Capture (EDC) system being used for this trial. For details about accessing the EDC system and completing the on-line SAE report form, please refer to the CCTG Generic Data Management Guidebook for EDC Studies posted on the MA.32 section of the CCTG website (www.ctg.queensu.ca).

Within 24 hours: Complete preliminary Serious Adverse Event Report and submit to CCTG via EDC system.

Within 10 days: Update Serious Adverse Event Report as much as possible and submit report to CCTG via EDC system.

EDC SAE web application interruption:
In the rare event that internet connectivity to the EDC SAE system is disrupted, please print and complete a paper copy of the SAE Report, available from the trial specific website.

FAX paper SAE Report to:

MA.32 Study Coordinator
Canadian Cancer Trials Group
Fax No.: 613-533-2814

Please use the same timelines for submission as for direct EDC reporting.

Once internet connectivity is restored, the information that was FAXED to CCTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

Local internet interruption:
If you are unable to access the EDC SAE system, and cannot access a paper copy of the SAE Report from the trial website, please phone the MA.32 trial team (613-533-6430) to obtain a copy of the SAE Report by FAX. Once completed, the report must be FAXED back to CCTG as indicated above. Once internet connectivity is restored, the information that was FAXED to CCTG on the paper SAE Report must also be entered by the site into the EDC SAE web application.

In cases of prolonged internet interruptions, please contact the CCTG Safety Desk for further instructions (613-533-6430).

11.3 Reporting Malignancies or Myeloid Dysplasia

Malignancies or myeloid dysplasia that are unexpected AND related to protocol treatment in the opinion of the investigator must be reported as Serious Adverse Events as described in Section 11.0 and 11.2, within 15 working days of when diagnosis is known to the investigator. Other malignancies occurring or recurring during the trial, which are considered unrelated or expected should only be reported on the case report form.

11.3.1 *Other Protocol Reportable Events – Pregnancy Reporting and Exposure Reporting*

a. Pregnancy Prevention

WOCBP and males who are enrolled in the trial must have agreed to use contraceptive method(s) as described in Ineligibility Criterion 5.2.8. Investigators may wish to additionally advise the female partners of male participants about pregnancy prevention guidelines when appropriate and compliant with local policy.

b. Pregnancy Reporting

The investigator is required to report to CCTG any pregnancy occurring in female participants, and female partners of male participants. Pregnancies occurring up to 30 days after the completion of study treatment must also be reported.

The investigator should report the pregnancy in a timely manner, within 24 hours of learning of the pregnancy using the CCTG Pregnancy Reporting Form available from the trial webpage.

Once informed consent has been obtained, the form should be updated to provide further pregnancy information and to reflect the outcome of the pregnancy. All follow-up reports must be submitted to CCTG in a timely manner. For pregnant partner of trial participant (and pregnant participants, if required by local policy), a copy of the signed signature page of the pregnancy follow-up consent must be submitted to CCTG.

Documents outlined above (including updates) must be sent to the CCTG safety desk (613-533-2812/safety-desk@ctg.queensu.ca).

If the pregnancy results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect, then an SAE report must be additionally submitted as described above. Please note, hospitalization for labour/delivery alone does not constitute an 'inpatient hospitalization' for the purposes of pregnancy reporting.

c. Exposure Reporting *(non-study participants)*

The investigator is required to report to CCTG any incidence of exposure to study agent(s). Exposure is defined as significant, direct, contact/inhalation/consumption of agent(s) by non-study participant (an individual who is not otherwise participating in this clinical trial). An example of an exposure includes a non-study participant swallowing study medication. The investigator is responsible for determining significance, based on the agent to which the individual is exposed.

The investigator should report the exposure in a timely manner, within 24 hours of learning of the exposure, using the CCTG Exposure Reporting Form available from the trial webpage.

Once informed consent has been obtained, the form should be updated to provide further exposure information and to reflect the outcome of the exposure as the information becomes available upon appropriate follow-up of the exposed individual (follow-up for at least 30 days after exposure). All follow-up reports must be submitted to CCTG in a timely manner. A copy of the signed exposure follow-up consent signature page must also be submitted to CCTG.

Documents outlined above (including updates) must be sent to the CCTG safety desk (613-533-2812/safety-desk@ctg.queensu.ca).

If the exposure results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect, then an SAE report must be additionally submitted as described above.

11.3.4 *Blinded Studies and Patient Unblinding*

Centre requests for participant unblinding as a result of a pregnancy or exposure are acceptable. However, the usual unblinding rules (see section 8.1.6) must be followed.

11.4 CCTG Responsibility for Reporting Serious Adverse Events to Health Canada (Office of Clinical Trials)

The CCTG will provide expedited reports of SAEs to Health Canada (Office of Clinical Trials) for those events which meet regulatory requirements for expedited reporting, i.e. events which are BOTH serious AND unexpected, AND which are thought to be related to protocol treatment (or for which a causal relationship with protocol treatment can not be ruled out).

11.5 CCTG Reporting Responsibility to Apotex

All serious adverse events that are judged to be serious, unexpected and related to study treatment (that is, regulatory reportable) will also be reported to Apotex, the provider of the metformin and placebo for this clinical trial.

11.6 Reporting Safety Reports to Local Research Ethics Boards

CCTG will notify all Investigators of all Safety Reports (Serious Adverse Events (SAEs) from this trial and Safety Updates (SUs) from other clinical trials) that are reportable to regulatory authorities in Canada as reported to the CCTG. This includes all serious events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment. Investigators must notify their Research Ethics Boards (REBs) and file the report with their Product Monograph. The date of REB Submission for SAEs and SUs will need to be entered into the CCTG trial MA.32 web based safety monitoring utility and documentation of REB submission must be retained in the study binder on site.

For this purpose, the REB submission template letter provided by CCTG should be used. Please note:

- this letter must be either printed on institutional letterhead or contain the centre identification/REB name;
- the date of REB submission must be provided;
- this form must be signed by one of the approved participants (according to the participants list) for this trial.

The submission of these events to your ethics board should be done as soon as possible (we suggest within 30 days). REB submissions greater than 90 days from the date of notification will be regarded as delinquent and a major deficiency will be assigned.

12.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

Interruption of Discontinuation of Treatment

Subjects whose treatment is interrupted for any reason except intolerable toxicity will be encouraged to resume and continue with their assigned therapy.

Compliance (and reasons for non-compliance) should be noted on the follow-up report. A formal pill count will be done for this trial. Patient reported compliance will be employed and unused pills (returned by the patient at each dispensation of a new treatment kit) will be counted and recorded. The visit schedule for those subjects who discontinue therapy should not be modified as endpoints will be assessed for as long as the patient can be followed and an intent-to-treat analysis will be performed.

12.1 Criteria for Discontinuing Protocol Treatment

Subjects may stop protocol treatment in the following instances:

- Intercurrent illness which would, in the judgement of the investigator, affect assessments of clinical status to a significant degree, and require discontinuation of protocol therapy (Please consult protocol section 8).
- Unacceptable toxicity as defined in Section 8
- Intercurrent illness (e.g. including diabetes, congestive heart failure) precluding continuation of study medication. (Please consult protocol section 8.)
- Tumour progression or disease recurrence as defined in Section 10.0.
- Development of a new invasive primary cancer (other than basal cell carcinoma or squamous cell carcinoma of the skin that has been adequately treated)
- Request by the patient.
- Completion of therapy as outlined in Section 8.0. Efforts should be made to maintain the investigations schedule and continue follow-up, even if subjects discontinue protocol treatment prematurely and/or no longer attend the participating institution.

12.2 Therapy After Protocol Treatment is Stopped

Patient management following stoppage of protocol treatment is at the discretion of the Investigator. Metformin and matching placebo are identical in appearance as are the bottles in which they are provided. Blinding is critical to the integrity of this clinical drug trial. However, in the event of a medical emergency in an individual subject, in which knowledge of the investigational product is critical to the subject's management, the blind for that subject may be broken by the treating physician. Before breaking the blind of an individual subject's blinded treatment, the Investigator should have determined that the information is necessary, i.e. that it will alter the subject's immediate management. In many cases, particularly when the emergency is clearly not investigational product-related, the problem may be properly managed by assuming that the subject is receiving active product without the need for unblinding. The need to break the blind must first be discussed with the CCTG. For any treatment code unblinding, the reason and parties involved must be documented in the patient’s medical record. Treatment identification information should be kept confidential and should be disseminated only to those individuals that must be informed for medical management of the patient. The CCTG must be notified as soon as possible of any emergency situation in which the drug code was broken. See List of Contacts for details.

12.3 Follow-up Off Protocol Treatment

Follow-up will continue after treatment completion according to the plan described in protocol section 9.

13.0 CENTRAL REVIEW PROCEDURES AND TISSUE COLLECTION

13.1 Central Pathology Review

There will be no central pathology review for this study.

13.2 Tissue Collection

The collection of a representative block of the diagnostic tumour tissue (if available) and the adjacent normal tissue (part of the standard resection) is an important part of this trial. This is mandatory for site participation in the study, but the participation of subjects is optional. Blocks will be carefully banked as part of the CCTG tissue/tumour bank at Queen's University in Kingston, Ontario. Tumour blocks will be the preferred material to collect, as one of the objectives will be to create tissue micro arrays. These will optimize the amount of tissue available to investigators and permit the preservation of the tumour block submitted. If, at any time, the submitting hospital requires the block to be returned for medical or legal concerns, it will be returned by courier on request.

The tissue may be used by researchers now or in the future to better understand the nature of breast cancer and how patients respond to treatment. Samples will be used for research purposes only and will not be sold. A scientific review process of any proposals to use the tissue will take place and any proposals approved will have undergone ethics approval. Patients will not be identified by name. The only identification of tissue will be by a patient study number assigned at the time of randomization to the trial the surgical/ histology number and/or patient initials. Material issued to researchers will be anonymized and only identified by a coded number.

Diagnostic pathology reports are received as part of the supporting documentation required for this trial. Receipt of these will initiate a request directly from the Queen's Department of Pathology to pathology departments for a representative tumour block.

Testing for hereditary genetic defects predisposing to malignant disease will not be carried out without the expressed consent of the subject.

All subjects on whom a diagnostic tumour block is collected will be aware of this retrieval and will have given their consent.

13.3 MA.32 Use of Tumour Blocks

As part of the embedded correlative science for the MA.32 protocol, the following research is to be conducted on submitted tumour blocks:

Insulin Receptor (IR)

Our core analyses will examine IR expression on formalin fixed, paraffin embedded breast cancer tissue collected at breast cancer diagnosis. IR is commonly expressed on breast cancer cells *[Mulligan, 2007]*, and is believed to mediate insulin action on breast tissue; activation of the receptor by insulin initiates signaling via the PI3Kinase pathway, leading to proliferation. IR expression is essential for indirect (insulin dependent) metformin effects. Given reports that IGF-1R may dimerize with IR in breast cancer *[Frasca, 2003]* we will evaluate IGF-1R in secondary analyses.

LKB1

LKB1 expression is key to the ability of metformin to affect AMPK activity within tumors and to suppress the growth-promoting outputs of this signaling pathway (i.e. mTOR-regulated protein translation). *[Lizcano, 2004; Shaw, 2004]* LKB1 expression is essential for direct (insulin independent) effects of metformin.

Phosphoantibody Markers of Activation of Key Signaling Pathways

Expression of IR and LKB1 will be indicative of the capacity of tumor cells to respond to indirect (insulin and IR mediated) and direct (insulin independent, LKB1 mediated) effects of metformin respectively, however, the expression of these factors cannot distinguish whether the pathways underling these responses are actually activated. Multiple other genetic factors may alter pathway activation. As a result, activation markers of these pathways [PI3K (STMN1), PKB/Akt (P-PKB/Akt,) mTOR (P-4E-BP1) and IRS-1 (P-IRS-1)] will be evaluated as predictors of metformin benefit. If one or more of these biomarkers are activated at breast cancer diagnosis, it is predicted that metformin benefit is possible. If none of these pathways is activated, it is predicted that metformin benefit will not be seen, regardless of IR and/or LKB1 expression.

Genomic/Gene Expression Profile Predictive of Metformin Benefit

Large-scale genomic studies over the past two decades have identified numerous recurrent genetic events in breast cancer, such as the amplification of HER2 oncogene or the mutations of the BRCA1 and BRCA2 tumor suppressor genes, defining specific subgroups of patients and influencing their clinical management. More recent studies are focusing on building a comprehensive, genome-wide understanding of various types of breast cancer. We plan to use such analyses to search for a genomic/gene expression profile predictive of metformin benefit. In the case of observed metformin benefit, we will perform comprehensive genomic/gene expression analysis of peripheral blood and available tumour material. Considering rapid technical advances in the genomic analysis arena, at the time of analysis, we will choose the most appropriate methodology to delineate the genetic/gene expression predictors of metformin benefit.

13.4 Blood Collection and Analysis

Investigation of a core group of blood variables (at baseline, 6 months after enrolment and at 48 months of treatment) and tumor related factors (at diagnosis) that will be examined as predictors of metformin benefit in this trial is outlined below. We will also collect additional samples that will allow us to examine a broader array of both prognostic and predictive factors in future work. The blood collection for fasting glucose and insulin is a mandatory part of the baseline, 6-month and 48 months of treatment measurements of MA.32.

