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CANADIAN CANCER TRIALS GROUP (CCTG)

OPTION-DDR: A RANDOMIZED PHASE III TRIAL INVESTIGATING **P**LATINUM AND **T**AXANE CHEMOTHERAPY IN METASTATIC CASTRATION RESISTANT PROSTATE CANCER PATIENTS WITH ALTERAT**ION**S IN **D**NA **D**AMAGE **R**ESPONSE (DDR) GENES

CCTG Protocol Number: **PR.25**

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CONFIDENTIALITY STATEMENT

This protocol contains information that is confidential and proprietary. The contents of this protocol, its amendments and any information that may be added to this document or provided as a part of the conduct of this trial may not be used for any other purpose and may not be disclosed to any other person or entity without the prior written permission of CCTG (and other applicable parties as designated by CCTG).

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STUDY ACKNOWLEDGMENT/DISCLOSURE (SA/D)

I understand that this protocol and any supplementary information that may be added to this document, contains information that is confidential and proprietary and must be kept in confidence.

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, in accordance with any modifications that may occur over the duration of the study, 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 confirm that all data will be submitted in a timely manner and will be accurate, complete and supported by source documents. I will complete any protocol specific training required by the sponsor and that I understand the requirement to inform additional site personnel with delegated duties of this information.

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 understand that this trial will be registered on a public trial registry and that my contact information and site name will be included in the registry listing.

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 enrollment 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.

_____	_____	_____
Qualified Investigator Signature	Printed Name	Date

Protocol Number: CCTG PR.25

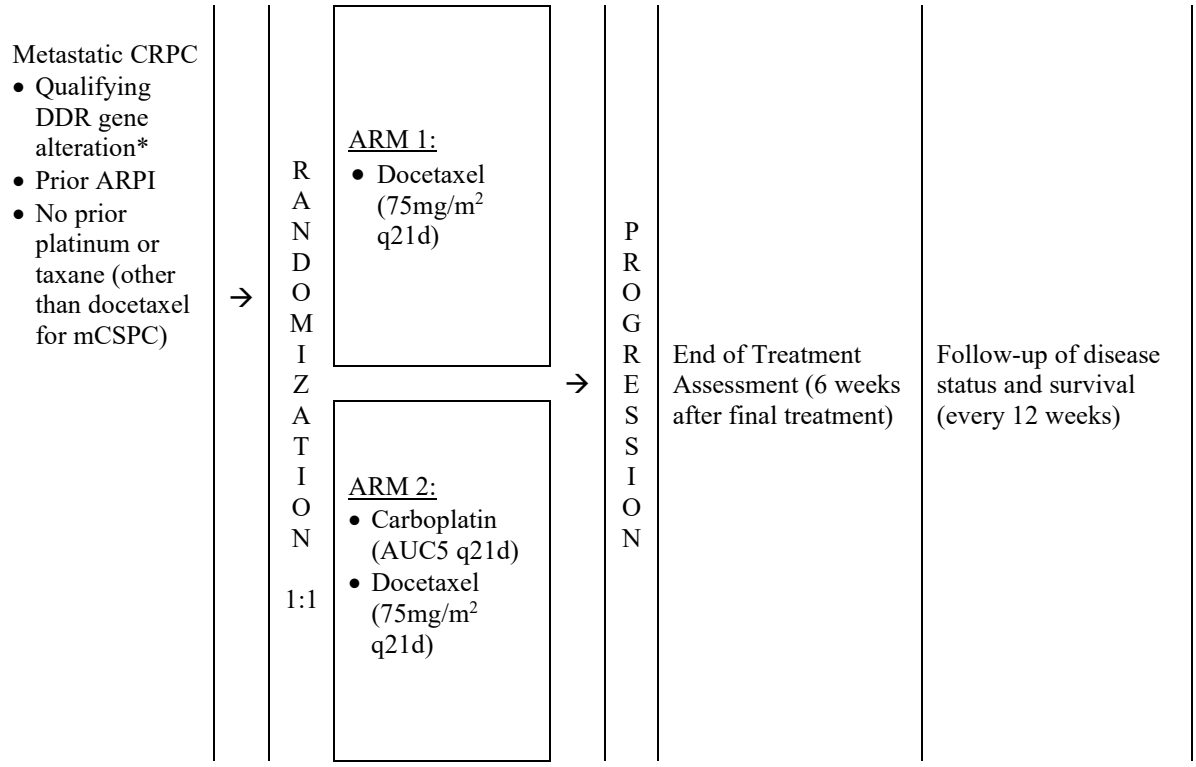
CENTRE: _____

TREATMENT SCHEMA

This is a multi-centre, open-label, randomized phase III trial comparing docetaxel to docetaxel and carboplatin in participants with metastatic castration resistant prostate cancer (mCRPC) who are suitable candidates for docetaxel therapy, harbor alterations in DNA Damage repair (DDR) genes, and who have received prior treatment with Androgen Receptor Pathway Inhibitors (ARPI).

Stratification:

- BRCA2 status (qualifying BRCA2 alteration vs other qualifying alteration). Note that if co-occurring BRCA2 and non-BRCA2 alterations are present, the patients will be considered as BRCA2 for stratification purposes.
- Prior treatment with poly-ADP ribonuclease polymerase (PARP) inhibitor (yes or no)
- Prior treatment with docetaxel for metastatic castration sensitive prostate cancer (yes or no)



N = 236 participants

* Qualifying DDR gene alterations are defined as Tier I or Tier II (clinically significant/likely clinically significant or pathogenic/likely pathogenic) germline or somatic alterations involving one or more of the following genes: BRCA1, BRCA2, ATM, ATR, BRIP1, BARD1, CDK12, CHEK1, CHEK2, ERCC2, FANCA, FANCC, FANCD2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L.

1.0 OBJECTIVES

1.1 Primary Objective

To compare overall survival (OS) in participants with mCRPC harboring DDR gene alterations who receive carboplatin in addition to docetaxel, compared to those receiving docetaxel alone.

1.2 Secondary Objectives

Key Secondary Objective:

- To compare the two treatment arms with respect to radiographic progression-free survival (rPFS) (as defined by PCWG3 and RECIST 1.1)

Additional Secondary Objectives:

To compare the two treatment arms with respect to:

- PSA response (defined as reduction in PSA from baseline by 50%)
- Progression free survival (as defined by PCWG3 and RECIST 1.1)
- Time to next systemic therapy
- Safety and tolerability (CTCAE version 5.0)
- Patient-reported Quality of Life (QoL) as quantified by FACT-P, FACT-Taxane, and the FACT-BP questionnaires
- Economic Evaluation, including both healthcare utilization and health utilities, the latter measured using EQ-5D-5L

1.3 Tertiary Objectives

- To compare treatment outcomes, including response rates, PFS, and OS, across different DDR gene alterations
- To compare OS in participants by ethnic or cultural origin and determine if differences in OS (if any) are associated with social determinants of health. Please consult this link for Statistics Canada's definition of "Ethnic or Cultural Origins".
- To determine if DDR gene alteration patterns differ across ethnic or cultural groups
- To compare genetic testing patterns in different centres within Canada

2.0 BACKGROUND INFORMATION AND RATIONALE

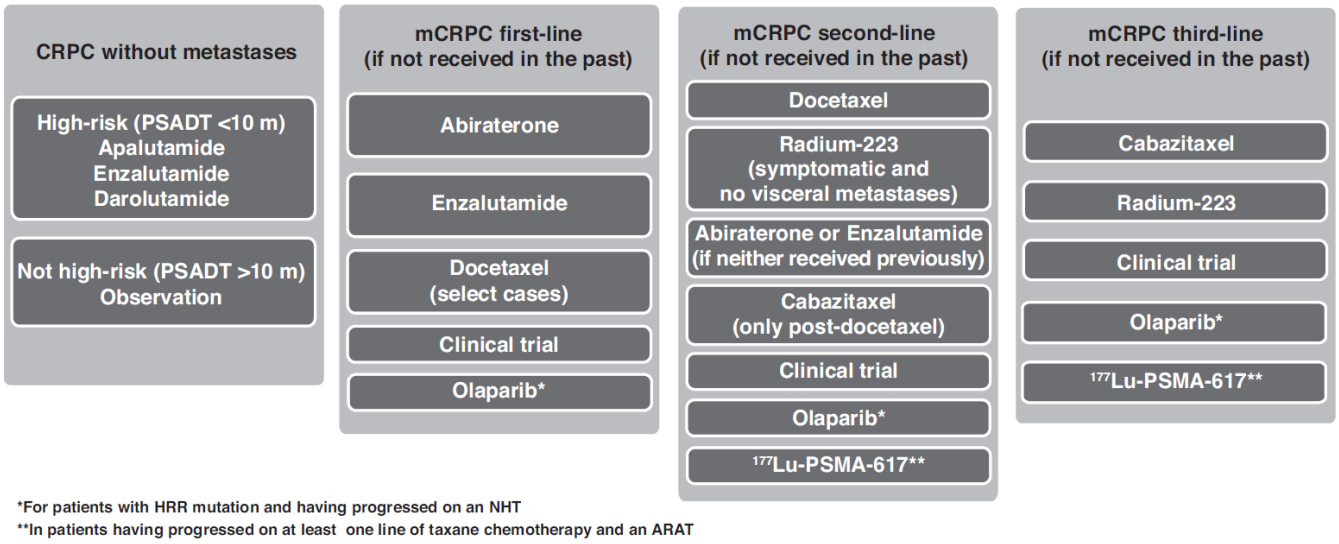
2.1 Metastatic Castration Resistant Prostate Cancer

Prostate cancer is the commonest cancer occurring in Canadian males, and the third most common cause of cancer death in men in Canada. Thirteen Canadian men die of prostate cancer each day. Metastatic castration resistant prostate cancer (mCRPC) is defined as metastatic prostate cancer that progresses despite androgen deprivation therapy (ADT), usually achieved by surgical or medical castration (testosterone levels < 1.7nmol/l). mCRPC is associated with a median overall survival of between 36-42 months *[Armstrong 2020; Saad 2023]*. mCRPC is invariably fatal *[Turco 2022]* and commonly preceded by a number of adverse events associated with a significant deterioration in health and quality of life. Therefore, improving outcomes in patients with mCRPC represents an unmet clinical need. This trial represents a unique opportunity to provide these individuals with personalized treatment to potentially improve their overall survival and quality of life.

2.2 Current Treatment of Metastatic Castration Resistant Prostate Cancer

The backbone treatment for advanced prostate cancer remains ADT. This is achieved using gonadotrophin releasing hormone (GNRH) agonists, such as leuprolide, goserelin or antagonists, such as degaralix. Alternatively, surgical orchidectomy can be used as a method of ADT. Management of advanced prostate cancer has benefitted from the development of a number of systemic therapy agents that have been demonstrated to improve overall survival (OS), including: the taxane chemotherapies docetaxel *[Tannock 2004]* and cabazitaxel *[de Bono 2010]*; the androgen receptor pathway inhibitors (APRIs) abiraterone, enzalutamide, apalutamide, and darolutamide; the cellular immunotherapy sipuleucel-T *[Kantoff 2010]*; radio pharmaceuticals radium 223 and ^{177}Lu-PMSA-617; and the PARP inhibitors, olaparib, niraparib, rucaparib, and talazoparib. With the number of therapeutic agents and treatment indications rapidly expanding, the treatment algorithm for advanced prostate cancer is complex and dynamic; however, as a general rule, most patients will receive an ARPI either when starting ADT, or as their initial treatment after progression on ADT. Following progression on an APRI, docetaxel would be the next treatment for most patients, with exceptions for patients who have BRCA1/2 or ATM mutations who would qualify to receive olaparib, or radium 223 for patients with symptomatic bone metastases and no soft tissue disease. Currently, cabazitaxel and ^{177}Lu-PMSA-617 are approved for use only after progression on prior docetaxel (Figure 1). Though there are a number of systemic therapy options available for patients, outcomes remain poor with a median OS of 12-19 months in pre-treated mCRPC patient populations. Better therapeutic strategies are desperately needed.

Figure 1: Summary of Recommended Treatment of CRPC *[Saad 2022]*



2.3 DNA Damage Repair Genes and mCRPC

Genomic instability is a hallmark of cancers. Rapid cellular proliferation leads to the accumulation of DNA aberrations. Alterations in pathways that repair DNA damage leads cells to have a proliferative advantage *[Conteduca 2021]*. Approximately 25% of mCRPC patients have alterations in DNA damage response (DDR) genes, with approximately half occurring in tumour tissue (somatic) only and BRCA2 pathogenic variants being the most frequent *[Robinson 2015; Abida 2017; de Bono 2020]*. mCRPC patients with DDR gene alterations (DDR-alt) have distinct clinical features from DDR gene wild type (DDR-wt) patients, including worse outcomes when treated with ARPIs *[Clark 2022]* and clinical benefit from poly(adenosine diphosphate[ADP]-ribose) polymerase (PAPR) inhibitors. PARP is a critical enzyme involved in base-excision repair (BER), a type of single stand DNA repair mechanism *[Farmer 2005]*. PARP inhibitors (PARPi) prevent normal function of this enzyme and trap PARP at the site of single strand DNA breaks, leaving them unrepaired. During DNA replication, advancement of the replication forks converts these single stand breaks into double strand breaks. Double strand DNA breaks are typically repaired by high-fidelity homologous recombination (HR), a process involving BRCA1 and BRCA2 as well as numerous other enzymes. In the setting of functional HR, PARP inhibition is inconsequential. However, in the setting of impaired HR, attempts to repair these double strand DNA breaks are made by error prone mechanisms, such as non-homologous end joining (NHEJ) resulting in an accumulation of chromatid breaks and fragmentation of the genome, which are ultimately lethal to the cell *[Mateo 2017]*. The strategy of combining processes that are individually non-lethal (in this case defective HR and PARP inhibition), that together are lethal, is referred to as synthetic lethality *[Iglehart 2009]*.

Two PARPi – olaparib and rucaparib – have shown clinical benefit in large, randomized phase III clinical trials in mCRPC patients with specific DDR-alt *[de Bono 2020; Fizazi 2023]*, with olaparib receiving Health Canada approval in August 2020 *[AstraZeneca 2020]*. Both of these drugs were approved based on trials that performed pre-screening tumour NGS of >4000 patients in order to randomize <500. Rucaparib was investigated in a narrow panel of DDR gene alterations (BRCA1/2 or ATM only); similarly, olaparib was primarily investigated in patients with BRCA1/2 or ATM, though a cohort of patients with other DDR gene alterations, including BRIP1, BARD1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54L was also included in the registration trial. Patients with BRCA2 alterations appear to derive the greatest benefit from PARP inhibitors, with minimal benefit in patients with ATM alterations. PARPi are also clearly active in other less frequently occurring DDR gene alterations, though a PFS or OS benefit has not been clearly demonstrated in part due to low patient numbers *[Mateo 2016; Mateo 2020; Hussain 2020]*.

Because of the Health Canada approval of olaparib and subsequent provincial reimbursements, tumour and/or germline NGS has also received provincial reimbursement as a companion diagnostic in most jurisdictions. While olaparib is only available for patients with BRCA1/2 or ATM alterations, most Canadian jurisdictions offer broad panel NGS testing (Table 1). Because of this, most Canadian patients with mCRPC have access to tumour NGS testing to identify DDR gene alterations as part of their routine clinical care.

Table 1: Availability of NGS Testing at Participating Centres

Participating Site	**Germline**			**Somatic**		
	Limited Panel*	Broad Panel**	Validated Test	Limited Panel*	Broad Panel**	Validated Test
CHU de Québec - Hôpital l'Énfant-Jésus, Québec City		X	Yes	X		Yes
QEII Health Sciences Centre, Halifax		X	Yes	X		Yes
William Osler Health System, Brampton Civic Hospital	X	X	Yes	X	X	Yes
Odette Cancer Centre, Toronto		X	Yes	X	X	Yes
Grand River Regional Cancer Centre, Kitchener		X	Yes		X	Yes
North York General Hospital		X	Yes		X	Yes
Ottawa Hospital Research Institute	X	X	Yes	X	X	Yes
Cambridge Memorial Hospital	X	X	Yes	X		Yes
London Regional Cancer Program		X	Yes	X		Yes
CancerCare Manitoba, Winnipeg	X		Yes			No
Allan Blair Cancer Centre, Regina	X		Yes	X		Yes
Tom Baker Cancer Centre, Calgary		X	Yes		X	No
Cross Cancer Institute, Edmonton		X			X	Yes
BCCA – Vancouver Cancer Centre		X	Yes		X	Yes

*BRCA1/2, ATM only; **BRCA1/2, ATM, others

2.4 Docetaxel

Docetaxel is a member of the taxane family of chemotherapeutics, which also includes paclitaxel and cabazitaxel. Taxanes are microtubule toxins that stabilize the microtubule by preventing depolymeriation. This process prevents microtubule shortening, an essential process for cell division, ultimately resulting in mitotic arrest and apoptosis or mitotic slippage *[Herbst 2003]*.

While docetaxel serves as an important node in the treatment algorithm for mCRPC, it is not clear what its efficacy is in the current treatment landscape. Docetaxel was the first systemic therapy agent to demonstrate an improvement in overall survival in the landmark phase III TAX327 study *[Tannock 2004]* where docetaxel and prednisone given either every 3 weeks or weekly was compared to mitoxantrone and prednisone in patients with mCRPC and no prior exposure to chemotherapy. This study demonstrated that treatment with docetaxel given every 3 weeks was associated with an improved OS compared to mitoxantrone with median OS of 18.9 vs 16.5 months, respectively. Docetaxel was also favoured in a number of secondary endpoints including PSA response and improvements in quality of life. Based on this study, docetaxel became the standard of care in first line mCRPC.

It is important to note that the TAX327 trial took place in an era prior to the availability of other survival prolonging therapies, notably the APRIs, which have largely supplanted docetaxel as first line therapies for advanced prostate cancer disease states, including mCRPC, non-metastatic castration resistant prostate cancer (nmCRPC), and metastatic castration sensitive prostate cancer (mCSPC). As such, it is not clear what the efficacy of docetaxel is in an ARPI pre-treated population. A number of retrospective studies have suggested attenuated efficacy, with lower response rates and overall survival than was seen in TAX327 *[Mezynski 2012; Schweizer 2014]*, with some evidence of cross resistance between ARPIs and docetaxel *[van Soest 2013]*. More recently, the PRESIDE trial *[Merseberger 2022]*, which investigated docetaxel with either enzalutamide or placebo in patients with disease progression on enzalutamide, demonstrated a PSA ≥50% response in 25% of patients treated with docetaxel+placebo, which is considerably lower than the expected 45-50% PSA ≥50% response rate seen in ARPI naive patients *[Tannock 2004; Petrylak 2004]*. What impact this has on survival outcomes is not known. While the above studies took place in biomarker unselected populations, the existing data suggests similar efficacy in patients with DDR-alt compared to DDR-wt *[Mateo 2018; Castro 2019]*. The TRITON-3 study, a randomized phase III in mCRPC patients with BRCA1/2 or ATM alterations previously treated with ARPI tested the efficacy of rucaparib vs physician's choice, and included docetaxel as an option. This study did not report the PSA or objective response rate for docetaxel, but did report the median rPFS, which was 8.3 months and identical to what has been demonstrated the PRESIDE trial of biomarker unselected mCRPC patients post enzlutamide *[Merseberger 2022]* suggesting similar efficacy in these populations.

2.5 Platinum-based Chemotherapy

Platinum-based chemotherapy (PBC) is one of the most widely used classes of cytotoxic chemotherapy in oncology. Once activated in the cytoplasm, platinum agents bind to DNA bases, creating DNA adducts that can be either intra- or inter-strand cross-links. These cross-links prevent DNA transcription and DNA replication, initiating cell cycle arrest and an attempt to repair the lesions through DNA repair pathways. A number of DNA repair pathways are used to repair platinum-DNA adducts. Intra-strand cross links are primarily repaired by the nucleotide excision repair (NER) pathway, while interstrand cross links generates double strand DNA breaks that are either repaired through high fidelity homologous recombination (HR) pathway or the error-prone non-homologous end-joining (NHEJ) pathway. If these DNA lesions are not repaired or DNA damage severe enough, apoptosis is triggered *[Dasari 2014]*.

Loss of functional DDR genes has been demonstrated to increase sensitivity to PBC in a number of different cancers. For example, in breast cancer patients the presence of BRCA mutations or high homologous recombination deficiency (HRD) score is associated with improved pathologic response after treatment with neoadjuvant PBC *[Telli 2016]*. Similar findings have been demonstrated in epithelial ovarian cancer, with either BRCA mutation, or high HRD score, predicting higher response rates and prolonged PFS *[Dann 2012; Wen 2022; Feng 2023]*. Interestingly, BRCA wildtype patients and high HRD scores show better response to PBC than patients with low HRD scores, suggesting that defects in non-BRCA HR genes, or alternatively epigenetic or post-translational suppression of BRCA also sensitize to PBC.

A clear benefit of PBC for patients with mCRPC has not yet been demonstrated and it is not typically used in this disease. The only randomized phase III trial of PBC in mCRPC investigated satraplatin vs placebo in a biomarker unselected population which did not improve OS, and thus was not licensed in this indication *[Sternberg 2009]*. However, consistent with what has been shown in other cancers, PBC may be more effective in mCRPC with DDR-alt, though this evidence is currently limited to small, mostly retrospective studies and case reports. One retrospective study of mCRPC patients who received PBC showed that DDR-alt patients had higher PSA and soft tissue responses compared to DDR-wt with a trend towards improved OS despite being significantly more likely to have received platinum monotherapy as opposed to combination therapy *[Schmid 2020]*. Another retrospective study demonstrated that in DDR-alt patients who had received second-line therapy after progression on ARPI, carboplatin-based chemotherapy had the highest PSA response rate (67%), and longer OS than taxane chemotherapy *[Kwon 2021]*. A prospective phase II trial of carboplatin and docetaxel in patients with biallelic inactivating alterations in BRCA1/2 and other HRD genes demonstrated a PSA ≥50% response rate in 7/8 patients (88%) with BRCA1/2 or ATM alterations, and 3/5 patients with other HRD gene alterations (60%) which is higher than the expected historical response rate of docetaxel of 26% *[Cheng 2020]*. In this study 3 patients with BRCA2 alterations were previously treated in PARPi, with 2 of these patients achieving PSA declines of >50%. Importantly, while PARPi and PBC may share common resistance mechanisms *[Vidula 2020]*, responses to PBC have been reported in DDR-alt mCRPC after progression on prior PARPi *[Mota 2020; Slootbeek 2023; Cheng 2020]*. This is in keeping with what has been demonstrated in ovarian cancer, where PBC and PARPi are used sequentially, with PARPi maintenance after PBC delaying progression *[Moore 2018; Gonzalez-Martin 2019]*, and PBC remaining active after progression on PARPi *[Ang 2013; Romeo 2022]*, though perhaps at attenuated rates *[Frenel 2022]*. Direct comparisons of the efficacy of PARPi and PBC in mCRPC patients are currently limited. One small retrospective study showed no difference in progression-free survival (PFS) with olaparib compared to carboplatin *[Berchuck 2020]*. This question is being examined by at least one prospective clinical trial (NCT04038502). Based on these data, several guidelines and expert consensus statements include PBC as an option for patients with DDR-alt *[NCCN 2023; EUA Guidelines 2022; Saad 2021; Gillessen 2022]* though the quality of evidence is low, and in the absence of prospective randomized trials, the risks and benefits of PBC in this biomarker-defined population are unknown. Likely reflecting the lack of data, utilization of PBC appears to be low with <10% of patients receiving it, even in patients with known DDR-alt *[George 2020; Castro 2019]*.

2.6 Platinum and Taxane Combination Chemotherapy Safety and Dosing

Platinum and taxane combination chemotherapy protocols are perhaps the most widely used in oncology. This is due to non-overlapping mechanisms of action that result in combinatorial efficacy in a broad range of cancers, but also a very manageable adverse event profile and acceptable tolerability for patients. Because of this, most medical oncologists will have extensive experience using platinum and taxane combination chemotherapy.

A dose-finding study in patients with advanced ovarian cancer tested doses of carboplatin up to AUC 7 (using the Calvert formula with creatinine clearance (CrCl) measured by 51Cr EDTA) combined with docetaxel at 75mg/m2. The combination was well tolerated with low rates of non-hematologic toxicity, including sensory neuropathy, with grade 2 or higher events occurring in <10% of patients in all cohorts. The dose-limiting toxicity was myelosuppression leading to a recommended docetaxel dose of 75mg/m2 and a carboplatin dose of AUC 5 (if CrCl measured by ^{51}Cr EDTA) or AUC 6 (if CrCl calculated using Cockcroft-Gault formula) [*Vasey 2001*]. At this dose, rates of complicated neutropenia were low, with 3 patients (14%) having grade 4 neutropenia >7 days, 1 (3%) having febrile neutropenia, and 1 (3%) requiring dose reduction.