After an overnight fast of at least 12 hours, participants will provide the following blood specimens: 1 tube for immediate glucose analysis (performed according to established institutional practice), light green topped tubes (containing lithium heparin - for plasma), red topped tubes (for serum) and lavender topped tube (for DNA). *Lavender topped tubes for DNA should be collected even for patients who consent to blood banking but refuse genetic testing. DNA may be used to study gene expression without fitting the definition of genetic testing. (Please see the MA.32 Sample Consent Form for definitions.)* The green topped tubes will be centrifuged within half an hour of collection and the plasma collected frozen immediately in 1 ml aliquots at -80°C. The redtopped tubes will sit for 30 minutes at room temperature and then be centrifuged and the collected serum frozen immediately in 1 ml aliquots at -80°C. Lavender topped tubes (whole blood in EDTA) will be collected and frozen at -80°C in 1 ml aliquots for subsequent thawing and DNA extraction. Specimens will be stored at participating centers immediately after collection and then shipped to a central laboratory, frozen on dry ice, in batches of 10 sets or more (1 set = entire blood collection at one patient visit), for subsequent storage and ultimate analysis. Our plan to collect lymphocytes for DNA at both baseline and 6 months will provide the necessary sample to evaluate not only germline DNA but also potential changes in DNA methylation as a result of the metformin intervention.

13.5 MA.32 Use of Blood Samples

Insulin (plasma)

Our core analyses will explore the indirect, insulin mediated, effect of metformin as a predictor of invasive disease free survival (primarily), overall survival and breast cancer free interval, including an evaluation of both baseline fasting insulin (primarily), change in insulin over 6 months (secondarily) and at 48 months of treatment. This primary focus on insulin reflects the recognition that insulin at diagnosis is a prognostic factor in breast cancer, and it reflects the major impact metformin has on insulin levels; our primary hypothesis is that higher insulin level at baseline will predict metformin benefit in the overall study population. Additionally, in exploratory analyses we will examine the relationship between change in insulin during the first 6 months of metformin administration and invasive disease free survival and overall survival in women randomized to metformin (change in insulin is expected to occur primarily in the metformin arm).

Glucose (plasma)

Fasting glucose levels have been associated with breast cancer risk in some but not all studies; their effect on prognosis is unknown. It is not clear whether the effect on risk is a direct one or whether glucose is a surrogate for insulin in these published studies. We plan to examine whether baseline glucose predicts metformin benefit independent of insulin or whether glucose modifies effects of insulin as a predictor of metformin benefit. We will also investigate Homeostasis Model Assessment (HOMA) *[Vaccaro O, 2004]*, an empirically derived estimate of insulin sensitivity calculated from a single measure of fasting insulin and glucose that correlates well with the gold standard frequently sampled intravenous glucose tolerance test, as a predictor of metformin benefit, focusing on whether it provides additional prediction beyond insulin alone.

Research Blood Samples Taken at Baseline and Again at 6 Months and at 48 Months of Study Treatment

Type of Tube	One Tube (7 ml) (1.4 teaspoons)	Light Green Top Tubes (3 x 4.5 ml) (2.7 teaspoons)	Red Top Tube (2 x 6 ml) (2.4 teaspoons)	Lavender Top Tube (1 x 6 ml) (1.2 teaspoons)
To be used for	Plasma for Fasting Glucose *(done locally according to institution's procedures & mandatory)*	Insulin *(done centrally & mandatory)* Plasma for storage for future research *(optional)*	Serum for storage for future research *(optional)*	DNA extraction *(done centrally & optional)* *Lavender topped tubes for DNA should be collected even for patients who consent to blood banking but refuse genetic testing. DNA may be used to study gene expression without fitting the definition of genetic testing. (Please see the MA.32 Sample Consent Form for definitions).*

TOTAL VOLUME DRAWN = 38.5 ML (7.8 Teaspoons, 2.6 Tablespoons)

Please see also Appendix X and Correlative Sciences Lab Manual posted on the web-site Trial Page.

13.6 Central Data Review

CCTG receives core support from the Canadian Cancer Society. To ensure efficient use of limited funding, the CCTG has, over the past 40 years, optimized their risk based trial oversight and monitoring program. A critical component is central data review of submitted deidentified source documents, allowing source data verification and confirmation of key aspects including eligibility, endpoints and safety outcomes. Depending on the trial's design, these source documents may include such source documents as surgical and histopathology reports to confirm disease stage and type, imaging reports to confirm extent of disease and assess efficacy, or include submission of tumour samples (to confirm diagnosis and eligibility or DICOM images (to verify response or radiation therapy planning). These source documents are reviewed by experienced data managers and physicians and are critical to ensuring the accuracy of the data and consistency of conclusions drawn.

The collection of this critical data involves submission of source documents by mail and/or fax.

See Appendix III (Documentation for Study) for details of supporting document requirements for this trial and for requirements for the redaction of personal identifiers. Although it remains the centres responsibility to ensure adequate redaction of any information provided to CCTG, submitted source documents are reviewed prior to acceptance at CCTG; in the case of incomplete redaction, documents are destroyed and the site assigned a violation and required to resubmit.

All patients will provide written informed consent for submission of source documents, and the rationale and documents to be collected will be detailed in the informed consent document.

14.0 STATISTICAL CONSIDERATIONS

14.1 Objectives and Design

The primary objective of this study is to compare invasive disease-free survival (IDFS) in pre- and post-menopausal women with T1-T3, N+/-, ER/PgR+/-, HER2 +/- invasive breast cancer. Eligible subjects will be randomized to one of the following two treatment groups: metformin (850 mg po bid for 5 years, experimental arm) or placebo (one caplet po bid for 5 years, control arm). Subjects will be stratified by: 1) ER and PgR status (both negative vs. either ER or PgR positive), 2) Body Mass Index ($\leq$ 30 kg/m^2 versus > 30 kg/m^2), 3) HER2 (Positive = 3+ over-expression by IHC in > 30% of invasive tumour cells *OR* HER2 gene amplification by FISH/CISH> 6 HER2 gene copies per nucleus, *OR* a FISH/CISH ratio: HER2 gene copies to chromosome 17 signals of $\geq$ 2.2. All other results will be considered negative.) and 4) Chemotherapy administration (any versus none). We will also compare overall survival, distant relapse free survival, breast cancer free survival, breast cancer specific mortality, incidence of contralateral invasive breast cancer, health-related quality of life, body mass index between metformin and placebo arm. The intent-to-treat (ITT) population will comprise all randomized patients, will be based on the allocated treatment regardless of whether the patient received the assigned treatment, and will be based on the at-randomization values of the stratification factors. The adverse events in the two different treatment groups will also be compared. The embedded correlative science studies are described in Section 13 of this protocol.

A minimization procedure *[White,1978]* will be used to allocate patients with equal probabilities to one of the two treatment groups.

Based on recommendation from DSMC after the second interim analysis, only the study subjects with ER/PgR+ will be included as the primary analysis in the final analysis.

14.2 Primary Endpoints and Analysis

The primary endpoint of this study is invasive disease-free survival. It is defined as the time from randomization to the time of documented ipsilateral and contralateral invasive breast tumour, local/regional invasive recurrence, distant recurrence, death from breast cancer, death from non-breast cause, death from unknown cause, second primary invasive cancer (non-breast, except for adequately treated BCC or SCC of the skin). If a subject has not had invasive disease or died at the time of data cut-off for final analysis of the primary endpoint, IDFS will be censored on the date of last follow-up. The survival experiences of subjects in both treatment arms will be described by the Kaplan-Meier method. Stratified two-sided log-rank tests adjusting for stratification factors as defined in the protocol will be the primary method to compare IDFS between metformin and placebo arm. As an exploratory analysis, a Cox proportional hazards model will be used to identify and adjust for factors significantly related to invasive disease-free survival.

All subjects will be evaluated for toxicity from the time of their first oral dose of study medication. Toxicities will be graded using the current CTCAE version (as per protocol Appendix V). The incidence of toxicities by arm will be summarized by type of adverse event. A Fisher's Exact Test will be used to compare toxicities between two arms.

14.3 Sample Size and Duration of Study

The sample size for this study is calculated in order to compare invasive disease-free survival (IDFS) between subjects randomized to receive metformin versus placebo. At the time of study initiation, the 5 year IDFS for subjects allocated to the placebo arm was estimated to be 85.0%, based on a population of pre- and post-menopausal women with T1-T3, N+/-, ER/PgR +/-, HER2 +/- invasive breast cancer. With an overall two-sided alpha of 0.05 a total of 431 events were required to provide 80% power to detect a hazard ratio (HR) of 0.76 between the two treatment arms after taking into account two planned interim analyses. This HR was selected because it was the HR seen in the WINS study of dietary fat reduction/weight loss in the adjuvant breast cancer setting, described in protocol Section 2.

Analysis of compliance for the first 241 patients was performed. The drug discontinuation rate at 6 months in MA.32 is **8.3%** in the first 241 subjects; an additional **1.7%** discontinuation was seen beyond 6 months **(total 10%).** Rates are likely higher on the metformin (vs placebo) arm because most discontinuations were due to Gl toxicity. Although MA.32 is a pragmatic study, and thus will assess effectiveness that includes non- compliance, we believe these drug discontinuation rates are higher than will be seen in future clinical practice (due to investigator inexperience with metformin and patient reluctance to continue a drug with side effects in the absence of documented benefit) and thus a more conservative HR should be targeted for this study. The issue of drug non-compliance was discussed by the Trial Committee in December 2011 and the option of enrolling a higher risk population to target a more conservative HR was endorsed. This would be achieved by restricting enrolment of subjects with T1cN0 tumours to those with ER/PR and HER2 negative (triple negative) status and requiring the presence of at least one adverse prognostic factor for T2N0 tumours (i.e. at least one of: ER and PgR negative, HER2 positive, histologic grade 3, Ki67 > 14%, Oncotype Recurrence Score $\geq$ 25 or lymphovascular invasion). The changes in eligibility criteria would increase the IDFS event rate for entire study population from an estimated 15% to 19%. The resulting higher event rate (554 events) would allow detection of a HR 0.785 given our current sample size of 3582 assuming 3 years of accrual and an additional 3 years of follow-up, with an overall two-sided alpha of 0.05 and 80% power after taking into account two interim analyses (see Section 14.5 for details). This is the HR one obtains when we adjust our original HR of 0.76 for a 10% drug discontinuation rate. The HR of 0.785 represents an absolute improvement of 3.7% in 5 year IDFS from 81% to 84.7% for those allocated to metformin. The total duration of the trial would be six years.

Based on the recommendation of DSMC after the second interim analysis, the final analysis will include only study subjects who were ER/PgR+ and be performed when 554 events are observed from these subjects. Because of the alpha spending during the first two interim analyses, the nominal two-sided significant level for the final analysis will be 0.037. With 554 events in the final analysis, there will be 78% power to detect the hazard ratio of 0.785 at two-sided 3.7% level or 80% power to detect a hazard ratio of 0.78. It is expected that additional 4 years of follow-up from November 2015 would be required to observe the required number of events.

2021 Update
As of October 31, 2020, the event number for the IDFS endpoint was 446 and an additional 40 months is estimated to reach the target number of events (554) based on the current event rate. Analysis of data based on 446 events is associated with 68% power (reduced 10% from 78%) to detect a target HR of 0.785 at two-sided 0.037 level or 80% power to detect a hazard ratio of 0.757. The HR of 0.757 represents an absolute improvement of 3.8% in 5 year IDFS from 83.0% to 86.8% for ER/PgR+ patients allocated to metformin and approximates the target HR proposed in the overall population at the time of study initiation.

Given the estimated retention of power to detect the target HR using a time based analysis with a last contact date of October 31 2020 compared to the additional time and resources to reach 554 events to trigger the final analysis of the primary endpoint the study design will be amended to incorporate a time based analysis. The critical p value for the final analysis will be 0.037 to account for the prior interim analyses. As of October 31, 2020, the median followup for the patients in the hormone receptor positive study population is estimated to be 95 months. The change in study design has been endorsed by an independent statistician.

In addition to the time based analysis described above, the protocol will be amended to include two new secondary endpoints that provide additional information regarding the anticancer and cancer prevention impact of metformin by measurement of breast cancer specific mortality and incidence of contralateral invasive breast cancer respectively.

14.4 Safety Monitoring

Adverse events will be monitored on an ongoing basis by the central office and their frequencies reported annually at investigators' meetings.

14.5 Interim Analysis

Two interim analyses are planned for this study when 185 and 370 events are observed, to allow early termination of the study if the results are extreme. Lan-DeMets error spending function will be used to assess for superiority, and futility for superiority *[Lan 1983]*. The early stopping boundaries are based on a power family with power 3, which approximates the O'Brien-Flemming boundaries *[Jennison 2000]*. The actual p-values for superiority and futility will be calculated based on the number of events observed at the time of interim analysis, controlling the two-sided Type I error of 0.05 and the power of 80% at the end of the study.

If exactly 185 events are observed for the first interim analysis, the null hypothesis would be rejected early due to evidence of superiority at the first interim analysis if the p-value is less than or equal to 0.00185. The alternative hypothesis would be rejected for futility if the p-value is at least 0.971. If exactly 370events are observed for the second interim analysis, the nominal critical p-values for rejecting the null hypothesis and the alternative hypothesis would be 0.0138 and 0.468, respectively. The nominal significant level for the final analysis of the primary endpoint is 0.0463 when 554events are observed, to maintain the overall two-sided alpha of 0.05.

Results of the interim analysis will be supplied to DSMC who will make their recommendation regarding continuation of the trial.

No additional interim analysis will be performed.

2021 update:
After the second interim analysis and the change of the study population to the hormone positive patients, no additional interim analysis is planned and the critical p-value for the final analysis will be 0.037 as described in Section 14.3.

14.6 Quality Of Life Analysis

The EORTC QLQ-30 Global Score will be used for our primary assessment of quality of life but subscales and specific symptoms (diarrhea, bloating, flatulence, dyspepsia, abdominal cramps, nausea and vomiting, taste alteration, limitation of activities because of gastrointestinal symptoms, joint/musculoskeletal symptoms) will be used for our secondary hypothesis.

Since QOL is not part of the primary outcome, we will measure QOL on a proportion of participants. We want to detect a small to medium effect size of ~0.3 in either the primary assessment or the 10 subscales (diarrhea, bloating, flatulence, dyspepsia, abdominal cramps, nausea, vomiting, metallic taste, limitation of activities by gastrointestinal symptoms, joint/musculoskeletal symptoms) of quality of life in the overall quality of life sub-study population. We also want to detect an effect size of 0.5 for these outcomes in each of the sub-study groups defined by adjuvant endocrine therapy use at the time of randomization (tamoxifen, aromatase inhibitor, no endocrine therapy). With significance at the 5% level and 80% power, we will need a total of 296 subjects (148/arm) in each of the 3 hormone therapy defined groups (888 or 444/arm in the full HRQOL sub-study) to detect an effect size of 0.5 in each hormonal group; this sample size will allow us to detect an effect size of 0.289 for the entire HRQOL sub-study population. (Although subjects in the Quality of Life sub-group will not be stratified by endocrine therapy use, it is expected that, given the diversity inherent in the enrolment process, these three groups of subjects will be more or less evenly balanced between the metformin and placebo groups.) These estimates have taken into account expected dropouts (10%) and non-completion rates (20%). we have applied the Bonferroni correction to account for the multiplicity problem.

It is anticipated that approximately 90% of the Quality of Life participants will also contribute Physical Activity and Diet Data yielding a sample size of about 800 subjects and an 80% power to detect an effect size of 0.304 for either the primary assessment or the 10 subscales.

The EORTC QLQ-C30 and the Trial Specific Checklist will be mandatory prior to randomization, at 6 months and then annually in subjects participating in the HRQOL portion of the study. Scoring of questionnaires will be conducted by the central office of CCTG according to the scoring manual of the EORTC QLQ-C30. The Trial Specific Checklist items will be scored individually.

Analyses of HRQOL data will be conducted and presented according to the standard approach of the CCTG. The levels of fatigue and overall QoL will be evaluated according to diet and physical activity in the metformin and placebo groups in the subset of QoL participants with diet and physical activity assessment.

15.0 PUBLICATION POLICY

15.1 Authorship of Papers, Meeting Abstracts, Etc

15.1.1 The results of this study will be published. Prior to trial activation, the chair will decide whether to publish the trial under a group title, or with naming of individual authors. If the latter approach is taken, the following rules will apply:

- The first author will generally be the chair of the study.
- A limited number of the members of the Canadian Cancer Trials Group and may be credited as authors depending upon their level of involvement in the study.
- Additional authors, up to a maximum of 15, will be those who have made the most significant contribution to the overall success of the study. This contribution will be assessed, in part but not entirely, in terms of patients enrolled and will be reviewed at the end of the trial by the study chair.
- In the event of a separate paper dealing with the quality of life outcomes, the first author will generally be the Quality of Life Coordinator on the trial committee.

15.1.2 In an appropriate footnote, or at the end of the article, the following statement will be made:

> "A study coordinated by the Canadian Cancer Trials Group. Participating investigators included: (a list of the individuals who have contributed patients and their institutions)."

15.2 Responsibility for Publication

It will be the responsibility of the study chair to write up the results of the study within a reasonable time of its completion. If after a period of six months following the analysis of study results the draft is not substantially complete, the central office reserves the right to make other arrangements to ensure timely publication.

15.3 Submission of Material for Presentation or Publication

Any manuscripts reporting the results of this clinical trial should be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts should be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release.

16.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

(This section applies to Canadian Sites only; CTSU sites please refer to the CTSU Logistical Appendix. ICR-CTSU sites please refer to the ICR- CTSU-specific Appendix. IBCSG sites please refer to the IBCSG-specific Appendix.)

16.1 Institution Eligibility for Participation

Selected member centres in good standing of the CCTG are eligible to participate in this study. Any centre joining the CCTG is required to sign a Participating Centre Study Agreement and have Standard Operating Procedures regarding the conduct of clinical trials.

The CCTG will submit via fax to Health Canada for each participating Canadian centre prior to local activation a completed Health Canada Clinical Trial Site Information Form.

Because this trial is affected by U.S. legislation, U.S. federal regulations for the protection of human subjects apply. Canadian and U.S. institutions must have a Federalwide Assurance (FWA) number issued by the Office for Human Research Protections (OHRP) of the Department of Health and Human Services. By means of this assurance, the institution and its REB agree to abide by U.S. standards regarding, for example, constitution of the REB.

16.2 Investigator Qualifications

For all investigators (principal investigators and co-investigators) the following documentation must be on file with the CCTG:

- A current curriculum vitae, updated and submitted within two years at the time of randomization.
- Documentation indicating completion of training in the protection of human research participants (e.g. NCI U.S. Completion Certificate).
- Completion of the required CCTG GCP training modules.
- A current NCI U.S. investigator number. An NCI U.S. investigator number is obtained by completing and signing a FDA 1572 form, a Supplemental Investigator Data Form, and a Financial Disclosure Form. These forms and a current CV are submitted to the NCI U.S. by the investigator.

For the principal investigator only:

- A Health Canada Qualified Investigator Undertaking Form must be completed and signed by the principal investigator of the study at participating Canadian centres and received by the CCTG central office before that centre can be locally activated.

16.3 REB (Research Ethics Board) Approval for Protocols

Each participating centre will have on file with the CCTG central office, as part of its membership/ agreement documents, a description of its ethics review process and composition of its REB.

REB Composition

Membership of an REB approving this protocol must be consistent with Canadian regulatory requirements, summarized as follows:

- at least 5 members;
- majority of members are Canadian citizens or permanent residents;
- includes 2 members whose primary expertise and experience are in a scientific discipline with broad experience in the methods and areas of research to be approved (1 of these is from a medical discipline);
- includes 1 member knowledgeable in ethics;
- includes 1 member knowledgeable in Canadian laws relevant to the biomedical research to be approved;
- includes 1 member whose primary experience and expertise are in a non-scientific discipline;
- includes 1 member who is from the community or is a representative of an organization interested in the areas of research to be approved and who is not affiliated with the CCTG or the centre where the clinical trial is to be conducted.

A Health Canada REB Attestation Form must be completed and signed by the REB representative. Alternatively, an attestation to the following may be included in the signed local ethics approval document:

- The membership of the Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations;
- The Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practice; and
- The Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent for the trial which is to be conducted by the qualified investigator named at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.

This documentation must be received by the CCTG central office before the centre can be locally activated.

Initial Approval

Member centres wishing to participate in a trial are required to obtain full board local ethics approval of the protocol and consent form (see below) by the appropriate REB.

Annual Re-Approvals

This trial is NCI US affiliated and therefore U.S. regulations regarding the Protection of Human Subjects apply (U.S. Code of Federal Regulations Title 45, Part 46). These regulations require that re-approvals of research be conducted at least once per year for as long as data are being submitted on trial patients, even through the follow-up period. Furthermore, these regulations require that annual re-approvals must be full board as long as the study is open to accrual or patients are receiving protocol treatment or undergoing protocol mandated interventions.

Amendments/Administrative Updates

All amendments or administrative updates to the protocol must undergo review by local REBs. Amendments/administrative updates will be circulated to all participating sites in a standard format with clear instructions regarding REB review. If full board approval of an amendment is required it will be specified.

Amendments will be reviewed and approved by Health Canada prior to central implementation of the amendment, and by REBs prior to local implementation, EXCEPT when the amendment eliminates an immediate hazard to clinical trial subjects. Amendments will be distributed with Health Canada REB attestation forms which must be completed. For each amendment CCTG will collect documentation of REB approval, a completed REB attestation form.

REB Refusals
If an REB refuses to approve this protocol (or an amendment/administrative update to this protocol) the CCTG must be notified immediately of the date of refusal and the reason(s) for the refusal. Notification will then be made to Health Canada.

Serious Adverse Events, Safety Updates, Investigator Brochure Updates and Product Monograph Updates
During the course of the study serious adverse events, safety updates, investigator brochure updates or product monographs may be sent to you for reporting to your REB. The date of REB submission for these documents will need to be entered into the MA.32 web based safety monitoring utility and documentation of REB submission must be retained in the study binder on site.

16.4 Informed Consent

Informed Consent Document
The REB of an institution must approve the consent form document which will be used at that centre prior to its local activation; changes to the consent form in the course of the study will also require REB approval.

It is essential that the consent form contain a clear statement which gives permission for 1) information to be sent to and 2) source medical records to be reviewed by the CCTG and other agencies as necessary. The consent form must include all ICH-GCP consent elements. In addition, the consent form should include all elements required by CCTG policy, and centres receiving funding from NCEHR, SSHRC and/or CIHR should include elements from the Tri Council Policy Statement (TCPS).

Informed consent forms that do not contain all ICH-GCP required elements will require an amendment and will lead to the delay of local activation. A complete list of the elements required by regulations, guidelines and CCTG policy can be found by accessing the CCTG website at http://www.ctg.queensu.ca/private/ethics/consent_RE_Checklists.html.

Because this study is NCI U.S. affiliated, U.S. regulations regarding consent form content also apply.

The sample consent form provided in the protocol includes all the required elements, as well as the "additional" and "suggested" elements relevant to this study. REBs must consider the sample consent as the basis for review, as this form has been approved by the U.S. National Institutes of Health. Significant changes of wording or deletions of the adverse event or alternative therapy sections of the sample consent must be justified by the REB in writing; note however that additions to these sections are rarely a problem.

Consent Process/Patient Eligibility

Patients who cannot give informed consent (i.e. mentally incompetent patients, or those physically incapacitated such as comatose patients) are not to be recruited into the study. Patients competent but physically unable to sign the consent form may have the document signed by their nearest relative or legal guardian. Each patient will be provided with a full explanation of the study before consent is requested.

16.4.1 *Obtaining Consent for Pregnancy/Exposure Reporting*

Information from and/or about the subject (i.e. the pregnant female, the newborn infant, male partner, exposed individual) should not be collected about or from them unless or until they are a willing participant in the research. The rights and protections offered to participants in research apply and consent must be obtained prior to collecting any information about or from them. If the main consent form adequately addresses the collection of information regarding the outcome of a pregnancy of a trial participant, a "Pregnancy Follow-up" consent form will not be required by CCTG.

Trial-specific consent forms for "Pregnancy Follow-up" and "Exposure Follow-up" can be found on the trial webpage. The appropriate consent form must be used to obtain consent from any non-trial participant (such as the pregnant partner or exposed individual).

Participants will not be withdrawn from the main trial as a result of refusing or withdrawing permission to provide information related to the pregnancy/exposure. Similarly, male participants will not be withdrawn from the main study should their partner refuse/withdraw permission.

Obtaining Consent for Research on Children

In the case of collecting information about a child (i.e. the child resulting from a pregnant participant/partner or an exposed child), consent must be obtained from the parent/legal guardian.

For reporting an exposure, the parent/guardian is required to sign an "exposure follow-up" consent form (even if they are a participant in the main study) prior to collecting information about the child.

16.5 Retention of Patient Records and Study Files

ICH Good Clinical Practice guidelines apply to CCTG studies. It is the responsibility of CCTG to inform the investigator/institution as to when trial related records no longer need to be retained. The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

CCTG will notify all the trial investigators/institutions and all the regulatory authorities if clinical development of an investigational product discontinues or when trial related records no longer need to be retained.

16.6 Centre Performance Monitoring

This study is eligible for inclusion in the Centre Performance Index (CPI). Reports are to be submitted according to the schedule in Appendix IV (Documentation for Study).

16.7 On-Site Monitoring/Auditing

CCTG site monitoring/auditing will be conducted at participating centres in the course of the study as part of the overall quality assurance programme. The monitors/auditors will require access to patient medical records to verify the data, as well as essential documents, standard operating procedures (including electronic information), ethics and pharmacy documentation (as applicable)

As this trial is conducted under a CTA with Health Canada, your site may be subject to an inspection by the Health Canada Inspectorate. In addition, as this trial is NCI US affiliated, findings will be reported to the NCI US Clinical Trials Monitoring Branch as required.

The above mentioned documentation, in addition to any submitted source documents, may be accessed remotely in the event of a public health emergency either through remote access to Electronic Medical Records or through a secure file sharing portal.

16.8 Case Report Forms

A list of reports to be submitted, as well as expectation dates, are to be found in Appendix IV – DOCUMENTATION FOR STUDY.