A number of studies have been conducted in mCRPC using platinum and taxane combinations and have demonstrated safety and acceptable adverse event profile in this population. Aparicio *et al. [2013]* conducted a phase II study in mCRPC patients with "anaplastic" clinical features, using carboplatin AUC5 and docetaxel 75mg/m2 every 21 days, followed by second line cisplatin 25mg/m2 and etoposide 120mg/m2 for 3 days every 21 days upon progression. In this study, 113 patients received a total of 544 cycles of carboplatin and docetaxel, with a median number of cycles of 4 per patient (range 1-12); 74 patients received 226 cycles of cisplatin and etoposide with a median of 4 cycles per patient (range 1-6). Grade ≥3 adverse events were uncommon: grade 4 adverse events included thrombosis (n=2), thrombocytopenia (n=1); grade 3 events included infections with normal or grade ≤2 absolute neutrophil count (n=8), febrile neutropenia (n=3), fatigue (n=2), and nausea (n=2). No treatment related deaths were seen after carboplatin and docetaxel. Corn *et al. [2019]* conducted a phase I-II study of cabazitaxel and carboplatin in mCRPC patients. In the phase I portion of the study, cohorts of patients were treated with cabazitaxel 20-25mg/m2 and carboplatin AUC 3-4. No dose limiting toxicities were seen in any of the treatment cohorts, leading the authors to recommend the maximum tested doses, cabazitaxel 25mg/m2 and carboplatin AUC4, as the recommended phase II dose. In the phase II portion of the study, the combination therapy demonstrated low rates of grade ≥3 toxicities, with only fatigue (20%) anemia (23%), thrombocytopenia (14%), and neutropenia (16%), occurring in ≥10% of patients.

2.7 Rationale for Experimental Arm: Docetaxel and Carboplatin

As discussed above, the combination of docetaxel and carboplatin has been demonstrated to be safe with an acceptable adverse event profile both in mCRPC as well as other cancers. The accumulating evidence from retrospective studies, case reports, case series, and small prospective studies, suggests that PBC is highly active in mCRPC patients with DDR-alt, even in the setting of prior PARPi use. Based on these data, several guidelines and expert consensus statements include PBC as an option for patients with DDR-alt *[NCCN 2023; EUA Guidelines 2022; Saad 2021; Gillessen 2022]*. These guidelines and consensus statements include PBC as an option although the quality of evidence is low and the risks and benefits of PBC in this biomarker-defined population are unknown. Likely in reflection of this lacking data, utilization of PBC appears to be low, with <10% of patients receiving it, even in patients with known DDR-alt *[George 2020; Castro 2019]*.

This trial addresses this data gap and unmet need. This trial evaluates the combination of carboplatin and docetaxel in comparison to docetaxel alone rather than sequential monotherapy. This is because in medical oncology practice combination treatment is more likely to improve response rates. While the number of available mCRPC therapies continues to expand, docetaxel remains an important treatment, with some therapies, such as cabazitaxel and Lu-177-PSMA-617, only approved after use of docetaxel. The efficacy of docetaxel was demonstrated prior to other survival-prolonging therapies being developed. Docetaxel is currently used after progression on ARPIs in most patients where its efficacy appears quite modest with an expected PSA response rate of 25-30% both in biomarker unselected as well as DDR-alt patient populations *[Mezynski 2012, Merseburger 2022]*. This trial aims to improve patient outcomes by introducing more effective, biomarker-directed therapy at this critical treatment step. Combination therapy is likely to be more beneficial than using carboplatin as a single agent sequentially after progression on other survival-prolonging therapies, when multiple treatment resistance mechanisms are induced and patient attrition, which can approach 50% per line of therapy *[Shore 2021; George 2020]*, reduces the number of patients that would potentially benefit.

PR.25 is an open-label, randomized phase III trial in which participants are randomized in a 1:1 fashion to receive either docetaxel 75mg/m^2 IV every 3 weeks, +/- carboplatin AUC 5 IV every 3 weeks (initial doses of docetaxel 60mg/m^2 and of carboplatin AUC 4 will be allowed as per investigator discretion). Treatment will continue until either radiographic progression or intolerable side effects. Qualifying gene alterations will involve one or more of the following genes: BRCA1, BRCA2, ATM, ATR, BRIP1, BARD1, CDK12, CHEK1, CHEK2, ERCC2, FANCA, FANCC, FANCD2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L. Only Tier I or II somatic or germline alterations (also referred to as clinically significant/likely clinically significant, or pathogenic/likely pathogenic) in qualifying genes will be considered eligible. This classification will be based on American College of Medical Genetics and Genomics (ACMG) Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer *[Li 2017]*. This will include most frameshift mutations that result in a premature stop codon, as well as somatic biallelic gene deletions. Participants with monoallelic gene deletions in isolation will not be eligible. Additional genes with a defined role in DDR pathway may be considered by the trial committee, on a per-gene basis according to the latest literature and ACMG standards.

2.8 Quality of Life

QoL outcomes are essential to allow a balanced assessment of any potential benefits to inform clinical decisions. The QoL impact of adding carboplatin to docetaxel in mCRPC has not been well studied to date and therefore our assumptions on QoL impact are derived from literature in other diseases, such as ovarian cancer. QoL will be evaluated using the Functional Assessment of Cancer Therapy – Prostate (FACT-P) questionnaire, the Functional Assessment of Cancer Therapy – Bone Pain (FACT-BP) questionnaire, and the Functional Assessment of Cancer Therapy – Taxane (FACT-T) questionnaire. The FACT-P is a standardized, validated questionnaire in metastatic prostate cancer that addresses domains important to participants such as physical and emotional functioning *[Esper 1997]*. The FACT-T scale includes a 16-item questionnaire which assesses important side effects associated with taxane chemotherapy such as peripheral neuropathy, which carboplatin may worsen. This specific questionnaire has been shown to have excellent internal consistency, reliability, validity, and responsiveness to change *[Cella 2009]*. The FACT-BP includes a 15-item questionnaire that measures the number of painful sites, the intensity of pain and interference of pain in the patient's physical, social, mental, and general functioning.

QoL instruments will be completed at baseline, every 6 weeks, and at the end of treatment to balance the need to adequately capture the impact of each treatment arm without being excessively burdensome.

2.9 Health Economics

Economic analyses objectives are to determine an incremental cost effectiveness ratio reported as a difference in cost per life-year gained between the 2 arms. The mean overall cost per patient for each of the two study treatment arms will be calculated. The main cost components will be calculated in the following data prior to failure as defined in the protocol: cost of treatments/medications/surveillance during responsive disease (PFS phase), cost for progressive disease which will include best supportive care (BSC) or subsequent line of treatments (if appropriate). Disease management, AE and disease monitoring costs will be also estimated. Specifically:

1) A cost-utility analysis will be completed from the government payer perspective, over a lifetime horizon through prospectively collected utility (EQ-5D-5L) data;
2) Exploratory economic analyses using same methodology in stratification subgroups (BRCA2 status, prior PARP inhibition, and prior docetaxel treatment) may be considered.

The robustness of the model results will be assessed using one-way and multi-way sensitivity analyses. Major drivers of medical care costs, namely hospitalization, chemotherapy, and survival, will be varied ±20% to examine the impact on the base-case incremental cost effectiveness ratios. Bootstrapping and the development of a cost-effectiveness acceptability curve will also be conducted.

2.10 Social Determinants of Health

Social determinants of health (SDoH) are the non-medical factors that influence health outcomes and the social and economic conditions in which people are born, grow up, live, work, and age *[Asare 2017, Vickers 2023]*. SDoH are associated with disparities in cancer outcomes, and certain determinants such as English proficiency, socio-economic status, education level, geographical location, race/ethnicity, and sexual orientation are associated with lower clinical trial enrollment *[Asare 2017, Aziz-Bose 2022, Vickers 2023]*. Collecting SDoH data is essential for contextualizing outcome disparities and ensuring representation of equity-deserving groups and populations previously underrepresented in clinical trials *[Aziz-Bose 2022]*.

Data predominantly from the US has demonstrated underrepresentation of racialized persons in clinical trials, and there is limited data available for the Canadian population. Furthermore, historically patients self-identifying as Black have worse outcomes compared to the general population. More recent analysis of US trial populations has indicated that these outcomes are due to social determinants of health and that when patients have access to good quality health care their outcomes are equivalent. We will explore whether differences in outcomes within patient groups can be explained by social determinants of health rather than self-reported ethnic or cultural origins. Furthermore, we will evaluate both standard of care testing and ctDNA to determine whether there are differences in somatic and germline alterations in cancer associated genes in patients with different self-reported ethnic or cultural origins. These have hitherto not been evaluated in the Canadian population.

In this study we will rely on questions that have previously been used to collect SDoH data *[Pinto 2016, Gotfrit 2020, Yuan 2021, Williams 1997, Adekoya 2023]*. Participants enrolled in this trial will have the option to complete the SDoH questionnaire prior to enrolment. The questionnaire will take 5-10 minutes to complete and will be administered and collected through the CCTG System for Patient Reported Outcomes (SPROUT). The data will be entered by the participant directly into electronic devices (desktop computer, tablet, other mobile device).

2.11 Correlative Studies

This trial leverages standard of care genomic testing performed in Canada to inform familial risk and to identify patients who may be eligible to receive PARP inhibitors. Throughout Canada, different assays are utilized with different sensitivities. This study enables us to gain a snapshot of the different methods of analysis for genomic testing within different Canadian provinces. We would like to explore the frequency of DDR alterations within different ethnic groups within Canada.

The trial will also prospectively collect circulating tumour DNA (ctDNA) from participants at baseline, 3 weeks into treatment and upon progression. ctDNA is highly fragmented double stranded extracellular DNA which is released by cells undergoing apoptosis. The advantage of ctDNA is that it enables evaluation of the diversity of clones from different sites within one patient with mCRPC *[Kwan 2022]*. ctDNA evaluation is more readily acceptable to patients, as well as cheaper and easier to collect than fresh tissue biopsies in individuals with mCRPC. Furthermore, due to the high prevalence of bone metastases in mCRPC, biopsies derived from bone have a high failure rate in terms of DNA extraction due to the processing requirements.

ctDNA has been used to identify DDR gene alterations. ctDNA has previously shown excellent correlation with tissue derived DNA for DDR gene alterations. The sampling strategy in this trial enables evaluation of both spatial and temporal heterogeneity amongst patients with prostate cancer. The trial will utilize ctDNA to identify mechanisms of resistance and sensitivity to platinum and or docetaxel, as well as to evaluate ctDNA dynamics as a treatment response. Furthermore, we aim to look at the distribution of DDR gene alterations within different ethnic groups within Canada. ctDNA collated during this study will form a biorepository to enable further evaluations of the impact of chemotherapy on ctDNA.

3.0 BACKGROUND THERAPEUTIC INFORMATION

3.1 Docetaxel

Docetaxel is an established chemotherapeutic agent in solid tumour oncology. It is licensed in Canada for the treatment of castration resistant prostate cancer in combination with prednisone. Docetaxel is delivered by intravenous infusion and acts by disrupting the microtubular network in cells that are essential for vital mitotic and interphase cellular functions. Docetaxel promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. Docetaxel binds to free tubulin thereby decreasing the critical intracellular concentration of tubulin. The promoted polymerization of microtubules leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, resulting in the inhibition of mitosis in cells. The binding of docetaxel to microtubules does not alter the number of protofilaments in the bound microtubules.

Serious warnings/ precautions associated with Docetaxel include immunosuppression with infection, allergic reactions, enterocolitis and second malignancies.

Please refer to the most recent Product Monograph for additional information.

Please refer to Section 7.1 for the schedule of administration on study.

3.2 Carboplatin

3.2.1 *Name, Chemical Information and Structure*

Consult the most recent version of the Product Monograph for current information.

3.2.2 *Mechanism of Action*

Carboplatin is a synthetic analogue of cisplatin. Like cisplatin, carboplatin interferes with DNA intrastrand and interstrand crosslinks in cells exposed to the drug. DNA reactivity has been correlated with cytotoxicity.

3.2.3 *Pharmaceutical Data*

Supplied:
Carboplatin is commercially available from the Canadian market and will not be supplied for this study.

Storage:
Centres should follow manufacturer's guidelines for storage and preparation.

Route of Administration:
Intravenous.

4.0 STUDY POPULATION

Individuals with metastatic castration resistant prostate cancer who are suitable for treatment with docetaxel, have documented qualifying genetic alterations in DNA Damage Repair (DDR) genes, and have received prior ARPI therapy.

4.1 Eligibility Criteria

The eligibility criteria for this study have been carefully considered. Eligibility criteria are standards used to ensure that participants who enter this study are medically appropriate candidates for this therapy and to ensure that the results of this study can be useful for making treatment decisions regarding other participants with similar disease(s).

These eligibility criteria are expected to be followed. Any proposed variance must be discussed with CCTG prior to participant enrolment:

4.1.1 Histologic diagnosis of adenocarcinoma of the prostate. The presence of neuroendocrine or small cell carcinoma will be exclusionary.

4.1.2 *Prior Therapy*

Prior Systemic Therapy:
Prior treatment with any ARPI, such as abiraterone, enzalutamide, apalutamide, or darotlutamide, is required.

Participants are allowed any other prior systemic therapy for advanced prostate cancer, and are not limited on the number of lines of therapy, with the exception of what is listed in Section 4.2.1 below.

Participants must have recovered to ≤ grade 1 from all reversible toxicity related to prior systemic or radiation therapy, with the exception of chemotherapy induced alopecia and grade 2 peripheral neuropathy, and have adequate washout as follows:

- 2 weeks or 5 half lives (whichever is longer) for oral therapies (such as abiraterone, apalutamide, enzalutamide, darolutamide, and olaparib)
- Standard cycle of standard IV or IM therapies (such as radium 223 or Lu-177-PSMA-617)
- 2 weeks, 5 half lives, or standard cycle length (whichever is longer) for investigational agents

Prior Surgery:
Previous major surgery is permitted provided that surgery occurred at least 28 days prior to participant enrollment and that wound healing has occurred.