17.0 REFERENCES

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APPENDIX I - PATIENT EVALUATION FLOW SHEET

Required Investigations	Pre-study*	6 mo	12 mo	24 mo	36 mo	48 mo	60 mo	Post study treatment
History & Physical								
Waist & Hip Circumference, Blood Pressure	X	X	X	X	X	X	X	
Performance Status	X							
Weight, BMI	X	X	X	X	X	X	X	X
Height	X							
Medical History, Menopausal Status	X							
Concomitant Meds	X							
Hematology*								
Hemoglobin	X	X	X	X	X	X	X	
WBCs,	X	X	X	X	X	X	X	
Granulocytes	X	X	X	X	X	X	X	
Platelets	X	X	X	X	X	X	X	
MCV	X	X	X	X	X	X	X	
Biochemistry*								
AST	X	X	X	X	X	X	X	
ALT	X	X	X	X	X	X	X	
Alkaline Phosphatase	X	X	X	X	X	X	X	
Serum Creatinine	X	X	X	X	X	X	X	
Serum Bilirubin	X	X	X	X	X	X	X	
Serum Vitamin B_{12}	X		X		X		X	
Fasting Glucose, Fasting Insulin *(same draw)*	X	X				X		
Radiology								
Mammogram	X		X	X	X	X	X	X
Chest X-ray (or Chest CT)	X							
Bone Scan (as necessary)	X							
CT Abdomen (as necessary)	X							
Other Investigations								
TNM Classification, Histologic Grade	X							
ER / PgR Status	X							
HER2 Status	X							
Initiation of new anti-diabetes medication (or confirmed diagnosis of diabetes). Cardiovascular hospitalization (stroke, myocardial infarction) or death		X	X	X	X	X	X	X
Blood Sample for Correlative Science (serum, plasma, DNA) (optional)	X	X				X		
Adverse Events								
CTC AE (version 4) Grade 3, 4 and 5 only	X	X	X	X	X	X	X	X
Quality of Life (888 subjects) *sample size achieved 2011NOV04*								
EORTC QLQ-C30	X	X	X	X	X	X	X	
Trial Specific Checklist	X	X	X	X	X	X	X	
Physical Activity & Diet								
Block Alive Screener (Diet)	X	X	X	X	X	X	X	
Physical Activity Items (NHS II)	X	X	X	X	X	X	X	

** Please see protocol section 6 for timing of pre-study investigations*

APPENDIX II - PERFORMANCE STATUS SCALES/SCORES

PERFORMANCE STATUS CRITERIA

Karnofsky and Lansky performance scores are intended to be multiples of 10.

ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.	100	Fully active, normal.
		90	Able to carry on normal activity; minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light housework, office work.	80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly.
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play; able to participate in all quiet play and activities.
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

* The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

APPENDIX III - DRUG DISTRIBUTION, SUPPLY AND CONTROL

Detailed information and instructions about drug distribution, transfer, returns, destruction and accountability will be provided in a separate document, in time for you to review this information and consider your participation in this clinical trial.

General

In order to initiate study drug distribution, CCTG must receive the address and the name of a contact person to whom the study drug will be shipped at each site. This will be accomplished as part of the local activation process.

Distribution

Metformin and Placebo will be provided by Apotex Inc. and supplied free-of-charge, through CCTG, to study participants. Study drugs will be organized into patient specific treatment "kits". Each treatment "kit" will contain one bottle of either blinded Metformin or Placebo. Participating sites will be pre-stocked with treatment kits. In North America once a patient has been successfully randomized through the CCTG electronic data capture system, the identity of the treatment kit which should be given to the patient will be transmitted back to the submitter. Site Pharmacy stock will be re-supplied automatically as treatment kits are used. Kits to be re-supplied to each patient will be identified and communicated to the site automatically prior to each patient follow-up visit. All drug orders will be shipped directly to the Pharmacist designated responsible for MA.32 Study Drugs.

Each treatment bottle will be labeled with the following:

1. NCIC CTG MA32.
2. Treatment Box Number
3. Number of Tablets
4. Instructions (Safety/Handling)
5. Storage Instructions
6. Blank line for Investigator name & phone #
7. Lot Number/Expiry Date
8. Blank line for patient initials

Questions about drug orders, transfers, returns, destruction or accountability should be addressed to:

CCTG
MA.32 Team (RE: Drug Supply & Distribution)
10 Stuart Street
Queen's University
Kingston Ontario, Canada
K7L 3N6

Phone: 613-533-6430
Fax: 613-533-2814

Drug Accountability

The Investigator, or a responsible party designated by the Investigator (e.g. the responsible Pharmacist), must maintain a careful record of the receipt, disposition return and destruction of drugs received for use in this clinical trial using the NCI Investigational Agent Accountability record available on the NCI home page (http://ctep.info.nih.gov) or MA.32 Trial Page. (Please note that the original accountability logs provided by the study are to be continued for this trial.) As this is a double blinded study, a separate Investigational Agent Accountability Record must be maintained for each CCTG patient on this protocol as required by regulation.

Subject Compliance

Subjects are to bring study drug bottles to every protocol-mandated visit (to assist in assessing patient – reported compliance). Both patient reported compliance and a pill count will be employed. Returns and destruction of same should be documented in the NCI Accountability Log for each patient. Patient returns and expired drug should be destroyed on site as per local standard operating procedures and documented on the Investigational Agent Accountability record. Instructions on handling of unused drug will be provided by the CCTG at trial closure.

APPENDIX IV - DOCUMENTATION FOR STUDY

Follow-up is required for patients from the time of randomization and will apply to all randomized patients.

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection except Quality of Life, Physical Activity, Diet and SAE reporting. For details of accessing the EDC system and completing the on-line Case Report Forms please refer to the "CCTG EDC Generic Data Management Guidebook" posted on the MA.32 area of the CCTG web-site (www.ctg.queensu.ca).

The electronic CRFs to be used in this trial, through the EDC system, are as follows:

Electronic Folder	Required at	To be completed electronically	Supporting Documentation*	
			Mandatory Submission To be submitted immediately after the report they refer to has been submitted electronically	Submission On Request To be submitted immediately after request
Eligibility Checklist	At time of randomization	At time of randomization	Consent form**, copies of protocol mandated baseline radiology, operative, and diagnostic pathology reports	additional clinical, laboratory or imaging reports that may impact on decision regarding eligibility
Baseline Report	At time of randomization	Within 6 weeks of randomization		
Telephone Follow-up Report	One month after start of study drug	Within 2 weeks of telephone contact		
Correlative Studies Report (Tumour and Blood)	At time of randomization	Within 6 weeks of drawing of 6 month sample	Diagnostic pathology report *(for tumour tissue only)*	
Treatment Report	At time of clinic visit	Within 6 weeks of clinic visit	Mammogram reports	additional clinical, laboratory or imaging reports that may inform evaluation of safety
End of Treatment Report	As soon as off treatment status is confirmed	Within 2 weeks of end of treatment		
Relapse/Progression Report	Upon disease progression	Within 6 weeks of confirmation	Copies of protocol-mandated imaging and non-protocol mandated imaging relevant to disease assessment , operative and pathology reports	

table continued on next page …

Electronic Folder	Required at	To be completed electronically	Supporting Documentation*	
			Mandatory Submission To be submitted immediately after the report they refer to has been submitted electronically	Submission On Request To be submitted immediately after request
Short Follow-up Report	Annually after off treatment	Within 6 weeks of clinic visit	Mammogram reports (as appropriate – please see protocol section 9), Radiology reports for protocol -mandated imaging and non-protocol mandated imaging if relevant to disease assessment	Additional clinical ,laboratory or imaging reports that may inform evaluation of safety
Death Report	Upon patient death	Within 6 weeks of patient death	Autopsy report if autopsy was done	Additional clinical, laboratory or imaging reports that may inform evaluation of cause of death
SAE Report***	Within 24 hours of event	Complete report within 10 days		Additional clinical, laboratory or imaging reports that may inform evaluation of safety including, admission and discharge summaries/notes

*** See section 11.0 Serious Adverse Event Reporting for details.

** For Canadian centres, it is acceptable to submit only the signature page(s) of the main consent and only the check box page(s)/signature page(s) of the optional consent provided that the version date of the consent form is indicated. Centres are expected to redact the participant's name and signature on the submitted copy, leaving only a portion visible (e.g. initials or loops) to confirm that a person has signed but that cannot identify that individual.

* Source documents other than those listed above may be requested to confirm eligibility, compliance, endpoints, and/or serious adverse events. Supporting documents should be submitted immediately after the report they refer to has been submitted electronically. EDC forms submitted without supporting documentation are not considered submitted and will be reflected in the Centre Performance Index (CPI) as not submitted. All relevant patient identifiers, other than the CCTG patient ID assigned at enrollment, and any other prohibited personal information must be fully and completely redacted (blacked-out) on all source documentation, per national and local privacy protection regulations and requirements,. Acceptable methods include:

- fully opaque sticker/tab placed over the identifiers prior to submission
- fully opaque black marker; prior to submission please ensure that the information is no longer visible on the scanned document
- electronic black box placed over identifiers in PDF document that is subsequently printed.
- fully opaque black marker; please ensure that the information under the marker cannot be still be seen on the scanned document (often markers are translucent and the identifiers can in fact be seen after scanning)

Note that supporting documents must include the participant's trial code, CCTG patient serial number, and participant initials (or a two/three masking letter code assigned by your centre).

The CRFs to be used in this trial outside the EDC system are as follows:

Report	To be completed	Due at CCTG	Supporting Documentation Required
Quality of Life, Physical Activity, Diet Questionnaires	At intervals defined in Appendix I	Within 6 weeks of completion of questionnaires	

APPENDIX V - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

The descriptions and the grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 will be utilized for Adverse Event (AE) reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4. Please note that only Grade 3, 4 and 5 events are to be collected – except if an event qualifies as an SAE or if the event is recorded as a reason for going off study treatment. A copy of the CTCAE version 4 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

APPENDIX VI - QUALITY OF LIFE ASSESSMENT

Introduction

Data derived from Quality of Life measured in clinical trials can help to select the optimal intervention, describe patient's experience or provide prognostic information. Studies have shown that measuring Quality of Life provides additional information compared to measuring adverse events alone. Current literature reveals interesting things; two in particular are:

- additional and useful information may be obtained from quality of life measurements
- a growing consensus that the goal of medical care today for most patients is the preservation of function and well-being in everyday life.

We have reached the stage where the collection of information about psychological distress, social disruption, emotional trauma and painful side-effects is not only necessary but a routine component in many protocols.

Quality of life data can be used in a variety of ways:

- to try to achieve the best possible outcome for patients
- to evaluate the extent of change in the quality of life of an individual or group across time
- to evaluate new treatments and technologies
- to support approval of new drug applications
- to try to provide the best value for health care dollars
- to compare costs and benefits of various financial and organizational aspects of health care services

In the future, approval of not only drugs but also new therapies or methods of delivery will most likely be based on a combination of quality of life, survival, response, and adverse event data.

Instructions for Administration of a Quality of Life Questionnaire. The instructions below are intended as a guide for the administration of the Quality of Life questionnaire.

1. Preamble

   Quality of life data are collected for research purposes, and will usually not be used for the patient's individual medical care. The assessment is in the form of a self report questionnaire. Therefore, it must be completed by the patient only, without translation, coaching or suggestions as to the "correct" answer by relatives or health care personnel.

   The usual scheduled times to obtain the questionnaires are as follows:

   - pre-randomization or pre-registration (baseline)
   - during treatment / follow-up

   The information provided by the patient in the completed questionnaire is confidential and should not be discussed with or shown to anyone who is NOT mentioned in the consent form signed by the patient.

   If a particular question has not been answered, please document the reason(s) in the appropriate space on the questionnaire. If the whole questionnaire has not been completed, please document the reason(s) on the appropriate case report forms.

2. Pretreatment Assessment

   It should be explained to the patient that the purpose of the questionnaire is to assess the impact of treatment on different areas of the patient's life, e.g.: psychological distress, social disruption, side-effects, et cetera.

   The CRA should collect the questionnaire as soon as it has been completed, check to see that each question has been answered and gently remind the patient to answer any inadvertently omitted questions. If a patient states that s/he prefers not to answer some questions and gives a reason(s), the reason(s) should be noted on the questionnaire. If a specific reason is not given, this also should be noted on the questionnaire.

3. Assessments During Treatment

   The quality of life questionnaire should be given to the patient before being seen by the doctor, and prior to treatment on the day of treatment, as required by the schedule in the protocol. If the patient does not have a doctor visit scheduled, or if it was not possible for the patient to complete the questionnaire before being seen by the doctor, she should still complete the questionnaire prior to treatment.

A patient may, on occasion, be reluctant to complete the questionnaire because they feel unwell. In that case, you may express sympathy that things are below par, but state that this is exactly the information we require if we are to understand more about how quality of life is affected. You may also remind them that it takes only a few minutes to complete.

It defeats the whole purpose of the assessment if it is delayed until the patient feels better!

4. What If . . .

   The patient should complete the questionnaires at the clinic. The exception is that the design of some trials may require the patient to take the questionnaire home with them after leaving the clinic, and complete it on the specific day, because a return visit to the clinic is not scheduled.

   There may be circumstances when the patient does not complete the questionnaire as required in the clinic. Three situations are described below. In these cases, it is beneficial if quality of life data can still be collected.

   A. The patient leaves the clinic before the questionnaire could be administered, or someone forgets to give the questionnaire to the patient.

      Contact the patient by phone informing him or her that the questionnaire was not completed. Ask the patient if s/he is willing to complete one:
      If yes, mail a blank questionnaire to the patient, and make arrangements for return of the questionnaire in a timely fashion. Record the date it was mailed and the date received on the questionnaire.

      If this is not feasible, then ask the patient if s/he is willing to complete a questionnaire over the phone. If the patient agrees, read out the questions and range of possibilities, and record the answers. Make a note on the questionnaire that the questionnaire was completed over the phone.

      If no, note the reason why the questionnaire was not completed on the appropriate case report form.

B. The patient goes on an extended vacation for several months and won't attend the clinic for regular visit(s).

Ensure that the patient has a supply of questionnaires, with instructions about when to complete them, and how to return them. If it is known beforehand, give the patient blank questionnaires at the last clinic visit; if the extended absence is not known in advance, mail the blank questionnaires to the patient. Written instructions may help ensure that the patient stays on schedule as much as possible.

C. The patient does not want to complete the questionnaire in clinic.

Should the patient not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the patient's wishes is likely to result in the questionnaire not being completed at all, then the patient may take the questionnaire home with instructions that it is to be completed the same day. When the questionnaire is returned, the date on which the questionnaire was completed should be noted and a comment made on the questionnaire as to why the patient took it away from the clinic before completion.

5. Waiving the Quality of Life Component

The only time that we will not require a patient to complete the quality of life questionnaires is if s/he is not literate in either English or French (or other languages that the questionnaire may be available in). In other words, if the assistance of a translator is required to comprehend the questions and reply, the questionnaires should not be completed. Translation of the questions is not acceptable. Please indicate on questionnaire.

6. Unwillingness to Complete Quality of Life Questionnaire

If a patient speaks and reads English or French (or other languages that the questionnaires may be available in), but does not wish to complete the questionnaires then she is NOT eligible and should NOT be put on study.

7. Inability to Complete Quality of Life Questionnaire (for reason other than illiteracy in English or French)

An eligible patient may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the patient is completing the QOL assessment in the clinic, the questionnaire should be read to them and the answers recorded by a health care professional (e.g. preferably the clinical research associate assigned to the trial, but another clinic nurse, a doctor or social worker who is familiar with the instructions for administering the questionnaires would be acceptable). If the patient is completing the questionnaire at home, and a telephone interview by the clinical research associate is not possible, then a spouse or friend may read the questions to the patient and record the answers. However, this method should be a last resort, and the spouse or friend should be instructed to not coach or suggest answers to the patient. Whichever method is used, it should be recorded on the questionnaire.

If these special arrangements are not possible or feasible, then the patient would not be required to complete the questionnaires, and this should be reported on the appropriate case report form.

The Quality of Life Questionnaires will be administered to the first 888 eligible English/French speaking subjects. English-speaking subjects from this sub-set of 888 subjects will also do the Physical Activity and Diet Questionnaires. (The Physical Activity and Diet Questionnaire are available and validated only in English.)

Quality of Life Questionnaire – ENGLISH

NCIC CTG Trial: **MA.32**

This **page** to be completed by the Clinical Research Associate

Patient Information

CCTG Patient Serial No: _____ Patient Initials: ____ ____ ____ (first-middle-last)

Institution: _____ Investigator: _____

Scheduled time to obtain quality of life assessment: please check (√)

☐ Prior to randomization

During protocol therapy:

☐ 6 months ☐ 12 months ☐ 24 months ☐ 36 months ☐ 48 months ☐ 60 months

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required?___ Yes___ No If yes, reason:_____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed: __ __ __ __ - __ __ __ - __ __
yyyy mmm dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

CCTG use only

Logged: _____	Study Coord: _____	Res Assoc: _____	Data Ent'd:	Verif:
_____ - ____ - ____	_____ - ____ - ____	_____ - ____ - ____	_____	_____

Quality of Life Questionnaire (MA.32)

The MA.32 study will employ, in a sub-set of 888 subjects, 2 instruments:

1. EORTC QLQ C-30
2. Trial Specific Checklist (last 7 questions of QoL questionnaire)

The first 888 English or French-speaking eligible subjects to be enrolled will comprise this sub-set of subjects. These instruments will all be made available, to active sites, in paper format, for completion by subjects. Links to the instruments are provided here to facilitate their presentation to your local REB, with the protocol and consent form, for approval.

The time required for subjects to complete each questionnaire is as follows:

Questionnaire	Time Required to Complete
EORTC QLQ C-30 http://www.eortc.be/home/qol/downloads/f/C30/QLQ-C30%20English.pdf http://www.eortc.be/home/qol/downloads/f/C30/QLQ-C30%20FrenchCanadian.pdf	20 minutes
Trial Specific Checklist 31. Did you have bloating of your abdomen (stomach or belly)? Avez-vous ressenti un ballonnement à l'abdomen (à l'estomac ou au ventre)? 32. Did you have pain or cramps in your abdomen (stomach or belly)? Avez-vous ressenti de la douleur ou des crampes a l'abdomen (a l'estomac ou au ventre)? 33. Did you have heartburn? Avez-vous ressenti (souffert de) brûlures d'estomac? 34. Did you have gas? Avez-vous eu des gaz? 35. Did you limit your activities because of gastro-intestinal problems? Avez-vous limité vos activités en raison de problèmes gastro-intestinaux? 36. Did you have a metallic taste? Avez-vous eu un goût métallique? 37. Do you have aching muscles or joints? Avez-vous ressenti des douleurs aux muscles ou aux jointures?	5 minutes

APPENDIX VII - PHYSICAL ACTIVITY AND DIETARY QUESTIONNAIRES

On the same sub-set of 888 MA.32 subjects, physical activity and dietary intake behaviours will also be addressed through the use of the following two instruments:

1. Physical Activity Items of the Nurses Health Study II Questionnaire
2. Block Alive Screener (Diet)

Physical activity patterns and dietary intakes will be assessed in order to measure changes in these behaviours over time and to evaluate differences in these changes between Metformin and placebo groups. It will then be possible to adjust for changes in diet and physical activity in assessment of study outcomes.

The Physical Activity and Diet Questionnaires will be administered to the English-speaking subjects in the 888 subject sub-set because the Physical Activity and Diet Questionnaires are available and validated only in English.

These instruments will all be made available, to active sites, in paper format, for completion by subjects. Copies of the instruments are provided here to facilitate their presentation to your local REB, with the protocol and consent form, for approval.

Questionnaire	Time Required to Complete
Physical Activity Items of the Nurses Health Study II Questionnaire *(Sample available in this Appendix)*	5 minutes
Block Alive Screener *(Sample available in this Appendix)*	10 minutes

Nurses Health Study II Physical Activity Questionnaire – **ENGLISH**

CCTG Trial: **MA.32**

This **page** to be completed by the Clinical Research Associate

Patient Information

CCTG Patient Serial No: _____ Patient Initials: ____ ____ ____ (first-middle-last)

Institution: _____ Investigator: _____

Scheduled time to obtain physical activity assessment: please check (√)

☐ Prior to randomization

During protocol therapy:

☐ 6 months ☐ 12 months ☐ 24 months ☐ 36 months ☐ 48 months ☐ 60 months

Were ALL questions answered? ___ Yes ___ No If no, reason: _____

Was assistance required? ___ Yes ___ No If yes, reason: _____

Where was questionnaire completed: ☐ home ☐ clinic ☐ another centre

Comments: _____

_____

Date Completed: __ __ __ __ - __ __ __ - __ __
yyyy mmm dd

PLEASE ENSURE THIS PAGE IS FOLDED BACK BEFORE HANDING TO THE PATIENT FOR QUESTIONNAIRE COMPLETION.

CTG use only

Logged: _____	Study Coord: _____	Res Assoc: _____	Data Ent'd:	Verif:
_____ - ____ - ____	_____ - ____ - ____	_____ - ____ - ____	_____	_____

AMEND #1: 2011-AUG-15

1. Below is a list of activities. Please put an X in the box that best represents the time you spent doing each activity over the course of a usual week, during the past month.

During the past month, about how much time did you spend doing these recreational activities each week?	zero	1 to 4 min.	5 to 19 min.	20-59 min.	1 hour	1 to 1.5 hours	2 to 3 hours	4 to 6 hours	7 to 10 hours	11 or more hours
a) walking for exercise or walking to work										
b) jogging (slower than 10-minute miles)										
c) running (10-minute miles or faster)										
d) bicycling (including stationary bicycle)										
e) tennis, squash, racquetball										
f) lap swimming										
g) other aerobic exercise (aerobic dance, ski or stair machine, etc.)										
h) any other vigorous activities (lawn mowing, etc.)										
i) lower intensity exercise (yoga, stretching, Pilates, toning)										
j) weight training or resistance exercises (including free weights or machines such as Nautilus)										

2. Below is a list of activities. Please put an X in the box that best represents the time you spent doing each activity over the course of a usual week, during the past month.

During the past month, about how much time did you spend doing these activities each week?	0 hours	1 hour	2 to 5 hours	6 to 10 hours	11 to 20 hours	21 to 40 hours	40 to 60 hours	61 to 90 hours	over 90 hours
a) standing or walking around at work or away from home									
b) standing or walking around at home									
c) sitting at work or away from home or while driving									
d) sitting at home while watching TV/videos/DVDs?									
e) other sitting at home (that is, not watching TV/videos/DVDs)?									

3. What is your usual walking pace outdoors? ***(please circle one answer)***

a) unable to walk

b) easy, casual (less than 2 mph)

c) normal, average

d) brisk pace (3 to 3.9 mph)

e) very brisk/striding (4 mph or faster)

4. How many flights of stairs (not individual steps) do you climb daily?
(please circle one answer)

a) 2 flights or less

b) 3 to 4 flights

c) 5 to 9 flights

d) 10 to 14 flights

e) 15 or more flights

FOOD QUESTIONNAIRE

RESPONDENT ID #

TODAY'S DATE

Jan Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec

DAY

2008 2009 2010 2011 2012 2013 2014 2015 2016 2017

ABOUT YOU

SEX
- Male
- Female

If female, are you pregnant or breast feeding?
- No
- Yes
- Not female

AGE

WEIGHT pounds

HEIGHT ft. in.

ABOUT THIS SURVEY

- This form is about the foods you usually eat. It will take about 10 - 15 minutes to complete.
- Please answer each question as best you can. Estimate if you aren't sure.
- USE ONLY A NO. 2 PENCIL.
- Fill in the ovals completely, and erase completely if you make any changes.

INSTRUCTIONS

Think about your eating habits over the past year or so. Remember breakfast, lunch, dinner, snacks and eating out.

There are two kinds of questions for each food:

- **"How Many Days per Week"**, on average, do you usually eat the food
- **"How Much"** do you usually eat of the food.

	HOW MANY DAYS PER WEEK? NONE OR LESS THAN 1	1 DAY	2 DAYS	3-4 DAYS	5-6 DAYS	EVERY DAY	HOW MUCH ON THOSE DAYS?		
1. Glasses of milk, not counting on cereal or coffee (any kind).							1 8 oz glass	2	3+
2. Real 100% fruit juice, like orange juice, apple juice, or fruit smoothies. Don't count fruit flavored soft drinks or drinks like Sunny Delight.							Small 6 oz glass	1 cup	2+ cups
3. Vegetable juice, like tomato juice, V8, carrot.							Small 6 oz glass	1 cup	2+ cups
4. Snapple, Koolaid, instant lemonade, instant iced tea, cordial - regular or sugar-free							1 glass	2	3+
5. Drinks with some juice, like Hawaiian Punch, Sunny Delight, Knudsen, Hi-C, cranberry juice.							1 glass	2	3+
6. Any kind of soft drink, soda or pop, like Coke, cola, Sprite, Gingerale, Crush, Fanta, regular or sugar-free.							1 glass/can	2	3+
7. Beer							1 glass/can	2	3+

PLEASE DO NOT WRITE IN THIS AREA

SERIAL #

	HOW MANY DAYS PER WEEK?						HOW MUCH ON THOSE DAYS?		
	NONE OR LESS THAN 1	1 DAY	2 DAYS	3-4 DAYS	5-6 DAYS	EVERY DAY			
27. ALL other vegetables you eat, as a side dish or in any kind of dish, not counting salad or potatoes.	○	○	○	○	○	○	○ 1/2 cup altogether	○ 1 cup	○ 2 cups
28. Bread, rolls, bagels.	○	○	○	○	○	○	○ 1 slice	○ 2	○ 3+
29. Biscuits, muffins, croissants.	○	○	○	○	○	○	○ 1	○ 2	○ 3+
30. Snack chips like potato chips, tortilla, corn chips, Fritos, Doritos, popcorn (not pretzels).	○	○	○	○	○	○	○ 1 small handful	○ 1 oz bag 1 cup	○ Big bag 2 cups
31. Crackers, like Ritz, soda-crackers, Cheez-Its, or any other snack cracker.	○	○	○	○	○	○	○ 3-4 small crackers	○ 5-10 crackers	○ a lot
32. Ice cream, ice cream bars.	○	○	○	○	○	○	○ 1/2 cup	○ 1 cup	○ 2+ cups
33. Doughnuts.	○	○	○	○	○	○	○ 1	○ 2	○ 3+
34. Cake, cookies, or snack cakes like cupcakes, Twinkies or any other pastry.	○	○	○	○	○	○	○ 1 small piece	○ 1 medium	○ 2+
35. Pie including fast-food pies or snack pies.	○	○	○	○	○	○	○ 1 small piece	○ 1 medium	○ 2+
36. Chocolate candy like chocolate bars, M&Ms, Mars Bars, Reeses.	○	○	○	○	○	○	○ 1 mini	○ 1 medium	○ 1 large
37. Any other candy (not chocolate) like hard candy, Lifesavers, Skittles, Starburst.	○	○	○	○	○	○	○ 1-2 pieces	○ 1/2 package	○ 1 package
38. Margarine (not butter) on bread or on vegetables.	○	○	○	○	○	○	○ 1 teaspoon	○ 2 teaspoons	○ 3 teaspoons
39. Butter (not margarine) on bread or on vegetables.	○	○	○	○	○	○	○ 1 teaspoon	○ 2 teaspoons	○ 3 teaspoons
40. Fat or oil in cooking.	○	○	○	○	○	○			

For each of the questions below, please fill in the oval that best describes your usual eating habits.