Radiation:
Prior external beam radiation is permitted provided a minimum of 7 days have elapsed between the last dose of radiation and date of enrollment. Exceptions may be made for low-dose, non-myelosuppressive radiotherapy after consultation with CCTG. Concurrent radiotherapy is not permitted.

4.1.3 Radiologically documented presence of metastatic disease within 28 days prior to randomization.

- Both a CT scan and a bone scan are required within 28 days prior to randomization.
- CT scans must be contrast-enhanced. If use of contrast is not clinically indicated, a non-contrast chest CT scan in addition to an MRI of the abdomen and pelvis is acceptable.
- Participants with brain metastases that are eligible (see Section 4.2.7 below) must have a CT scan or MRI of the brain within 28 days prior to randomization.

4.1.4 Disease progression after ARPI therapy as assessed by the investigator with at least one of the following:

- PSA progression with a minimum of two rising PSA values at least 1 week apart, at least 25% and 2ug/L above baseline/nadir.
- Radiographic progression of soft tissue disease by RECIST 1.1 criteria or bone metastases by PCWG3 criteria.

4.1.5 Medical or surgical castration with serum testosterone levels <50ng/dL or <1.7mmol/L.

4.1.6 Qualifying Tier I or Tier II (clinically significant/likely clinically significant or pathogenic / likely pathogenic) germline or somatic alterations involving one or more of the following DDR genes: BRCA1, BRCA2, ATM, ATR, BRIP1, BARD1, CDK12, CHEK1, CHEK2, ERCC2, FANCA, FANCC, FANCD2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, RAD54L. Monoallelic gene deletions in isolation will not be eligible.

4.1.7 Age 18 years or older.

4.1.8 Eastern Cooperative Oncology Group (ECOG) Performance Status of ≤ 2.

4.1.9 Participants must have adequate organ and marrow function measured within 14 days prior to enrolment including:

Hematology	Hemoglobin	≥ 90 g/L
	Absolute neutrophils	≥ 1.5 x 10^9/L
	Platelets	≥ 100 x 10^9/L
Biochemistry	Bilirubin	≤ ULN (upper limit of normal)*
	AST and/or ALT	≤ 1.5 x ULN;
	Serum creatinine *and / or:* Creatinine clearance**	≤ 1.25 x ULN >30 mL/min

* If confirmed Gilbert's, eligible providing ≤ 1.5 x ULN.

** Creatinine clearance to be measured directly by 24 hour urine sampling or as calculated by Cockcroft and Gault equation below:

Females: GFR = $\frac{1.04 \times (140\text{-age}) \times \text{weight in kg}}{\text{serum creatinine in } \mu\text{mol/L}}$

Males: GFR = $\frac{1.23 \times (140\text{-age}) \times \text{weight in kg}}{\text{serum creatinine in } \mu\text{mol/L}}$

4.1.10 Life expectancy > 12 weeks.

4.1.11 If the participant and the participant's partner are of childbearing potential, they must agree to use medically accepted methods of contraception (e.g. barrier methods, including male condom, female condom, or diaphragm with spermicidal gel) during the course of the study and for 6 months after the last dose of study drug.

4.1.12 Participant is able (i.e. sufficiently fluent) and willing to complete the quality of life and health utility questionnaires in either English or French. The baseline assessment must be completed within required timelines, prior to enrolment. Inability (lack of comprehension in English or French, or other equivalent reason such as cognitive issues or lack of competency) to complete the questionnaires will not make the participant ineligible for the study. However, ability but unwillingness to complete the questionnaires will make the participant ineligible.

4.1.13 Participant consent must be appropriately obtained in accordance with applicable local and regulatory requirements. Each participant must sign a consent form prior to enrollment in the trial to document their willingness to participate.

4.1.14 Participants must be accessible for treatment and follow-up. Investigators must assure themselves the participants enrolled on this trial will be available for complete documentation of the treatment, adverse events, and follow-up.

4.1.15 In accordance with CCTG policy, protocol treatment is to begin within 2 working days after participant enrolment.

4.2 Ineligibility Criteria

Participants who fulfill any of the following criteria are not eligible for admission to the study:

4.2.1 Received prior platinum chemotherapy (i.e. carboplatin, cisplatin, oxaliplatin, satraplatin) at any time; received prior taxane chemotherapy (docetaxel, paclitaxel, cabazitaxel) with the exception of docetaxel for mCSPC as long as it was no more than 6 cycles and at least 12 months have elapsed from their last treatment to the date of enrollment.

4.2.2 Active anticancer systemic therapy or investigational agents within 14 days of randomization.

4.2.3 Uncontrolled intercurrent illness including, but not limited to: active infection, symptomatic congestive heart failure (NYHA Class III or IV heart disease), unstable angina pectoris, cardiac arrhythmia, uncontrolled hypertension or psychiatric illness/social situations that would limit compliance with study requirements.

4.2.4 Participants with myelodysplastic syndrome/acute myeloid leukemia.

4.2.5 Malignancy within the previous 2-years with a > 30% probability of recurrence within 12 months, with the exception of non-melanoma skin cancer, and in-situ or superficial bladder cancer.

4.2.6 Participants with known symptomatic brain metastasis. However, participants with asymptomatic, treated brain metastases that have been stable for at least 12 weeks are eligible for study entry.

4.2.7 Participants with symptomatic or impending cord compression unless appropriately treated beforehand and clinically stable and asymptomatic.

4.2.8 Presence of a condition or situation, which, in the investigator's opinion, may put the participant at significant risk, may confound the study results, or may interfere significantly with participation in the study.

4.2.9 Live attenuated vaccination administered within 30 days prior to randomization.

Note: Seasonal vaccines for influenza are generally inactivated vaccines and are allowed. mRNA vaccines directed against COVID-19 are allowed. Intranasal vaccines are live vaccines and are not allowed.

4.2.10 For participants with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated. Participants with a history of hepatitis C virus (HCV) infection must have been treated and cured. For participants with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

4.2.11 Unable to obtain provincial reimbursement for carboplatin and docetaxel.

5.0 PARTICIPANT EVALUATION FLOWSHEET: PRE-TREATMENT, ON STUDY, AND AFTER TREATMENT

All participants entered on study must be evaluated according to the schedule outlined below with documentation submitted according to the schedule in Appendix III.

Required Investigations	Pre-study (prior to randomization)	During Protocol Treatment[13]	At Disease Progression[1]	After Protocol Treatment		
				6 weeks after end of treatment[2, 14]	Before confirmed progression[3, 14]	Every 12 weeks after progression
History and Physical Exam						
History and Physical exam (includes height at baseline only, weight)	Within 14 days					
ECOG PS[13]	Within 14 days	Day 1 of each cycle	X	X	Every 3 weeks	
Survival						X[16]
Hematology[13]						
Absolute neutrophils, WBC, hemoglobin, platelets	Within 14 days	Day 1 of each cycle		X		
Biochemistry[13]						
Bilirubin, AST or ALT, serum creatinine, creatinine clearance, sodium, calcium, magnesium, potassium, BUN or urea	Within 14 days	Day 1 of each cycle		X		
Radiology[14]						
CT chest/abdomen/pelvis[4]	Within 28 days	Every 9 weeks[5]	X		Every 9 weeks[5]	
99m technetium bone scan	Within 28 days	Every 9 weeks[6]	X[7]		Every 9 weeks[6]	
CT/MRI brain (only required if known brain metastases or otherwise clinically indicated)	Within 28 days	Every 9 weeks[5]	X		Every 9 weeks[5]	
Other Investigations[13]						
PSA	Within 14 days	Day 1 of each cycle	X[11]	X	Every 3 weeks	
Serum testosterone	Within 14 days	Day 1 of each cycle	X[11]	X	Every 3 weeks	
Correlative Studies[15]						
Whole blood (for cfDNA)	After randomization but before first dose of study treatment[8]	Day 1 of cycle 2[9]	X[11]			
Adverse Events[10, 14]						
Adverse events assessment (CTCAE Grade ≥3 and related to study treatment only)		Continuously				
Quality of Life						
FACT-P, FACT-Taxane, FACT-BP	Within 14 days	Day 1 of cycle 3 and every odd-numbered cycle onward	X[11]	X	Every 6 weeks	

table continues on following page…

Required Investigations	Pre-study (prior to randomization)	During Protocol Treatment[13]	At Disease Progression[1]	After Protocol Treatment		
				6 weeks after end of treatment[2, 14]	Before confirmed progression[3, 14]	Every 12 weeks after progression
Social Determinants of Health[12]						
SDoH Questionnaire	Within 14 days					
Health Economics						
EQ-5D-5L	Within 14 days	Day 1 of cycle 3 and every odd-numbered cycle onward	X[11]	X	Every 6 weeks	
Resource Utilization Assessment		Each cycle	X[11]	X	Every 6 weeks	

1. See Sections 8 and 10 for guidelines regarding ending treatment due to disease progression.
2. An End of Treatment visit is required regardless of reason(s) for ending treatment.
3. Participants who end treatment for reasons other than progression should maintain the same evaluation schedule until progression is confirmed.
4. CT scans must be contrast-enhanced. If contrast cannot be used, a non-contrast chest CT scan in addition to an MRI of the abdomen and pelvis is acceptable.
5. Tumour evaluations must be consistently performed every 9 weeks from randomization until objective disease progression is documented (as described in Section 8). Sites should adhere to this calendar-based schedule regardless of any delays in clinic visits. If a scan is done off schedule, future protocol-required scans should still be performed based on the original schedule, i.e. every 9 weeks counting from randomization (not from the date of the off schedule scan).
6. More frequent bone scans may be required to confirm disease progression. See Section 8.4.3.
7. A bone scan is required at the end of treatment, even if the baseline scan was negative.
8. Collection and immediate shipment of time sensitive samples MUST occur after enrollment. This is to ensure that the samples shipped to the Tumour Bank have a CCTG patient ID, which is required, in order to track and catalogue specimens.
9. Sample should be collected *before* administration of cycle 2 infusion, and should be collected even if treatment ends prior to this time point.
10. Adverse events (CTCAE Grade ≥3 and related to study treatment only) will be assessed at each study visit.
11. To be done at nearest visit after progression.
12. The Social Determinants of Health questionnaire is optional for participants, and not required for randomization. Participants must be given the opportunity to complete it. All other questionnaires are mandatory.
13. These laboratory tests may be performed locally for all visits. Results must be sent to the Qualified Investigator for review and for study data entry.
14. These study visits may be conducted by phone or videoconferencing technology (i.e. “virtual visits”), including adverse event assessments, in accordance with local laws and regulations.
15. Visits requiring protocol-mandated imaging and correlative blood sample collection must be performed at the enrolling centre.
16. Follow-up visits after confirmed progression are for survival tracking only, and may be performed virtually in accordance with local laws and regulations.

5.1 Telehealth Visits

As noted in the table above (see footnotes 13-16), certain visits may be performed virtually via telehealth. The Qualified Investigator is required to ensure that all labs and assessments that fall on a telehealth visit are completed. If labs are performed locally, results must be made available to the Qualified Investigator. The manner of the visit should be documented (site visit, video visit, etc.). Visits that require imaging and correlative blood collection must be performed at the enrolling centre.

5.2 Follow-up for Ineligible Participants

The follow-up requirements for ineligible participants who have received no protocol therapy include submission of the Baseline Report and End of Treatment Report plus and annual short follow-up form (Form 5S). Data submission for ineligible participants who have received at least one dose of protocol therapy should be followed according to the protocol to allow for treatment and adverse event assessment.

6.0 ENTRY/ENROLLMENT PROCEDURES

6.1 Entry Procedures

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 registering/enrolling participants will be provided at the time of study activation and will also be included in the "EDC Data Management Guidebook", posted on the PR.25 trial specific web-site. If sites experience difficulties accessing the system and/or registering/enrolling participants please contact the help desk (link in EDC) or the PR.25 Study Coordinator.

All eligible participants 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 at time of enrollment:

- trial code (CCTG PR.25)
- participant's initials (may be coded)
- informed consent version date(s), date(s) signed by participant, name of person conducting consent discussion and date(s) signed
- confirmation of the requirements listed in Section 4.0, including dates of essential tests and actual laboratory values
- BSA, height and weight
- Stratification factors

6.2 BSA Calculation

In calculating surface areas, actual heights and weights should be used, that is, there will be no downward adjustment to "ideal" weight. This principle applies to individuals whose calculated surface area is 2.2 m^2 or less. In those rare cases where a participant's surface area is greater than 2.2, the actual surface area or 2.2 may be used. CCTG BSA calculations are based on the Mosteller formula (the square root of the height in cm multiplied by the weight in kg divided by 3600).