41. What kind of milk do you usually drink?	○ Whole milk ○ Reduced-fat 2% milk ○ Low-fat 1% milk	○ Skim milk ○ Soy milk ○ Rice milk	○ I don't drink milk or soy milk	
42. If you drink soft drinks or pop, is it usually:	○ Diet or sugar free soft drinks	○ Regular ○ I don't drink soft drinks		
43. If you drink Snapple, KoolAid, instant iced tea, or instant lemonade, is it usually:	○ Sugar-free ○ Regular	○ I don't drink these		
44. If you eat hot dogs, are they usually:	○ Low Fat or turkey hot dogs	○ Regular hot dogs ○ I don't eat hot dogs		
45. If you eat lunch meats, are they usually:	○ Low Fat or turkey	○ Regular	○ I don't eat lunch meats	
46. If you eat snacks like chips, are they usually:	○ Trans-fat free	○ Regular	○ I don't know	○ I don't eat them

For each of the questions below, please fill in the oval that best describes your usual eating habits.

47. If you eat crackers, are they usually:
- Trans-fat free
- Triscuits, Graham crackers, Ry-Vita
- Saltines or other snack crackers
- I don't eat them

48. If you eat ice cream, is it usually:
- Low carb, low sugar
- Low fat or ice milk
- Regular
- Premium
- I don't eat it

49. If you eat cake, snack cakes, cookies and other pastries, are they usually:
- Low carb, low sugar
- Low fat
- Regular
- I don't eat it

50. If you eat chocolate candy, is it usually:
- Low carb, low sugar
- Low fat
- Regular
- I don't eat it

51. If you eat other candy, not chocolate, is it usually:
- Sugar-free
- Regular
- I don't eat it

52. When you use margarine, is it usually:
- Stick margarine
- Soft tub margarine
- Low-fat margarine
- Butter-margarine blend
- Non-hydrogenated and trans-fat free
- I don't eat it

53. What kind of fat or oil do you usually use in cooking? MARK ONLY 1 or 2.
- Spray oil (i.e. Pam), or no oil
- Butter
- Butter/margarine blend
- Stick margarine
- Soft tub margarine
- Low-fat margarine
- Corn oil, vegetable oil
- Olive oil, canola oil
- Lard, fatback, bacon fat
- Crisco
- Trans-fat free brand
- I don't know or don't cook

54. What kind of cold cereal do you usually eat?
Choose 1 or 2 that you eat most often.
(If you usually eat just one kind, mark one.)
- Low-carb cereals like Atkins, Low-Carb Special K
- Cheerios (plain), Shredded Wheat, Wheat Chex, Wheaties
- Sweetened cereals like Frosted Flakes, Honey Nut Cheerios, Fruit Loops, Cap'n Crunch, granola, instant sweetened oatmeal
- Other cold cereals, like Corn Flakes, Rice Krispies, Bran Flakes
- I don't eat cereal.

55. What kind of bread do you usually eat?
- Italian, French or local bakery
- Regular sliced white bread
- Dark bread like rye, cracked wheat
- 100% whole wheat
- I don't know or I don't eat bread

SOME LAST QUESTIONS ABOUT YOU

Are you
- Hispanic or Latino
- Not Hispanic or Latino

What race do you consider yourself to be? (MARK ALL THAT APPLY)
- White
- Black or African American
- Asian
- American Indian or Alaska Native
- Native Hawaiian or Other Pacific Islander
- Do not wish to provide this information

Thank you very much for filling out this questionnaire.
Please take a minute to go back and fill in anything you may have skipped.

PLEASE DO NOT WRITE IN THIS AREA

SERIAL #

APPENDIX VIII - 7TH EDITION OF THE TNM CLASSIFICATION OF MALIGNANT TUMOURS

The 7th Edition of the TNM Classification of Malignant Tumours has recently been released. To facilitate this process, educational resources have been made available to promote the use of staging (visit http://www.cancerstaging.org/staging/posters/breast8.5x11.pdf and http://www.cancerstaging.org/staging/changes2010.pdf).
These staging criteria should be used for new trials.

Onco*type* DX analyzes a panel of 21 genes within a tumor to determine a Recurrence Score. The Recurrence Score is a number between 0 and 100 that corresponds to a specific likelihood of breast cancer recurrence within 10 years of the initial diagnosis. In MA.32, an Oncotype Dx score $\geq$ 25 is considered an adverse prognostic factor when assessing eligibility of women with node negative breast cancer measuring between 1 and 2 cm.

- **Recurrence Score lower than 18**: This suggests a low risk of recurrence. The benefit of chemotherapy is likely to be small and will not outweigh the risks of side effects.
- **Recurrence Score between 18 and 31**: This score suggests an "intermediate" risk of recurrence. It's unclear whether the benefits of chemotherapy outweigh the risks of side effects.
- **Recurrence Score greater than 31**: A high risk of recurrence, and the benefits of chemotherapy are likely to be greater than the risks of side effects.

Ki67

Ki67 is a molecule that can be easily detected in growing cells in order to gain an understanding of the rate at which the cells within a tumor are growing.

Detection of Ki67 is carried out on biopsies, samples of tumor tissue. The goal of this assay is to evaluate an important characteristic of the cells within the tumor, the percentage of tumor cells that are actively dividing and giving rise to more cancer cells. The number obtained through this examination is termed the S-phase, growth, or proliferative fraction. This information can play an important part in deciding the best treatment for a cancer patient.

Estrogen and Progesterone Receptor Positive

Estrogen and progesterone receptor status must be known. *(Receptor positive by immunohistochemistry: ERICA or PgRICA versus both receptors negative. It is recommended that ER and PgR assays be considered positive if there are at least 1% positive tumour nuclei in the sample on testing in the presence of expected reactivity of internal [normal epithelial elements] and external control. [Hammond 2010]*

HER2 Positive versus Negative definition

Positive = 3+ over-expression by IHC in > 30% of invasive tumour cells

OR

HER2 gene amplification by FISH/CISH > 6 HER2 gene copies per nucleus

OR

a FISH/CISH ratio: HER2 gene copies to chromosome 17 signals of > 2.2

All other results will be considered negative.

APPENDIX IX – EVALUATION METHODOLOGIES

It is important that at least one individual, at each participating centre be trained to do the anthropometric measurements in a correct and consistent fashion so that the data may be compared over time. While these measurements are simple in concept, they should be performed, for this trial, according to the following procedures to ensure accuracy and consistency.

Height

Height will be measured in stocking feet using a stadiometer. Height should be recorded in metres.

Weight

Weight will be measured in indoor clothing (without shoes) using an appropriate clinical weight scale. Weight should be recorded in kilograms.

Waist and Hip Circumference

The circumference should be measured on subjects without heavy outer garments in a standing position. The contents of all pockets must be removed. All tight clothing, including the belt, must be loosened. The participant should stand with the feet fairly close together (about 12-15cm) with weight equally distributed on each leg. Participants should be asked to breathe out gently at the time of the reading of the measurement to prevent them from contracting their muscles or from holding their breath. The tape should be held firmly in a horizontal position. It is recommended that the observer is sitting by the participant while taking the measurement.

The waist measurement should be recorded at the level midway between the lower rib margin and the iliac crest, in centimeters, rounded to the nearest .0 or.5 cm.

The hip measurement should be recorded from the maximum circumference over the largest portion of the buttocks, in centimeters rounded to the nearest .0 or.5 cm.

BMI

SI units	$\mathrm{BMI} = \frac{\text{weight (kg)}}{\text{height}^2(\text{m}^2)}$	
Imperial units	$\mathrm{BMI} = \frac{\text{weight (lb)} \times 703}{\text{height}^2(\text{in}^2)}$	$\mathrm{BMI} = \frac{\text{weight (lb)} \times 4.88}{\text{height}^2(\text{ft}^2)}$

Blood Pressure

Hypertension – Detection, Diagnosis and Management

Measurements should be taken with a sphygmomanometer known to be accurate and by a health care provider or CRA who has been adequately trained in the measurement of blood pressure. A recently calibrated aneroid or a validated and recently calibrated electronic device can also be used. Use the arm not affected by surgery. In the case of bilateral breast carcinoma, choose one arm for measurement and use it consistently.

Reference: Canadian Hypertension Education Program. 2007 CHEP recommendations for the management of hypertension. 2007 (www.hypertension.ca/chep/).

NEW YORK HEART ASSOCIATION CLASSIFICATION OF CARDIAC DISEASE

Clinical Evaluation of Functional Capacity of Patients with Heart Disease in Relation to Ordinary Physical Activity				
Class	Cardiac Symptoms	Limitations	Need for Additional Rest *	Physical Ability to Work **
I	None	None	None	Full time
II	Only moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, and any activity increases discomfort	Extreme	Marked	Unable to work
* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician. ** At accustomed occupation or usual tasks. **Reference:** Bruce, RA: Mod Concepts Cardiovasc Dis 25:321, 1956. (Modified from New York Heart Association, 1953)				

APPENDIX X – CORRELATIVE SCIENCE PROCEDURES, BLOOD SAMPLING, PROCESSING AND SHIPPING

Blood

After an overnight fast of at least 12 hours, participants will provide the following blood specimens:

- ✓ 1 tube for immediate glucose analysis,
- ✓ 3 light green topped tubes (containing lithium heparin - for insulin & plasma),
- ✓ 1 red topped tube (for serum) and
- ✓ 1lavender topped tube (for DNA).

- The green topped tubes will be centrifuged within half an hour of collection and the collected plasma frozen immediately in 1cc aliquots at -80°C.
- The red topped tube will sit for 30 minutes at room temperature and then centrifuged and the collected serum frozen immediately in 1 cc aliquots at -80°C.
- The lavender topped tube (whole blood in EDTA) will be collected and frozen in 1 ml aliquots at -80°C for subsequent thawing and DNA extraction.

Specimens will be stored at participating centers immediately after collection and then shipped to a central laboratory, frozen on dry ice, in batches of 10 sets or more (1 set = entire blood collection from one patient visit), for subsequent storage and ultimate analysis. Our plan to collect lymphocytes for DNA at baseline, 6 months and at 48 months of treatment will provide the necessary sample to evaluate not only germline DNA but also potential changes in DNA methylation as a result of the metformin intervention.

Research Blood Samples Taken at Baseline and Again at 6 Months and at 48 Months of Study Treatment

Type of Tube	One Tube (7 ml) (1.4 teaspoons)	Light Green Top Tubes (3 x 4.5 ml) (2.7 teaspoons)	Red Top Tube (2 x 6 ml) (2.4 teaspoons)	Lavender Top Tube (1 x 6 ml) (1.2 teaspoons)
To be used for	Plasma for Fasting Glucose *(done locally according to institution's procedures & mandatory)*	Insulin *(done centrally & mandatory)* Plasma for storage for future research *(optional)*	Serum for storage for future research *(optional)*	DNA extraction *(done centrally & optional)* *Lavender topped tubes for DNA should be collected even for patients who consent to blood banking but refuse genetic testing. DNA may be used to study gene expression without fitting the definition of genetic testing. (Please see the MA.32 Sample Consent Form for definitions.*

TOTAL VOLUME DRAWN = 38.5 ML (7.8 Teaspoons, 2.6 Tablespoons)

Tumour blocks will be requested by the Queen's Department of Pathology and instructions will be included in the request as to where blocks should be sent. The request will be sent to the person named in the Correlative Studies Report. All blood frozen and stored at participating sites will be shipped, in batches, at intervals, on dry ice to:

Attn: Shakeel Virk
Pathology Coordinator
Canadian Cancer Trials Group Tumour Bank
Department of Pathology
4th Floor Richardson Labs Building
Stuart Street
Queen's University
Kingston, ON K7L 3N6
Tel: 613-533-2906
Fax: 613 548-2486

APPENDIX XI – CANCER TRIALS SUPPORT UNIT (CTSU) PARTICIPATION PROCEDURES

Registration/Randomization

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member Web site or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each CTSU investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll subjects. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site at http://www.ctsu.org

All forms and documents associated with this study can be downloaded from the MA.32 page on the CTSU registered member Web site (https://www.ctsu.org). Subjects can be randomized only after pre-treatment evaluation is complete, all eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS.

In order to participate in MA.32, sites must submit the "CCTG MA.32 Application to Participate", by fax, to CCTG. Both the site candidate and the CTSU Regulatory Office will be notified simultaneously by CCTG if the site meets the requirements to move forward with site registration.

Requirements for MA.32 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- IRB-approved consent form

Pre-study requirements for patient enrollment on MA.32

- Patient must meet all inclusion criteria, and no exclusion criteria should apply
- Patient has signed and dated all applicable consents and authorization forms
- All baseline laboratory tests and pre-study evaluations performed within the time period specified in the protocol. Please consult protocol section 6.0 for baseline investigations and protocol section 13 for blood banking and tumour banking information. Please do not send any tumour blocks until requested to do so by CCTG.
- Patient completed baseline QOL forms, Physical Activity Questionnaire and Diet Questionnaire per protocol section 6.0 and Protocol Appendices VI & VII.

CTSU Procedures for Patient Enrollment

1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009 between 9:00 a.m. and 5:30 p.m. Eastern Time, Mon-Fri.. Leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, e.g. within one hour, call the registrar cell phone at 1-301-704-2376.

2. Complete the following forms:

   CTSU Patient Enrollment Transmittal Form
   Eligibility Checklist

3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 5:30 p.m., Mon-Fri, Eastern Time (excluding holidays); however, please be aware that registrations received after 5:00 p.m. will be processed the next day. The CTSU registrar will check the investigator and site information to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and will follow-up with the site to resolve any discrepancies.

4. Once investigator eligibility is confirmed and enrollment documents are reviewed for compliance, the CTSU registrar will access the CCTG's on-line registration system, to obtain assignment of a treatment arm and assignment of a unique patient ID (to be used on all future forms and correspondence). The CTSU registrar will confirm registration by fax.

Data Submission and Reconciliation

The Medidata Rave™ web-based system will be used for electronic data capture (EDC). management and reporting on this trial. All case report forms (CRFs), with the exception of completed Quality of Life Questionnaires, Physical activity Questionnaires and Diet Questionnaires, will be electronic. Sites will be granted access to the EDC system following approval of all site registration documentation by the CTSU office. Questionnaires must either be downloaded from the MA.32 protocol web page located on the CTSU registered member web site (https://www.ctsu.org) or will be provided by CCTG to approved sites. Sites must use the current form versions and adhere to the instructions and submission scheduled outlined in the protocol. Submission of supporting documentation will also be required for this study. Supporting documents can be mailed or directly scanned/uploaded into the EDC system based on centre preference/capability. Mailed supporting documents should be sent directly to CCTG.

Completed electronic CRFs must be submitted directly to CCTG, electronically, via the EDC system. Submit all paper questionnaires and supporting documents directly to the CCTG at the address on the "Final Page" of the protocol. Do not send study data to the CTSU.

The CCTG will send query notices and delinquency reports directly to the site for reconciliation. These will be issued electronically, either directly through the EDC system (data queries for electronic CRFs) or by e-mail (data queries for paper questionnaires and delinquency reports). Please send query response and delinquent data to the CCTG via the appropriate route (electronic or paper) as applicable in each case, and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP IAM Account contact information current. This will ensure timely communication between the clinical site and the CCTG.

Special Materials or Substudies

Tumour tissue blocks (optional) and blood specimens (mandatory for insulin and glucose level determination) will be collected for MA.32 subjects. For details of specimen collection, please see protocol section 13 and the Sample Consent Form in Protocol Appendix XII.

Please do not send any tumour blocks until requested by the CCTG to do so.

Quality of Life, Physical Activity and Nutrition Sub-studies (Protocol Appendices VI & VII)

Order hard copy booklets from CCTG and submit completed forms, as outlined in the protocol, to CCTG at the address appearing on the protocol's "Final Page".

Serious Adverse Event (AE) Reporting (Protocol Section 11)

Please consult protocol section 11 for Serious Adverse Event Reporting.

Secondary AML/MDS/ALL reporting: Report occurrence of secondary AML, MDS, or ALL via the NCI/CTEP AML-MDS Report Form in lieu of AdEERS. Submit the completed form and supporting documentation as outlined in the protocol.

Drug Procurement (Protocol Appendix III)

1. Information on drug formulation, procurement, storage and accountability, administration, and potential toxicities are outlined in Appendix III of the protocol and a more detailed guide will be provided prior to site activation. Sites will be pre-stocked with an initial supply of blinded Metformin/Placebo and re-stocked according to use (which will be monitored by the CCTG "Mango" System)

2. You may navigate to the drug forms by selecting Pharmacy Forms from the document center tree on the MA.32 Web page.

Regulatory and Monitoring

Study Audit

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/ Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

For subjects enrolled through sites affiliated with the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. Per capita reimbursement will be issued by the credited Group provided they have endorsed the trial, or by the CTSU if the Group has not endorsed the trial.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up can be found in the CTMB Monitoring Guidelines and are available for download from the CTEP web page http://ctep.cancer.gov/monitoring/guidelines.html.

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU website.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from subjects enrolled in clinical trials at non-US sites.

Clinical Data Update System (CDUS) Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDUS data collected from the study-specific case report forms.

APPENDIX XII - A HEALTHY LIFESTYLE AFTER BREAST CANCER

Both the English and French copies of this document are available and posted on the MA.32 trial webpage.

Many patients with breast cancer are interested in adopting a healthy lifestyle. This often involves changes in diet and physical activity. The American Cancer Society has developed information that may be helpful to breast cancer patients who would like to make lifestyle changes. This information can be found on the American Cancer Society website (www.cancer.org). Four helpful documents are provided here:

1. Benefits of Good Nutrition
2. Nutrition After Treatment Ends
3. Make Exercise Work for You
4. Fitting in Fitness

Additional information is available on the American Cancer Society website.

We encourage you to adopt a healthy lifestyle and suggest that you discuss planned changes in lifestyle with your health care team so ensure they are right for you.

Benefits of Good Nutrition

Good *nutrition* is especially important if you have cancer because the illness itself, as well as its treatments, can affect your appetite. Cancer and cancer treatments can also affect your body's ability to tolerate certain foods and to use *nutrients*.

The nutrient needs of people with cancer vary from person to person. Your doctor, nurses, and a registered dietitian can help you identify your nutrition goals and plan ways to help you meet them. Eating well while you are being treated for cancer can help you:

- feel better
- keep up your strength and energy
- keep up your weight and your body’s store of nutrients
- tolerate treatment-related side effects
- lower your risk of infection
- heal and recover quickly
-

Eating well means eating a variety of foods that will give you the nutrients you need to protect your health while fighting cancer. These nutrients include *protein*, *carbohydrates*, *fat*, *water*, *vitamins*, and *minerals*.

Nutrients

Protein

We need protein for growth, to repair body tissue, and to keep our immune systems healthy. When your body doesn't get enough protein, it takes you longer to recover from illness and you have lower resistance to infection. People with cancer often need more protein than usual. After surgery, chemotherapy, or radiation therapy, extra protein is usually needed to heal tissues and to help prevent infection. Good sources of protein include lean meat, fish, poultry, dairy products, nuts, dried beans, peas and lentils, and soy foods.

Fats

Fats play an important role in nutrition. Fats and oils provide a rich source of energy for the body. They are used to store energy, insulate body tissues, and transport some types of vitamins through the blood. They also play an important role in food preparation by enhancing food flavor, making baked products tender, and conducting heat during cooking. You may have heard that some fats are better for you than others. When considering the effects of fats on your heart and cholesterol level, choose unsaturated fats (monounsaturated and polyunsaturated).

Monounsaturated fats are found mainly in vegetable oils such as canola, olive, and peanut oils. They are liquid at room temperature.

Polyunsaturated fats are found mainly in vegetable oils such as safflower, sunflower, corn, flaxseed, and canola oils. Polyunsaturated fats are also the main fats found in seafood. They are liquid or soft at room temperature. Certain polyunsaturated *fatty acids*, such as linoleic acid and alpha-linolenic acid, are called essential fatty acids, because the body cannot make them. They are needed to build cells and make hormones. Essential fatty acids must come from foods we choose.

Saturated fats (or saturated fatty acids) are mainly found in animal sources such as meat and poultry, whole or reduced-fat milk, and butter. Some vegetable oils like coconut, palm kernel oil, and palm oil are saturated. Saturated fats are usually solid at room temperature.

Trans fatty acids are formed when vegetable oils are processed into margarine or shortening. Sources of trans fats in the *diet* include snack foods and baked goods made with partially hydrogenated vegetable oil or vegetable shortening. Trans fats also are found naturally in some animal products, such as dairy products.

Carbohydrates

Carbohydrates give the body the fuel it needs for physical activity and for proper organ function. There are also good and bad sources of carbohydrates. The best sources of carbohydrates -- fruits, vegetables, and *whole grains* -- supply needed vitamins and minerals, *fiber*, and *phytonutrients* to the body's cells. Other sources of carbohydrates include bread, potatoes, rice, spaghetti, pasta, cereals, dried beans, corn, peas, and beans. Sweets (desserts, candy, and drinks with sugar) can supply carbohydrates, but provide very few nutrients.

Water

Water and *fluids* are vital to our health. All body cells need water to function. If you do not take in enough fluids or if you are vomiting or have diarrhea, you may become dehydrated. In general, a person should drink about eight 8-oz. glasses of water or clear liquid each day to be sure that all the body cells get the fluid they need.

Vitamins and minerals

Vitamins and minerals are needed for proper growth and development. They also allow the body to use the energy (*calories*) supplied in foods. A person who eats a balanced diet with enough calories and protein usually gets plenty of vitamins and minerals. But it can be hard to eat a balanced diet when you are being treated for cancer and have treatment side effects that last for long periods of time. When that is the case, your doctor or dietitian may suggest a daily multivitamin and mineral supplement. If you are thinking of taking a vitamin or supplement, be sure to discuss this with your doctor first. Some people with cancer take large amounts of vitamins, minerals, and other dietary supplements to try and boost their immune system or even destroy cancer cells. Some of these substances can be harmful, especially when taken in large doses. In fact, large doses of some vitamins and minerals may reduce the effectiveness of chemotherapy and radiation therapy. During treatment, it may be best to choose one with no more than the Daily Value (DV) for all nutrients and one without iron, unless your doctor thinks that you need iron. Again, discuss this with your doctor first.

Antioxidants

Antioxidants are substances that protect the body's cells from damage caused by *free radicals* (by-products of the body's normal processes). Examples of antioxidants include vitamin C, vitamin E, vitamin A (beta carotene), and selenium. If you want to take in more antioxidants, health experts recommend eating a variety of fruits and vegetables, which are good sources of antioxidants. Taking large doses of antioxidant supplements is usually not recommended while having chemotherapy and radiation therapy. Talk with your doctor to determine the best time to take antioxidant supplements.

Herbs

Herbs have been used to treat disease for hundreds of years. Today, herbs are found in many products, such as pills, liquid extracts, teas, and ointments. While many of these products are harmless and safe to use, others can cause severe and harmful side effects. Some may even interfere with proven cancer therapies, including chemotherapy, radiation therapy, and recovery from surgery. If you are interested in using products containing herbs, talk about it with your doctor or nurse first.

Safety considerations

Many people believe that if they find a pill or supplement in stores , it is safe and effective. The Food and Drug Administration (FDA) put out new rules in 2007 to help ensure that supplements contain what their labels claim they do. However, some of these rules will not be fully in effect until 2010. Even then, the supplement's safety and its effect on the body are not addressed by the new FDA rules. The FDA does not require manufacturers of these products to print possible side effects on their labels. The FDA cannot pull a dietary supplement or herbal product from the market unless it can prove that the product is unsafe.

Tell your health care team about any herbal products and supplements that you are using or are thinking about using. Bring the bottle(s) of the supplement to your doctor to talk about the dose and to be sure that the ingredients do not interfere with your health or cancer treatments. Some other safety tips:

- Ask your doctor or nurses for reliable information on dietary supplements.
- Check the product labels for both the quantity and concentration of active ingredients contained in each product.
- Stop taking the product immediately and call your doctor if you have side effects such as wheezing, itching, numbness, or tingling in your limbs.

Some people with cancer take large amounts of vitamins, minerals, and other dietary supplements in an effort to enhance their immune systems or even destroy cancer cells. Some of these substances can be harmful. In fact, large doses of some vitamins and minerals may reduce the cancer-fighting effects of chemotherapy and radiation therapy. If you would like to learn more about herbs and supplements, call us at 1-800-ACS-2345 or visit our web site at www.cancer.org.

Nutrition After Treatment Ends

Most eating-related side effects of cancer treatments go away after the treatment ends. Sometimes side effects such as poor appetite, dry mouth, change in taste or smell, trouble swallowing, or significant weight loss may last for some time. If this happens to you, talk to your health care team and work out a plan to address the problem.
As you begin to feel better, you may have questions about eating a healthful diet. Just as you wanted to go into treatment with the necessary nutrient stores that your diet could give you, you'll want to do the best for yourself at this important time. There's very little research to suggest that the foods you eat will keep your cancer from coming back. But eating well will help you regain your strength, rebuild tissue, and feel better overall. And certainly, what you eat can help reduce risk for other cancers.

Suggestions for healthy eating after cancer:

- Check with your doctor for any food or diet restrictions.
- Ask your dietitian to help you create a nutritious, balanced eating plan.
- Choose a variety of foods from all the food groups. Try to eat at least 5 to 7 servings a day of fruits and vegetables, including citrus fruits and dark-green and deep-yellow vegetables.
- Eat plenty of high-fiber foods, such as whole grain breads and cereals.
- Buy a new fruit, vegetable, low-fat food, or whole grain product each time you shop for groceries.
- Decrease the amount of fat in your meals by baking or broiling foods.
- Choose low-fat milk and dairy products.
- Avoid salt-cured, smoked, and pickled foods.
- If you choose to drink, drink alcohol only occasionally.
- If you are overweight, consider losing weight by reducing the amount of fat in your diet and increasing your activity. Choose activities that you enjoy. Check with your doctor before starting any exercise program.
- See "Nutrition and Physical Activity During and After Cancer Treatment: Answers to Common Questions" to help choose foods for a well-balanced meal plan.

Make Exercise Work for You

No matter when you start, exercise improves health. Even people who start exercising later in life appear to gain many of the same health benefits as people who've exercised their whole lives, according to research at Stanford University School of Medicine.

Physical activity throughout life can help protect against some cancers. For breast and prostate cancer, it may help by regulating hormone levels. For colon cancer, physical activity speeds up the digestive process, shortening the exposure of the bowel lining to harmful substances Exercise also helps reduce cancer risk by helping people maintain a healthy weight.