6.3 Stratification

Subjects will be stratified by:

- BRCA2 status (qualifying BRCA2 alteration vs other qualifying alteration). Note that if co-occurring BRCA2 and non-BRCA2 alterations are present, the patients will be considered as BRCA2 for stratification purposes.
- Prior treatment with poly-ADP ribonuclease polymerase (PARP) inhibitor (yes or no)
- Prior treatment with docetaxel for metastatic castration sensitive prostate cancer (yes or no)

6.4 Randomization

Randomization will be provided electronically.

At the time of enrolment, all data reported within the Patient Enrolment folder must be accurate, complete and verifiable against source documentation. If a system query is issued indicating that the participant is not eligible, enrolment within the EDC system will not proceed. CCTG should be contacted for assistance if needed. Under no circumstances should inaccurate data be entered in order to permit enrolment.

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

All eligible participants admitted to the trial will be followed by the coordinating centre. It is the responsibility of the physician in charge to satisfy himself or herself that the participant is indeed eligible before requesting enrollment.

All enrolled participants 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 participants are outlined in Section 5.1.

7.0 TREATMENT PLAN

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

In accordance with CCTG policy, protocol treatment is to begin within 2 working days of participant enrollment.

7.1 Chemotherapy Treatment Plan

7.1.1 *Drug Administration*

Arm	Agent(s)	Dose	Route	Duration	Schedule
1	Docetaxel	75mg/m^2	IV	1 day	Q 21 days
2	Carboplatin	AUC 5	IV	1 day	Q 21 days
	Docetaxel	75mg/m^2	IV	1 day	

Arm 1: This standard of care protocol-specified therapy (docetaxel) may be administered by a local healthcare provider (HCP) with appropriate reporting of therapy administration data and adverse event information to the Qualified Investigator. All decisions on care within the clinical trial are made by the Qualified Investigator. The Qualified Investigator is still required to report any protocol deviations and unanticipated problems that occur per standard procedures.

Arm 2: This investigational treatment (docetaxel and carboplatin) must be administered at the enrolling centre.

The suggested starting doses of study therapy are docetaxel 75mg/m2 and carboplatin AUC5. However at the investigator's discretion, a reduced dose of 60mg/m2 and/or AUC4 may be selected as the initial dose, in situations where the full dose may not be tolerated, i.e. elderly patients, ECOG PS 2. Investigators will be asked to select the starting dose of therapy prior to patient randomization.

Please refer to the product monographs of docetaxel and carboplatin respectively for dosing and treatment administration guidelines.

Carboplatin intravenous dose calculation: The carboplatin dose is based on the AUC formula of Calvert; the GFR and carboplatin dose should be recalculated prior to each new treatment cycle if required by toxicity and GFR changes.

Dose (mg) = Target AUC (mg/mL per min) x [CrCl (mL/min) + 25]

The maximum dose is based on a capped GFR estimate at 125 mL/min for participants with normal renal function. No higher estimated GFR values should be used. Please refer to the Product Monograph for more information.

7.1.2 *Dose Modifications*

Dose modifications (slowing/interruption of infusion rate, omission of a dose, or permanent discontinuation) based on treatment related toxicity will be allowed for carboplatin and/or docetaxel. Investigators may choose to reduce dosage of one or both drugs at their discretion. If the infusion cannot be administered, it should be omitted until the next planned infusion. The next cycle should not be given until the laboratory criteria are met and resolution of all drug-related toxicity to ≤ grade 2. Discuss with CCTG if asymptomatic/not felt to be clinically significant.

If the start of the next treatment cycle is delayed by > 21 days due to an adverse event(s) that is deemed related to carboplatin, the treating investigator should contact CCTG for approval before restarting dosing.

7.1.3 *Dose Adjustments*

Doses will be reduced for hematologic and other adverse events. Dose adjustments are to be made according to the system showing the greatest degree of toxicity. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (see Appendix IV).

Carboplatin
The major toxic effects of carboplatin which are anticipated to limit dosing are: fatigue, allergic reactions, myelosuppression (including thrombocytopenia and bleeding and infection), nausea and vomiting, electrolyte changes, anorexia, constipation, diarrhea, dysgeusia, arterial and venous thromboembolism, decreased renal function, rash, hypertension, hepatotoxicity, increased uric acid, ototoxicity including tinnitus, peripheral neuropathy and visual changes. Rarely, acute leukemia/myelodysplastic syndromes and other secondary cancers, tumour lysis, veno-occlusive disease of liver hemolytic anemia, hemolytic uremic syndrome and encephalopathy have been reported.

Docetaxel
The major toxic effects of docetaxel which are anticipated to limit dosing are: hepatotoxicity, neutropenia, hypersensitivity reactions and fluid retention.

If a patient experiences several adverse events and there are conflicting recommendations, please use the recommended dose adjustment that requires the greatest dose hold or discontinuation. Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (see Appendix IV).

Once a dose reduction has occurred, dose re-escalation with subsequent treatment cycles is not permitted. Only 2 dose reductions are permitted.

Table 1: Dose reductions for Carboplatin & Docetaxel

Dose schedule	Carboplatin dose level	Docetaxel dose level
Starting dose	5 AUC*	75 mg/m^2
First dose reduction	4 AUC	60 mg/m^2
Second dose reduction	3 AUC	45 mg/m^2
Third dose reduction	Discontinue	Discontinue

*If a full dose may not be tolerated in the investigator's estimation, participants can commence on carboplatin AUC 4 and/or docetaxel 60 mg/m^2, and would fall to AUC 3 and/or 45 mg/m^2 respectively at the first dose reduction.

Centres may use their written local/provincial dose modification guidelines, or the guidelines provided below.

Table 2: Guidelines for Hematologic Toxicities – Docetaxel and Carboplatin

Toxicity/CBC (x10^9/l)	Dose modification
ANC <1.5 but greater than 0.5 for 5-7 days OR platelets <100 but ≥ 25	Hold* and consider dose reduction by 1 dose level (DL)
Febrile neutropenia or ANC <0.5 for 5-7 days OR platelets <25	Hold* and restart at below 1DL
Grade 3 related organ/non-hematologic	Hold* and restart at below 1DL
Grade 4 related organ/non-hematologic	Discontinue

*Participants should only re-start treatment with carboplatin and/or docetaxel once AE has recovered to grade 2 and below and platelets ≥100 x10^9/l and neutrophils ≥1.5 x10^9/l.

Table 3: Guidelines for Renal Toxicities – Carboplatin

Creatinine Clearance (ml/min)	Carboplatin (% of previous dose)
20-50	Use Calvert formula
<20	Discontinue

Table 4: Guidelines for Hepatic Toxicities – Docetaxel

Bilirubin	AST and/or ALT		Alkaline Phosphatase	Dose Modification
	1.5 x ULN	And	≤ 2.5 x ULN	Standard Dose
	1.6 - 5 x ULN	And	2.5 - 5 x ULN	Reduce by 1DL
	> 5 x ULN	And/Or	> 5 x ULN	Discontinue
> ULN				Discontinue

In this trial, reduction of both agents is recommended, but not required, in the setting of toxicity.

7.1.4 *Duration of Therapy*

Participants may remain on either arm of the study providing the investigator feels they are benefiting from treatment and there is no evidence of progression or intolerable toxicity.

7.1.5 *Toxicity Events Monitoring*

Toxic effects will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) (Appendix IV). Only grade 3, 4 and 5 toxic events related to study treatment will be reported.

7.2 Concomitant Therapy

7.2.1 *Permitted*

Standard of care supportive medications including those antiemetics, steroids, antihistamines and analgesics are permitted provided they are not contraindicated in the product monographs of docetaxel and carboplatin.

7.2.2 *Not Permitted*

- Concurrent radiation treatment; (Note: if patients require palliative radiation consult CCTG for exception to this rule; protocol therapy will need to be held prior to and during the radiation).
- Concomitant administration of carboplatin and aminoglycosides results in an increased risk of nephrotoxicity and/or ototoxicity, and the drugs should be used concurrently with caution.
- The use of other nephrotoxic drugs results in a potentiation of renal effects by carboplatin. Combination therapy with other myelosuppressive drugs may necessitate changes in the dose or frequency of administration of carboplatin in order to minimize additive myelosuppressive effects.
- A decrease in phenytoin serum levels has been observed with concurrent administration of carboplatin and phenytoin/fosphenytoin. This may lead to exacerbation of seizures.
- Live attenuated vaccines, during treatment and for 30 days post discontinuation of docetaxel and/or carboplatin. Inactivated vaccines, such as the injectable influenza vaccine and the COVID-19 vaccine, are permitted.

8.0 CRITERIA FOR MEASUREMENT OF STUDY ENDPOINTS

8.1 Definitions

8.1.1 *Evaluable for Response*

All participants who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response. Participants who exhibit objective disease progression prior to the end of cycle 1 will be considered evaluable. Participants on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below *[Eisenhauer 2009]*.

8.1.2 *Evaluable for PSA Response*

All participants who have at least two additional PSA values after baseline, which are measured at least 4 weeks apart, will be evaluable for PSA response *[Bubley 1999]*.

8.1.3 *Evaluable for Adverse Events*

All participants will be evaluable for adverse event evaluation from the time of their first treatment.

8.1.4 *Evaluable for Quality of Life Assessment*

All participants who have completed the quality of life questionnaires are evaluable for quality of life.

8.1.5 *Evaluable for Health Economics Assessment*

All enrolled participants are evaluable for health economics. Those who have completed the health utility questionnaire will be evaluable for cost-utility analyses.

8.2 Response and Evaluation Endpoints

Response and progression will be evaluated in this study using the revised international criteria (1.1) proposed by the RECIST (Response Evaluation Criteria in Solid Tumours) committee *[Eisenhauer 2009]* and the recommendations of the Prostate Cancer Clinical Trials Working Group *[Scher 2008, Scher 2016]*.

8.2.1 *Measurable Disease*

Measurable *tumour lesions* are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray and as ≥ 10 mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥ 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumour measurements must be recorded in millimetres (or decimal fractions of centimetres). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

8.2.2 *Non-measurable Disease*

All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

8.2.3 *Target Lesions*

When more than one measurable tumour lesion is present at baseline all lesions up to *a maximum of 5 lesions total* (and a maximum of *2 lesions per organ*) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. Note that pathological nodes must meet the criterion of a short axis of ≥ 15 mm by CT scan and only the *short* axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed (see 8.2.4). At baseline, the sum of the target lesions (longest diameter of tumour lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

8.2.4 *Non-target Lesions*

All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as “present” or “absent”.

8.2.5 *Response*

All participants will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of *target* and *non-target* lesions and normalization of tumour markers. Pathological lymph nodes must have short axis measures < 10 mm (Note: continue to record the measurement even if < 10mm and considered CR). Residual lesions (other than nodes < 10 mm) thought to be non-malignant should be further investigated (by cytology specialized imaging or other techniques as appropriate for individual cases [RECIST 1.1]) before CR can be accepted.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumour lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumour burden appears to have increased by at least 73% in volume or, in select instances where tumour burden has increased sufficiently to require urgent intervention (e.g. radiation for spinal cord compression or drainage of a fluid collection). Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Table 1: Integration of Target, non-Target and New Lesions into Response Assessment:

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category also Requires
Target lesions ± non target lesions				
CR	CR	No	CR	Normalization of tumour markers, tumour nodes < 10 mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	Documented at least once ≥ 4 wks. from start of treatment
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Non target lesions ONLY				
No Target	CR	No	CR	Normalization of tumour markers, tumour nodes < 10 mm
No Target	Non-CR/non-PD	No	Non-CR/non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes	PD	

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

For participants with non-measurable disease only, best overall response will be non-CR/non-PD unless not evaluable, PD at first assessment, or CR.

8.3 Response Duration and Stable Disease Duration (RECIST 1.1)

Objective response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline). Stable disease duration will be measured from the time of start of treatment until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

8.4 PCWG3 Criteria for PSA Response and Progression

(as defined by Scher 2016)

All participants will be evaluable for PSA response provided follow-up PSA values are obtained to allow application of the definitions below *[Bubley 1999]*.

Response: 50% fall in PSA from baseline maintained for ≥ 4 weeks, and without evidence of disease progression documented at time of confirmatory values.

Non Response: Failure to achieve PSA response criteria.

PSA response duration will be measured from the time the measurement criteria for response are first met until the PSA increases by at least 25% above the nadir OR ≥ baseline value AND an absolute increase of ≥ 2 μg/L.

8.4.1 *PSA Progression*

(as defined by Scher 2016)

In PSA non-responders: PSA progression is defined as the date that a 25% or greater increase and an absolute increase of 2 ng/mL (μg/L) or more from the nadir (or baseline if no decrease from baseline is documented), which is confirmed by a second value obtained 3 or more weeks later.

In PSA responders: rise in PSA of 25% (minimum 2 ng/ml (μg/L)) above nadir value and confirmed by a second increasing value obtained 3 or more weeks later.

Time to PSA progression will be calculated from date of enrollment to date of PSA progression. If interval PSA values are collected or reported during cycle, only the end of cycle PSA (PSA collected for Day 1) will be used in response evaluation.

NOTE: Because with systemic treatment an initial rise in PSA may be followed by a drop, it is recommended participants receive at least 12 weeks of therapy even if PSA is rising, provided no other evidence of symptomatic or objective progression is seen, palliative radiation is not required and protocol therapy is tolerable (see Section 10.0).

Participants in whom PSA progression is confirmed after 12 weeks on study should discontinue treatment unless discussed with CCTG; exceptions may be made for participants who are believed to have symptomatic improvement or stability providing there is no objective disease progression.

8.4.2 *Clinical Progression*

Clinical progression is defined as the need for palliative radiotherapy, change in anti-cancer therapy, or cancer related decrease in ECOG performance status to ≥ 3.

8.4.3 *Bone Disease Progression*

For the purpose of evaluation of bone disease in this study, a bone scan will be done at baseline and must be repeated every 9 weeks after enrollment (or more frequently to confirm PD) and at end of study, regardless if positive or negative at baseline.

Only bone lesions on a bone scan will be considered for PD status.

Suspected PD at the first post-baseline bone scan:

- PD is suspected if ≥ 2 new bone lesions are seen on the first post-baseline scan and confirmed if 2 additional new bone lesions are seen at a repeat scan ≥ 6 weeks later.
- After the first post-baseline scan, PD is suspected if ≥ 2 new bone lesions are seen and confirmed if the same lesions are seen on a subsequent scan.
- The date of progression is the date of the first post-baseline scan, when the first two new lesions were documented.

Additionally, if a new bone lesion(s) are seen on the participant's CT it will also need to be confirmed with a bone scan and will ONLY be considered PD if the criteria above are met.

8.5 Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

8.5.1 *Clinical Lesions*

Clinical lesions will only be considered measurable when they are superficial and ≥ 10mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

8.5.2 *Chest X-ray*

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥ 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

8.5.3 *CT, MRI*

CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). Other specialized imaging or other techniques may also be appropriate for individual case [RECIST 1.1]. For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast). If contrast cannot be used, a non-contrast chest CT scan in addition to an MRI of the abdomen and pelvis is acceptable.

8.5.4 *Bone Scan*

99mTc-methylene diphosphonate radionuclide bone scintigraphy is the standard for bone imaging

8.5.5 *Ultrasound*

Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

8.5.6 *Endoscopy, Laparoscopy*

The utilization of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

8.5.7 *Tumour Markers*

Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalize for a participant to be considered in complete response.

8.5.8 *Cytology, Histology*

These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumour has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

9.0 SAFETY ISSUES

9.1 Documentation of REB Submission of of Product Monograph (PM) Required For Local Activation

Written documentation must be obtained confirming that the Product Monograph (PM) for Carboplatin was forwarded to the REB. The PM must be retained and filed with the trial protocol at your centre.

The PMs for standard of care agents are accessible on the manufacturer's website and not required for REB submission.

9.2 Serious Adverse Event Reporting

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for Adverse Event (AE) reporting (version can be found in Appendix IV). All appropriate treatment areas should have access to a copy of the CTCAE. A copy of the CTCAE can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

All serious adverse events (SAE) defined as per ICH guidelines (see below) and other adverse events must be reported 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.

9.2.1 *Definition of a Reportable Serious Adverse Event*

- All serious adverse events which are unexpected and related to protocol treatment must be reported in an expedited manner (see Section 9.2 for reporting instructions). These include events occurring from the first protocol treatment administration until 30 days after last protocol treatment administration and at any time afterwards. Note: adverse events which occur prior to the start of protocol therapy must only be reported as serious adverse events if they are directly related to a study specific procedure.
- 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 participant or may require intervention to prevent one of the events listed above.

9.2.2 *Serious Adverse Event Reporting Instructions*

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 PR.25 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:

PR.25 Study Coordinator
Canadian Cancer Trials Group
Fax No.: 613-533-2941

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 PR.25 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).

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

9.2.3.1 *Pregnancy Prevention*

Participants of childbearing potential who are enrolled in the trial must have agreed to use contraceptive method(s) as described in Eligibility Criterion 4.1.11. Investigators may wish to additionally advise the partners of participants about pregnancy prevention guidelines when appropriate and compliant with local policy.

9.2.3.2 *Pregnancy Reporting*

The investigator is required to report to CCTG any pregnancy occurring in participants, and partners of participants. Pregnancies occurring up to 6 months after the completion of study treatment must also be reported.

The investigator should report the pregnancy within 24 hours of learning of the pregnancy using the CCTG Pregnancy Reporting Form available from the trial webpage, under the "Toolbox" link. The Pregnancy Reporting Form should be updated to provide the outcome of the pregnancy.

Information from the trial participant's pregnant partner can only be collected following informed consent. A copy of the signed signature page of the pregnancy follow-up consent must be submitted to CCTG. Centres that require additional informed consent for the pregnancy notification and/or outcome from a pregnant trial participant or about the pregnant partner must submit a copy of the signed signature page of the Pregnancy Follow-up consent to CCTG.

All follow-up reports must be submitted to CCTG in a timely manner. All documents must be sent to the CCTG safety desk (Fax: 613-533-2812/ Email: safety-desk@ctg.queensu.ca).

If the pregnancy results in death (e.g. spontaneous abortion, stillbirth); 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.

9.2.3.3 *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 within 24 hours of learning of the exposure using the CCTG Exposure Reporting Form available from the trial webpage, under the "Toolbox" link.

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 for 30 days. 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 (Fax: 613-533-2812 / Email: 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.

9.2.4 *CCTG Responsibility for Reporting Serious Adverse Events to Health Canada*

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 cannot be ruled out).

9.2.5 *Reporting Safety Reports to Investigators*

CCTG will notify Investigators of all Safety Reports including all serious adverse events that are unexpected and related (i.e. possibly, probably, or definitely) to protocol treatment (SUSARs) from this trial as well as Safety Updates (single reports or line listings) from other clinical trials as reported to the CCTG.

The reports will be posted to the CCTG trial PR.25 web-based safety monitoring utility, available on the CCTG trial webpage, under the "Toolbox" link. Relevant safety reports requiring REB submission that are not submitted at the time of initial REB approval should be submitted to the REB as soon as possible (suggest within 30 days of the date of local activation). REB submissions greater than 90 days from the date of local activation will be regarded as delinquent and a major deficiency will be assigned. Centres being activated later in the life of the study only need to submit the latest version of the PM and PN and safety reports as described above.

Investigators must notify their Research Ethics Boards (REBs) of events which involve corrective action(s) to be taken as a result of the Safety Report such as protocol and/or informed consent changes. Safety reports that are not mandated by CCTG to be submitted to the REB are marked as "NR" (not required) in the safety report monitoring utility. However, local policy may still require REB submission of this information.

The date of REB Submission for these SAEs and SUs will need to be entered into the CCTG trial PR.25 web-based safety monitoring utility and documentation of REB submission must be retained in the study binder on-site. The REB submission template provided by CCTG can be used to assist with tracking, submission, filing and monitoring.

10.0 PROTOCOL TREATMENT DISCONTINUATION AND THERAPY AFTER STOPPING

10.1 Criteria for Discontinuing Protocol Treatment

Participants 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.
- Unacceptable toxicity as defined in Section 7.0.
- Tumour progression or disease recurrence as defined in Section 8.0.
- Request by the participants.
- Efforts should be made to maintain the investigations schedule and continue follow-up, even if participants discontinue protocol treatment prematurely and/or no longer attend the participating institution.

10.2 Therapy After Protocol Treatment is Stopped

At the discretion of the investigator.

10.3 Follow-up Off Protocol Treatment

All participants will be seen 6 weeks after completion of protocol therapy.

Participants who go off protocol treatment prior to disease progression will maintain the same evaluation schedule as those who remain on treatment. Participants who go off protocol treatment due to disease progression will be followed every 12 weeks for survival purposes only (see Section 5.0 for investigations to be performed).

11.0 CENTRAL REVIEW PROCEDURES

11.1 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 uploading documents through the password protected and secure CCTG electronic Supporting Document Upload Tool (SDUT) data capture linked system. 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 removed and the site assigned a deviation and required to resubmit.

All participants 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.

11.2 Central Radiology Review

There will be no central radiology review for this study.

11.3 Central Pathology Review

There will be no central pathology review for this study.

12.0 CORRELATIVE STUDIES

A detailed Correlative Studies Manual will be provided on the PR.25 trial specific website, which will include details regarding sample preparation, handling and shipping.

Specimens collected may be used by researchers now or in the future to better understand the nature of prostate cancer and how participants respond to treatment. Samples will be used for research purposes only and will not be sold. Participants will not be identified by name. The only identification on any sample will be by a patient study number assigned at the time of enrollment to the trial the surgical/ histology number and/or participant initials. Material issued to researchers will be anonymized and only identified by a coded number.

Genetic Testing

In the course of genetic testing for this study, there is a chance that "material incidental findings" may occur; these refer to unanticipated discoveries made in the course of research but that are outside of the scope of the research being conducted and that are reasonably determined to have significant welfare implications for the potential participant/participant [TCPS2]. These findings could be inherited changes that might predispose a person to particular cancers or other diseases, and may be passed on in families.

As the genetic testing done for this study will be conducted in a research lab, the results may not be validated. In order to validate the results, the testing must be repeated in a certified laboratory.

During the informed consent process, participants will be told about the remote possibility of material incidental findings being discovered, and given the opportunity to make informed choices about whether they wish to receive this information.

If a material incidental finding is discovered during the testing for this study and a participant consented to learning about the results, the following process will be followed:

- Results of the testing will be provided to the study QI/SI at the enrolling institution by the CCTG study team when a potential material finding is identified in one of their study participants by the research laboratory. The QI/SI at the enrolling institution will be responsible for following local SOPs with regard to confirming the result, ensuring if genetic counseling is available, obtaining REB approval (if required) and contacting the study participant.

12.1 Protocol-Mandated Correlative Studies

Whole Blood Collection for ctDNA (Mandatory)

Participants must consent to the submission of whole blood specimens for cfDNA in order to participate on this trial.

Specimens will be collected at the following time points:

1. Baseline;
2. On day 1 of cycle 2, or 3 weeks after commencing treatment;
3. Progression

When received at the CCTG Tissue bank (in 10mL Streck cfDNA tubes), whole blood will be centrifuged to obtain plasma and buffy coat, and frozen until time of correlative analyses. At that point, the plasma and buffy coat fractions will be used for cfDNA and white blood cell DNA (germline DNA surrogate; WBC DNA) extractions and QC according to standard protocols. It is expected that deep cfDNA and WBC DNA targeted sequencing will be performed using custom hybrid-capture technology and Illumina machinery. A minimum of 25ng of DNA from each sample is typically required for library preparation. Library preparation will incorporate unique molecular identifiers to aid in downstream digital error suppression and PCR de-duplication. Bioinformatic estimation of ctDNA fraction (ctDNA%), and detection of germline and somatic mutations, copy number changes, and structural rearrangements will be carried out in accordance with published protocols and computational pipelines (current examples include Tolmeijer *[2023]* and Herberts [*2022*]).

We expect to evaluate the following correlative objectives:

- Leveraging existing clinical genomic data together with baseline ctDNA genotyping to more comprehensively assess individual patient DDR gene alteration status, associated genomic instability, co-occurring alterations, and the effect of these genomic variables on patient outcomes. This will include assessments of BRCA2 reversion mutations, and other potential mechanisms of primary resistance, in patients with prior PARP inhibitor exposure.
- The extent to which baseline ctDNA% and 3-week ctDNA% (i.e. ctDNA dynamics/kinetics) can inform on patient response to treatment.
- Potential mechanisms of acquired resistance by searching for changes in genomic profiles at progression (relative to baseline).
- Residual plasma from DNA extraction will banked for future biomarker analyses.

13.0 STATISTICAL CONSIDERATIONS

13.1 Objectives and Design

PR.25 is a multi-centre, open-label, randomized phase III trial comparing docetaxel to docetaxel and carboplatin in participants with metastatic castration resistant prostate cancer (mCRPC) with alterations in DNA Damage repair (DDR) genes. A minimization procedure *[White 1978]* will be used to randomize patients with equal probabilities to one of the two treatment groups with the following factors: Centre; BRCA2 status (BRCA2 alteration vs other qualifying alteration); Prior treatment with poly-ADP ribonuclease polymerase (PARP) inhibitor (yes or no); Prior treatment with docetaxel for metastatic castration sensitive prostate cancer (yes or no).

The primary objective is to compare overall survival (OS) in participants with mCRPC harboring DDR gene alterations who receive carboplatin in addition to docetaxel, compared to those receiving docetaxel alone.

Secondary Objectives include comparing radiographic progression-free survival (rPFS); Progression free survival (PSA and imaging based); Time to next systemic therapy; Objective soft tissue response; Safety and tolerability (CTCAE v5.0); Patient-reported Quality of Life (QoL) as quantified by FACT-P, FACT-T, and the FACT-BP questionnaires; and Economic Evaluation, including both healthcare utilization and health utilities, the latter measured using EQ-5D-5L between the two treatment arms.