Choose Your Game

It's important to enjoy what you're doing so you won't get bored or think of it as a chore. To choose an activity that's right for you, ask yourself these questions:

Do you like to be social, or would you prefer time to yourself?
- Social butterflies should try activities that connect them with other people. Try to walk with friends, join a team or recreation association, or go line dancing.
- If you need time to yourself, walking, running, swimming, or gardening can give you time to reflect.

Do you need to get energized or wind down?
- For an energy boost, try aerobic activities that get the heart pumping.
- Reduce stress with activities like yoga or tai chi.

Are you goal-oriented, or do you like to stay flexible?
- If you like to feel a sense of accomplishment, choose activities where you can chart and monitor your progress like training for a run, or take up an activity with rising skill levels, like martial arts.
- For a more flexible routine, try walking or find an exercise video you can do at home.

Do you want to get away from it all or get involved?
- If you want to get away, choose outdoor activities like hiking, biking, or rollerblading.
- Make your workplace more health conscious with the ACS program Active for Life. Participants choose their own physical activities, form teams of coworkers, and enjoy a friendly competition for the highest number of minutes spent exercising.
- To get involved in the community, consider building homes for the disadvantaged, participating in charity walks and runs, helping an elderly neighbor with yard work, or tidying up a local school.

How Much Activity Should You Be Doing?

That depends on you.
- If you haven't been active, you should start with moderate activities and gradually increase the duration, frequency, and intensity as you become more fit. Work your way up to 30 minutes or more five or more days a week.
- If you are active but want to do more, increase the intensity, duration, or frequency of what you currently do. Moderate to vigorous activity for 45 minutes or more five of more days a week will increase your health benefits.
- If you are active and want to maintain your current level of fitness, try adding new activities to your routine to use different muscles and keep your interest.

Strike a Balance

Ads for expensive exercise equipment and special diets can make healthy living look complicated. But the truth is there's no secret to achieving the weight you want. It is as simple as balancing the calories you burn. When that doesn't happen, you gain weight.

Remember that everything you eat contains calories, and everything you do uses calories. For example, if you weight 150 pounds and are active, you need approximately 2,250 calories per day to maintain that weight, versus 1,950 calories if you are sedentary.

It helps to know that one pound of body fat equals 3,500 calories. That means that to lose one pound per week, you need to reduce your total calories by 500 per day. You can do this by eating 250 fewer calories a day, and burning an extra 250 calories through physical activity (e.g. walking 2.5 miles).

To Burn Off a Large Order of Fries (400 Calories)

A 160 pound person could burn off 400 calories in the time and activities shown below:

Activity	Minutes
Moderate walking	95
Scrubbing Floors	89
Dancing	70
Bicycling	39
Running	28

To plan the physical activity for weight loss, you'll want a ballpark idea of how many calories are burned in different activities. For example, if you weigh 150 pounds and did the following activities for an hour, you'd burn 324 calories gardening, 297 in brisk walking, and 216 calories playing with kids.

Less vigorous activities use fewer calories but still help in weight control. For a 150 pound person, an hour of strolling uses 206 calories, vacuuming or mopping—150 calories. Watching TV burns only 72 calories per hour. Find calorie counts for many other activities with our online calculator.

Staying Motivated

Be specific and choose variety. Rather than having general goals like "getting in shape" or "exercising more," choose concrete goals such as walking 30 minutes on Tuesdays and Thursdays, and doing stretching exercises five minutes each morning. The more variety you have, the more likely you will continue. A well-rounded exercise program that includes aerobic exercise, strength training using weights, and flexibility exercises - even when performed regularly in small increments - is key, according to the American College of Sports Medicine.

Incorporate fitness into your lifestyle. Begin to see exercise as an everyday opportunity. For example, use the stairs instead of the elevator, walk during lunch, or bike to work. Combine fitness with your family chores and activities, such as raking leaves or gardening.

Motivate yourself. Try visualization techniques to help your motivation. Imagine yourself being in shape and how it feels. Create a vision of yourself looking fit. Rather than focusing on feeling out of shape, picture yourself feeling energized after your workout. Also, reward yourself when you meet each of your goals.

Get a support system. Build a support system of family, friends, co-workers, and/or neighbors. They can help encourage you when your motivation is low. You can also exercise with someone else. Try to find a buddy who shares similar fitness interests. Many shopping malls have mall-walker programs where you can meet others.

Expect setbacks and prepare for obstacles. Things like time, illness, or bad weather may occasionally get in the way. Disruptions are inevitable. Accept them and move on. If you go off your program, you can always adapt and resume. Some exercise is always better than none at all.

If you are a male older than 45 , or a female over 55, and have not been regularly active, or have any health concerns, consult your physician before you begin an exercise program. Regardless of your age, if you have two or more of the following risk factors, consult your physician:

- High blood pressure
- High cholesterol
- Diabetes
- You currently smoke
- Family history of early onset heart disease (first degree relative with heart disease before age 65 for female relatives, or before age 55 for male relatives.)

Fitting in Fitness

Simple Steps Add Up

Did you know you benefit from even small amounts of moderate activity throughout the day? Regular physical activity is easier to fit in than you may realize and can significantly lower your lifetime risk for cancer --and heart disease and diabetes, too.

You'll find the American Cancer Society's physical activity guidelines for adults and children below. These recommendations are based on the latest scientific information to help reduce the risk of developing cancer. Read on for ways to fit in fitness that may surprise you, then learn how many calories are burned in common activities and exercises.

ACS Physical Activity Guidelines

Adults: Engage in at least 30 minutes of moderate to vigorous activity, above usual activities, on 5 or more days of the week; 45 to 60 minutes of intentional physical activity are preferable.

Children and adolescents: Engage in at least 60 minutes per day of moderate to vigorous physical activity for at least 5 days per week.

Moderate Activity is anything that makes you breath as hard as you do during a brisk walk. During moderate activities, you'll notice a slight increase in heart rate and breathing, but you may not break a sweat.

Vigorous Activities generally engage large muscle groups and cause a noticeable increase in heart rate, breathing depth and frequency, and sweating.

Other beneficial activities include those that improve strength and flexibility such as weight lifting, stretching, or yoga.

Examples of Moderate and Vigorous Physical Activities

	Moderate Activities	**Vigorous Activities**
Exercise and Leisure	Walking, dancing, leisurely bicycling, ice-skating or roller-skating, horseback riding, canoeing, yoga	Jogging or running, fast bicycling, circuit weight training, aerobic dance, martial arts, jump rope, swimming
Sports	Volleyball, golfing, softball, baseball, badminton, doubles tennis, downhill skiing	Soccer, field hockey or ice hockey, lacrosse, singles tennis, racquetball, basketball, cross-country skiing
Home Activities	Mowing the lawn, general lawn and garden maintenance	Digging, carrying and hauling, masonry, carpentry
Occupational Activity	Walking and lifting as part of the job (custodial work, farming, auto or machine repair)	Heavy manual labor (forestry, construction, fire fighting)

Active Substitutions

Looking for more ways to work in activity during your day? Think about how much time you spend sitting rather than being active. Then consider these simple substitutions that can help you get moving.

- Use stairs rather than an elevator.
- Walk or bike to your destination.
- Exercise at lunch with your workmates, family, or friends.
- Take a 10-minute exercise break at work to stretch or take a quick walk.
- Walk to visit co-workers instead of sending an email.
- Go dancing with your spouse or friends.
- Plan active vacations rather than only driving trips.
- Wear a pedometer every day and watch your daily steps increase.
- Join a sports team.
- Use a stationary bicycle or treadmill while watching TV.

No matter what kind of activity you choose, the important thing is to get moving. Try to fit in at least 30 minutes of exercise on 5 or more days of the week, and look for other opportunities to be active throughout the day.

APPENDIX XIII - EQUIVALENT HEMATOLOGY UNITS

The following units are equivalent to 10^9/L: 10^3/mm^3 10^3/uL 10^3/cmm 10^3/cumm 10^3/mcL 1000/mm^3 1000/uL 1000/cmm 1000/cumm 1000/mcL K/mm^3 K/uL K/cmm K/cumm K/mcL mil/mm^3 mil/uL mil/cmm mil/cumm mil/mcL thou/mm^3 thou/uL thou/cmm thous/cumm thous/mcL E9/L GIGA/L	<u>*For example*</u> if the WBC count is 5.3 x10^3/uL this is the same as 5.3 x10^9/L if platelets are 250 thou/mm^3 this is the same as 250 x10^9/L
The following units are equivalent to cells/mm^3: cells/uL cells/cmm cells/cumm cells/mcL /mm^3 /uL /cmm /cumm /mcL	<u>*For example*</u> if the WBC count is 5300 cells/uL this is the same as 5300 cells/mm^3 if platelets are 250,000 /uL this is the same as 250,000 cells/mm^3

APPENDIX XIV - EMERGENCY SITUATIONS AND COMPLIANCE

Management of Protocol Variances in Emergency Situations

Compliance with the trial protocol, its amendments and any information that may be added to this document or provided as a part of the conduct of this trial as well as any associated sub-studies should be ensured to every extent possible, however in emergency situations, specific variances from the protocol that occur as a result of efforts to minimize or eliminate hazards and protect the safety and well-being of patients are permissible.

In these rare circumstances, minor deviations that do not impact patient safety or willingness to participate or trial integrity, which have been justified and documented in the medical record by the QI/SI will not be considered to be REB reportable deficiencies requiring action, but must be reported to CCTG (e.g. in Electronic Data Capture (EDC) or using trial specific deviation logs as directed by CCTG) within 4 weeks of the end of the Emergency Situation, unless otherwise instructed by CCTG, and to your REB at the next amendment or annual approval.

Centres should also discuss these reporting requirements with their local REB, and review the trial website for additional guidance specific to the trial.

Minor Protocol Deviations:

- Missed or delayed protocol mandated visits or investigations on treatment or in follow up.
- Changes in study drug distribution (e.g. drug distributed remotely or IV drug given at satellite site), providing permitted by local SOPs, or written procedure established and is approved by CCTG or acceptable per further instruction from CCTG. *Note there will be no exceptions for injectable/IV investigational agents as must be administered at participating site.*
- Alternative methods for safety assessments (e.g. telephone contact, virtual visit, alternative location for assessment).
- Patient care and evaluations provided by non-research staff, providing overseen by QI/SI who must make all treatment decisions and ensure that all required information and results will be reported to allow central data submission. Includes physical exam, clinical laboratory tests, research blood collections that can be shipped centrally, imaging, non-investigational drug therapy*, standard radiation therapy, surgery, and other interventions that do not require protocol-specified credentialing*.

  **Must be approved by CCTG or acceptable per further instruction from CCTG.*
- Re-treatment following extended treatment delays if protocol specifies that excessive delays require discontinuation, providing other protocol requirements for discontinuation have not been met and either discussed with CCTG or acceptable per further instruction from CCTG.

Note:

- Applicable only to COVID-19 and other CCTG designated emergency situations.
- No waivers will be given for eligibility, including performance of protocol mandated tests/imaging.
- Deficiencies will be issued if patients are enrolled when trial is on accrual hold, for unreported Serious Adverse Events as well as changes in drug distribution/administration and/or re-treatment after extended treatment delays when not discussed and approved by CCTG or acceptable per further instruction from CCTG.
- Deviations or changes that are believed to impact patient safety, compromise the study integrity or affect willingness to participate are still considered Major Protocol Violations and must be reported to CCTG and your REB. These include more than a minimal delay in protocol therapy administration.

LIST OF CONTACTS

	Contact	Tel. #	Fax #
ELIGIBILITY CHECKLIST Must be completed prior to requesting a randomization.	Amy Hawkins Clinical Trials Assistant CCTG Email: ahawkins@ctg.queensu.ca	613-533-6430	613-533-2814
STUDY SUPPLIES Guides, Protocols	Available on CCTG Website: http://www.ctg.queensu.ca under: *Clinical Trials*		
PRIMARY CONTACTS FOR GENERAL PROTOCOL-RELATED QUERIES (including eligibility questions and protocol management)	Paul Stos Study Coordinator CCTG Email: pstos@ctg.queensu.ca or: Dr. Wendy Parulekar Senior Investigator CCTG Email: wparulekar@ctg.queensu.ca	613-533-6430 416-586-8605	613-533-2814 416-586-8659
STUDY CHAIR	Dr. Pamela Goodwin Study Chair Email: pgoodwin@mtsinai.on.ca		
SERIOUS ADVERSE EVENT REPORTING See protocol Section 11.0 for details of reportable events.	Dr. Wendy Parulekar Senior Investigator or: Paul Stos Study Coordinator CCTG	613-533-6430 613-533-6430	613-533-2814 613-533-2814
DRUG ORDERING See Appendix III for full details.	Amy Hawkins Clinical Trials Assistant(s) CCTG Email: ahawkins@ctg.queensu.ca	613-533-6430	613-533-2814

Cancer Trials Support Unit (CTSU) Address and Contact Information

To submit site registration documents:	For patient enrollments:	Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206	CTSU Patient Registration Please consult Appendix XI: Cancer Trials Support Unit (CTSU) Participation Procedures	Data management will be performed by the CCTG by means of a web-based Electronic data Capture (EDC) System. Electronic case report forms must be submitted electronically. Clinical reports and supporting documentation may be submitted by mail to: NCIC CTG – MA.32 Cancer Research Institute 10 Stuart Street, Queen's University Kingston, Ontario, Canada K7L 3N6 Phone – 613-533-6430 Fax – 613-533-2814 Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
For patient eligibility or treatment-related questions Contact the Study Coordinator of the Coordinating Group.		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Public Web site is located at: www.ctsu.org The CTSU Registered Member Web site is located at https://members.ctsu.org		

CTSU logistical information is located in Appendix XI