13.2 Study Endpoints and Analysis

All efficacy analyses will be based on the intention to treat population. The **primary endpoint** is OS defined as the time from randomization to the date of death from any causes or censored at last known alive before or on the data cut-off point for each analysis. OS distribution by treatment arm will be estimated using the Kaplan-Meier product-limit method and compared using the log-rank tests stratified by stratification factors at randomization. The Cox regression model will be used to estimate the treatment effect and its appropriate C.I. adjusted for stratification factors at randomization.

Secondary endpoints are as follows:

1. The time-to-event outcome of rPFS, PFS and the Time to next systemic therapy will be analyzed using methods similar to those for OS analysis
2. PSA 50% response rate and objective soft tissue response rate; the Cochran–Mantel–Haenszel test stratified by stratification factors at randomization will be used to test the difference between treatment arms;
3. For safety analysis, all patients who received as least 1 dose of study treatment will be evaluated for toxicities using CTCAEv5 and compared using a Fisher's Exact Test.

Subgroup analyses will be performed according to stratification variables with the exception of participating centre.

Gender will be collated through a voluntary self-administered questionnaire at baseline. However, given that self-identified gender is impacted by androgen deprivation treatment, the reported reduced incidence of prostate cancer in patients who self-identify other than male, and that only .33% of the Canadian population over the age of 15 identify as transgender or non-binary according to the 2021 census, only exploratory analyses to determine whether QOL outcomes and OS are influenced by socio-economic determinants of health, including gender, will be possible. Any findings will be included in presentations and publications reporting trial results.

13.3 Sample Size and Duration of Study

A literature review was conducted to estimate outcome for patients in the control arm. The most applicable study based on germline or somatic DDR-a selection demonstrated a median OS of 17 months after docetaxel in the setting of prior ARPI therapy. Assuming a median OS of 17 months in the control group, with 39 months of recruitment and 24 months of follow up, a **sample size of 236 patients** with 173 events (i.e. deaths) will be required to detect a HR of 0.65, with a 2-sided alpha of 0.05 and power of 80% adjusted for an interim analysis. The HR of 0.65 has been chosen based on what would be anticipated to be a clinically meaningful result in a pre-treated mCRPC population.

13.4 Safety Monitoring

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

The CCTG Data Safety Monitoring Committee (DMSC) will review progress and safety data (including SAEs and fatal SAEs) bi-annually.

13.5 Interim Analysis

For the primary endpoint, one planned interim analysis will be performed when around 87 deaths are observed. Based on the Lan-DeMet's error spending function with O'Brien-Fleming type of boundaries, we will consider the treatment effect significant if a 2-sided p-value of 0.005 or less is observed. The results will be submitted to CCTG's independent Data Safety Monitoring Committee (DSMC) for review who will advise on trial continuation according to the statistical stopping guideline. The significance level of 0.048 will be used for final analysis.

The trial's safety data will be reviewed by the DSMC every 6 months and will provide a brief report to the CCTG Director. If any serious safety issues are observed, recommended actions will be taken to address them. Ultimately, if serious safety issues cannot be addressed, the trial may be stopped.

13.6 Quality of Life Analysis

Health related quality of life (HRQL) is a secondary outcome in this phase 3 multicentre randomized trial. HRQL will be reported by participants using the Functional Assessment of Cancer Therapy – Prostate (FACT-P), the Functional Assessment of Cancer Therapy – Taxane (FACT-T), and the Functional Assessment of Cancer Therapy – Bone Pain (FACT-BP) quality of life questionnaires as per the detailed rationale above.

In this current proposed trial, carboplatin will be administered along with docetaxel once every 3 weeks (Treatment Arm) compared to docetaxel (Control Arm). Quality of Life will be assessed at baseline (Pre-study prior to randomization), every 6 weeks and at the end of treatment using the FACT-P, FACT-T, and FACT-BP questionnaires. This schedule will balance the need to adequately capture the impact of each treatment arm over time on participants over time without being excessively burdensome.

There are three key objectives to address with QOL endpoints:

1. The first concerns the extent to which the addition of carboplatin to docetaxel impacts men's QOL during treatment. The null hypothesis is that addition of carboplatin to docetaxel will have no negative impact on QOL compared to docetaxel.
2. The second objective addresses whether any gains in disease control afforded by carboplatin (as per the primary study endpoint) also impacts positively on QOL (particularly patient pain scores).
3. The third objective is whether the two arms differ in patient reported neurotoxicity and peripheral neuropathy especially since this side effect of taxane-based chemotherapy is well documented and may not only affect QOL but may also result in dose reduction or cessation of therapy altogether.

The changes from baseline for HRQoL endpoints scores will be analyzed using the repeated measures ANOVA, and linear mixed models will be used to estimate the difference between treatment arms adjusted for stratification factors at randomization. The change scores on all patient-reported measures at each time point will also be described including means, standard deviation, medians, and inter quartiles. Compliance (received vs expected forms) will be described. If missing data exceeds 10% of expected measures, sensitivity analyses will be conducted, and linear mixed models will be used to minimize the bias resulting from missing data. To determine clinical significance of any observed TOI differences between arms, a 7-point change will be considered clinically meaningful (representing a moderate effect size of 0.5 Std Deviation *[Cella 2009]*. To determine the effect of adding carboplatin to docetaxel on patient reported pain symptoms, the FACT-BP will be analyzed as per the published scoring manual (range of possible scores 0-60, higher scores indicate better HRQOL *[Broom 2009; Popovic 2012]*). To evaluate the clinical significance of any observed difference between arms, a 3-point difference will be considered clinically meaningful (representing a moderate effect size of 0.5 Standard Deviation, and a sensitivity analysis using a 6-point change will also be conducted, as recommended by FACIT *[Cella 2003]*. To assess the treatment related toxicity associated with each arm of the trial, especially peripheral neuropathy, the mean scores from the 16-item taxane subscale of the FACT-T instrument will be calculated. Higher scores indicate better QOL. A clinically meaningful difference in FACT-T will be a change of ≥ 1 standard error measurement *[Cella 2003]*.

13.7 Health Economics Analysis

Because determining health care value is critical to the adoption of new technologies and procedures in the health system and society, economic evaluation is embedded within the trial framework. Value is calculated by determining the incremental costs and benefits (life years, quality adjusted life years) across the two treatment arms from two perspectives, a health system and a societal perspective.

For the cost portion of the value assessment, we will determine both the health system and societal resources utilized by subjects in the trial. Health system resources will be identified as, but not limited to, clinic visits, treatments (radiation, surgery, medication), physician encounters, hospitalizations related to treatment and complications, emergent visits and diagnostics. The health system resources will be based on the trial protocol and data collected during the trial itself. Societal resources will be identified as, but not limited to, lost productivity related to treatment (e.g. time off work, change in status), and any significant out-of-pocket subject expenses (e.g. medications, travel, parking). Societal resources will be based on participant specific data collected alongside the quality of life portion of the study. Health system and societal resources will be quantified over the course of the trial to generate utilization information by participant in each study arm. Once quantified, the resources will be valued using health system unit costs (e.g. formularies, public sources) and societal unit costs (e.g. income). We will generate an average cost per study subject by treatment arm for an overall mean cost per study arm.

For the benefit portion of the value assessment, if the efficacy results are different between the two treatment arms, we will conduct a cost effectiveness analysis, evaluating both incremental costs and clinical outcomes (e.g. survival). If there is no significant clinical benefit, we anticipate that there will be differences in quality of life between the two treatment arms and will conduct a cost-utility analysis. As such, we will determine the health preference of study subjects to calculate a quality adjusted life year (QALY) by marrying the health preference value and the time frame in which one experiences that health state. Health preference will be measured with the EQ-5D-5L. The EQ-5D-5L is a well-used and standardized measure of health status for economic analyses (https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf). The EQ-5D-5L will be collected alongside the study QOL instrument.

Sensitivity analyses, variation in benefit, resources and costs, will be conducted to test the robustness of the incremental ratios calculated.

14.0 PUBLICATION POLICY

14.1 Authorship of Papers, Meeting Abstracts, Etc.

14.1.1 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 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 participants 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.
- In the event of a separate paper dealing with the economic outcomes, the first author will generally be the Committee on Economic Analysis liaison on the trial committee.

14.1.2 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 participants and their institutions)."

14.2 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.

14.3 Submission of Material for Presentation or Publication

Material may not be submitted for presentation or publication without prior review by the CCTG Senior Investigator, Senior Biostatistician, Study Coordinator, and approval of the Study Chair. Individual participating centres may not present outcome results from their own centres separately. Supporting groups and agencies will be acknowledged.

15.0 ETHICAL, REGULATORY AND ADMINISTRATIVE ISSUES

15.1 Regulatory Considerations

All institutions in Canada must conduct this trial in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) Guidelines.

This trial is being conducted under a Clinical Trial Application (CTA) with Health Canada. As a result, the conduct of this trial must comply with Division 5 of the Canadian Regulations Respecting Food and Drugs (Food and Drugs Act).

15.2 Inclusivity in Research

CCTG does not exclude individuals from participation in clinical trials on the basis of attributes such as culture, language, linguistic proficiency, age, religion, race, national or ethnic origin, Indigenous identity, colour, disability (except incapacity), sexual orientation, sex, gender identity, occupation, ethnicity, income, or criminal record, unless there is a valid reason (i.e. safety) for the exclusion.

In accordance with the Declaration of Helsinki and the Tri-Council Policy Statement (TCPS), it is the policy of CCTG that vulnerable persons or groups will not be automatically excluded from a clinical trial (except for incompetent persons) if participation in the trial may benefit the participant or a group to which the person belongs.

However, extra protections may be necessary for vulnerable persons or groups. It is the responsibility of the local investigator and research ethics board (REB) to ensure that appropriate mechanisms are in place to protect vulnerable persons/groups. In accordance with TCPS, researchers and REBs should provide special protections for those who are vulnerable to abuse, exploitation or discrimination. As vulnerable populations may be susceptible to coercion or undue influence, it is especially important that informed consent be obtained appropriately.

Centres are expected to ensure compliance with local REB or institutional policy regarding participation of vulnerable persons/groups. For example, if a vulnerable person/group would be eligible for participation in a CCTG clinical trial under this policy but excluded by local policy, it is expected that they would not be enrolled in the trial. It is the centre's responsibility to ensure compliance with all local SOPs.

It is CCTG's policy that persons who cannot give informed consent (i.e. mentally incompetent persons, or those physically incapacitated such as comatose persons) are not to be recruited into CCTG studies. It is the responsibility of the local investigator to determine the subject's competency, in accordance with applicable local policies and in conjunction with the local REB (if applicable).

Subjects who were competent at the time of enrollment in the clinical trial but become incompetent during their participation do not automatically have to be removed from the study. When re-consent of the participant is required, investigators must follow applicable local policies when determining if it is acceptable for a substitute decision maker to be used. CCTG will accept re-consent from a substitute decision maker. If this participant subsequently regains capacity, the participant should be re-consented as a condition of continuing participation.

15.3 Obtaining Informed Consent

It is expected that consent will be appropriately obtained for each participant/potential participant in a CCTG trial, in accordance with ICH-GCP Section 4.8. The centre is responsible for ensuring that all local policies are followed.

Additionally, in accordance with GCP 4.8.2, CCTG may require that participants/potential participants be informed of any new information may impact a participant's/potential participant's willingness to participate in the study.

Based upon applicable guidelines and regulations (Declaration of Helsinki, ICH-GCP), a participating investigator (as defined on the participants list) is ultimately responsible, in terms of liability and compliance, for ensuring informed consent has been appropriately obtained. CCTG recognizes that in many centres other personnel (as designated on the participants list) also play an important role in this process. In accordance with GCP 4.8.5, it is acceptable for the Qualified Investigator to delegate the responsibility for conducting the consent discussion.

CCTG requires that each participant sign a consent form prior to their enrollment in the study to document his/her willingness to take part. CCTG may also require, as indicated above, that participants/potential participants be informed of new information if it becomes available during the study. In conjunction with GCP 4.8.2, the communication of this information must be documented.

CCTG allows the use of translators in obtaining informed consent. Provision of translators is the responsibility of the local centre. Centres should follow applicable local policies when procuring or using a translator for the purpose of obtaining informed consent to participate in a clinical trial.

In accordance with ICH-GCP 4.8.9, if a participant is unable to read then informed consent may be obtained by having the consent form read and explained to the participant.

15.3.1 *Obtaining Consent for Pregnancy Reporting*

Information from the pregnant person should not be collected 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 from them. If the main consent form adequately addresses the pregnancy notification and 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. CCTG also considers the main consent form signed by the trial participant adequate consent for notification and collection of the outcome of a pregnancy of a trial participant's pregnant partner. Any information collected from the trial participant's pregnant partner can only be collected following their informed consent. Local REB policy should be followed to ensure appropriate consent is obtained.

A trial-specific consent form for Pregnancy Follow-up can be found on the trial webpage. The consent form must be used to obtain consent from any non-trial participant such as the pregnant partner.

Participants will not be withdrawn from the main trial for refusing or withdrawing permission to provide information related to the pregnancy. Similarly, trial participants will not be withdrawn from the main study should their partner refuse or withdraw permission.

15.3.2 *Obtaining Consent for Exposure Reporting*

Information from and/or about the subject (i.e. the exposed individual) should not be collected from and/or about 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 and/or from them.

A trial-specific consent form for Exposure Follow-up can be found on the trial webpage. The consent form must be used to obtain consent from any non-trial participant (such as the exposed individual).

Participants will not be withdrawn from the main trial for a refusal or withdrawal of permission from a non-trial participant to provide information related to the exposure.

15.3.3 *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/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.

15.4 Discontinuation of the Trial

If this trial is discontinued for any reason by the CCTG all centres will be notified in writing of the discontinuance and the reason(s) why. If the reason(s) for discontinuance involve any potential risks to the health of participants participating on the trial or other persons, the CCTG will provide this information to centres as well.

If this trial is discontinued at any time by the centre (prior to closure of the trial by the CCTG), it is the responsibility of the qualified investigator to notify the CCTG of the discontinuation and the reason(s) why.

Whether the trial is discontinued by the CCTG or locally by the centre, it is the responsibility of the qualified investigator to notify the local Research Ethics Board and all clinical trials subjects of the discontinuance and any potential risks to the subjects or other persons.

15.5 Retention of Participant Records and Study Files

All essential documents must be maintained as per C.05.012 and in accordance with ICH-GCP.

The Qualified Investigator must ensure compliance with the Regulations and the GCP Guideline from every person involved in the conduct of the clinical trial at the site.

Essential documents must be retained for 15 years following the completion of the trial at the centre (15 years post final analysis, last data collected, or closure notification to REB, whichever is later), or until notified by CCTG that documents no longer need to be retained.

In accordance with GCP 4.9.7, upon request by the monitor, auditor, REB or regulatory authority, the investigator/institution must make all required trial-related records available for direct access.

CCTG will inform the investigator/institution as to when the essential documents no longer need to be retained.

15.6 Centre Performance Monitoring

This study is eligible for inclusion in the Centre Performance Index (CPI).

Forms are to be submitted according to the schedule in the protocol. There are minimum standards for performance.

15.7 On-Site Monitoring/Auditing

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

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.

As this trial is conducted under a CTA with Health Canada, your site may be subject to an inspection by the Health Canada Inspectorate.

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APPENDIX I - 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 II - DRUG DISTRIBUTION, SUPPLY AND CONTROL

Carboplatin and docetaxel are commercially available, obtained from the Canadian market, and will not be supplied for this study.

APPENDIX III - DOCUMENTATION FOR STUDY

Follow-up is required for participants from the time of enrollment.

This trial will use a web-based Electronic Data Capture (EDC) system for all data collection except Quality of Life and Health Utility questionnaires. This data will be entered by the participant directly into electronic devices (desktop computer, tablet, other mobile device) through the CCTG **S**ystem for **P**atient **R**eported **Out**comes (SPROUT). Please refer to the Electronic Patient Reported Outcome User Guide, posted on the PR.25 webpage area of the CCTG website (www.ctg.queenu.ca)

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 PR.25 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 uploaded immediately after the report they refer to has been submitted electronically	Submission On Request To be uploaded immediately after request
Eligibility Checklist	Prior to randomization	At the time of randomization	Consent form** Diagnostic pathology & tumour measurement sheet (TMS) Genetic testing reports	Additional clinical, laboratory or imaging reports that may impact on decision regarding eligibility
Baseline Report	At the time of randomization	Within 2 weeks of randomization		
Correlative Studies Report (Blood)	Continuous running-log folder			
Treatment Report	Each cycle (q21d) while participant is receiving treatment	Within 2 weeks of each visit	Radiology reports for protocol-mandated imaging (CT and bone scans) and non-protocol mandated imaging if relevant to disease assessment, TMS	Additional clinical, laboratory or imaging reports that may inform evaluation of safety
End of Treatment Report	When the participant stops protocol treatment permanently	Within 2 weeks of the end of treatment		
6-week Follow-up Report	6 weeks after the participant's final protocol treatment	Within 2 weeks of the 6-week post-treatment visit	Radiology reports for protocol-mandated imaging (CT and bone scans) and non-protocol mandated imaging if relevant to disease assessment, TMS	Additional clinical, laboratory or imaging reports that may inform evaluation of safety
Relapse/Progression Report	Upon objective disease progression	Within 4 weeks of disease progression	Relevant radiology, operative, and pathology reports	

table continues on following page…

Electronic Folder	Required at	To be completed electronically	Supporting Documentation *	
			Mandatory Submission To be uploaded immediately after the report they refer to has been submitted electronically	Submission On Request To be uploaded immediately after request
Follow-up Report	Every 3 weeks after the 6-week post-treatment visit, <u>until</u> PD	Within 2 weeks of each follow-up visit	Radiology reports for protocol-mandated imaging (CT and bone scans) and non-protocol mandated imaging if relevant to disease assessment, TMS	Additional clinical, laboratory or imaging reports that may inform evaluation of safety
Short Follow-up Report	Every 12 weeks after the 6-week post-treatment visit <u>after</u> PD	Within 2 weeks of each follow-up contact		
Death Report	When participant dies	Within 4 weeks of knowledge of participant's death	Autopsy report if performed	
SAE Report***	At the time of the event	Within 24 hours		Additional clinical, laboratory or imaging reports that may inform evaluation of safety including, admission and discharge summaries/notes

* Scan and upload in the EDC Supporting Document Upload Tool (SDUT) - please refer to the slide set on the PR.25 website for guidance. Source documents other than those listed above may be requested to confirm eligibility, compliance, endpoints, and/or serious adverse events. Supporting documents should be uploaded <u>immediately</u> 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 participant 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:

- **<u>fully opaque</u>** sticker/tab placed over the identifiers prior to scanning
- **<u>fully opaque</u>** black marker; prior to upload 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 and then scanned. (*NOTE:* do <u>not</u> send the unprotected PDF file with black boxes included as those can be moved / removed easily after opening)
- electronic stripping of identifiers prior to upload (typically only possible for DICOM images)

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).

** Required 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/signature on the submitted copy, either partially (leaving only a portion to confirm that a person has signed but that cannot identify that individual) or fully, depending on local policy.

*** See Section 9.0 Serious Adverse Event Reporting for details.

The collection of the following information will ***NOT*** be done through the EDC system. Instead submit as follows:

Data	Required at	Collection /Submission
FACT-P, FACT-Taxane, and FACT-BP Questionnaires	• Baseline • Day 1 of cycle 3 and every odd-numbered cycle onward while on protocol treatment • Every 6 weeks after end of treatment, but before PD • At 6-week post-treatment visit • At PD	Participant to do direct electronic data entry and submission (desktop computer, tablet, other mobile device)*
Social Determinants of Health	• Baseline	Participant to do direct electronic data entry and submission (desktop computer, tablet, other mobile device)*
Health Utility Questionnaire	• Baseline • Day 1 of cycle 3 and every odd-numbered cycle onward while on protocol treatment • Every 6 weeks after end of treatment, but before PD • At 6-week post-treatment visit • At PD	Participant to do direct electronic data entry and submission (desktop computer, tablet, other mobile device)*
See Appendix V. Please also refer to the Electronic Patient Reported Outcome User Guide, posted on the PR.25 webpage area of the CCTG website (www.ctg.queenu.ca). Paper versions of the questionnaires are also available in the PR.25 trial website to be used as a back-up in rare cases, if electronic questionnaire completion by the participant is not possible (e.g. network down) or if the participant declines use of electronic means of completion. If the participant completes the questionnaire on paper, the site clinical trials personnel should then enter the information into the SPROUT system (for details see the User Guide).		

APPENDIX IV - NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for Adverse Event (AE) reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm .

APPENDIX V - QUALITY OF LIFE (AND HEALTH UTILITY) ASSESSMENT(S)

Introduction

The assumption that control of symptoms will automatically improve quality of life is probably true but hasn't yet been tested, especially in determining how certain symptoms may or may not affect quality of life. Current literature reveals interesting things; two in particular are:

- additional and useful information may be obtained from quality of life (and health utility) measurements
- a growing consensus that the goal of medical care today for most participants 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 and health utility data can be used in a variety of ways:

- to try to achieve the best possible outcome for participants
- 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 Quality of Life, Health Utility, and Social Determinants of Health Questionnaires

The instructions below are intended as a guide for the administration of the electronic Quality of Life, Health Utility, and Social Determinants of Health questionnaires.

This study will use the CCTG electronic **S**ystem for **P**atient **R**eported **Out**comes (SPROUT) to collect questionnaire data. SPROUT is a web-based, password protected, PIN-restricted system, which facilitates completion of the questionnaires by the participants electronically, through the use of desktop computers, tablets or other mobile devices. Sessions expire automatically after one hour, if a user remains logged in and the electronic device is left untouched. Hospital staff (CRAs) and participants are given access to different screens within SPROUT, and the CRA is automatically logged out of their (set-up) screens before the participant can access their (questionnaire completion) ones. The data entered electronically by the participant is not stored within the device, but rather gets imported in real-time directly into the CCTG database, using SSL encryption. Stored data is protected by the CCTG network firewall.

Detailed technical and logistical information regarding access and login into the SPROUT system, as well as data entry by participants and site staff is provided in a separate Electronic Patient Reported Outcome User Guide document, posted on the trial webpage. The User Guide also provides screen-shots for screens viewed by the participant and the site CRA within the SPROUT system.

1. Preamble

   Quality of life, health utility, and social determinants of health data are collected for research purposes, and will usually not be used for the participant's individual medical care. The assessment is in the form of a self-report questionnaire. Therefore, it must be completed by the participant 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-enrollment (baseline)
   - during treatment
   - during follow-up

   The information provided by the participant 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 participant.

   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. Pre-treatment Assessment

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

   The CRA should collect the clinic electronic device as soon as it has been completed.

3. Assessments During Treatment

   The quality of life and health utility questionnaires should be given to the participant before being seen by the doctor, and prior to treatment, as required by the schedule in the protocol (up to 3 days prior to treatment is acceptable). If the participant does not have a doctor visit scheduled, or if it was not possible for the participant to complete the questionnaire before being seen by the doctor, s/he should still complete the questionnaire prior to treatment.

4. Assessments During Follow-up

   The quality of life and health utility questionnaires should be given to the participant before being seen by the doctor, on follow-up visits as required by the schedule.

A participant 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 participant feels better!

5. What If . . .

The participant should complete the electronic questionnaires at the clinic.

However, there may be circumstances when the participant 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 and health utility data can still be collected.

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

Contact the participant by phone informing him or her that the questionnaire was not completed. Ask the participant if s/he is willing to complete one:

i) If yes, and the participant is able / willing to come back to the clinic, schedule an appointment as soon as possible after the "missed" visit when s/he can complete the questionnaire in an electronic device kept at the clinic.

ii) If yes but coming back into the clinic is not feasible, then ask the participant if s/he has internet / mobile access at home:

a. If yes, proceed to provide the participant with the link to the SPROUT system and the specific PIN number associated with the questionnaire they need to complete. Please also explain that the PIN has an expiration date (provide this date to the participant) and that the questionnaire should be completed before that date.

b. If not, and using the mail is possible, mail a blank paper questionnaire to the participant, 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. Enter the participant's responses into the SPROUT system once received back.

c. If not, and using the mail is not feasible, then ask the participant if s/he is willing to complete a questionnaire over the phone. If the participant agrees, read out the questions and range of possibilities, and record the answers in SROUT through an electronic device kept in the hospital. Make a note that the questionnaire was completed over the phone.

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

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

Inquire if the participant has internet / mobile access during their vacation. If yes, please provide the participant with the website link to the SPROUT system, the PIN number(s) associated with the questionnaire(s) that need to be completed and written instructions with respect to the date the participant should complete the questionnaire(s). If the participant will not have internet / mobile access during their vacation, ensure that the participant has a supply of paper questionnaires, with instructions about when to complete them, and how to return them. If it is known beforehand, give the participant blank questionnaires at the last clinic visit; if the extended absence is not known in advance, mail the blank paper questionnaires to the participant. Written instructions may help ensure that the participant stays on schedule as much as possible.

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

Should the participant not wish to answer the questionnaire in the clinic but insists on taking it home, and failing to comply with the participant's wishes is likely to result in the questionnaire not being completed at all, then the participant may take the questionnaire home with instructions that it is to be completed the same day. Ask if s/he has internet / mobile access at home.

i) If yes, proceed to provide the participant with the link to the SPROUT system and the specific PIN number associated with the questionnaire they need to complete. Please explain that the questionnaire should be completed on the same day.

ii) If not, give the participant a blank paper questionnaire, and make arrangements for return of the questionnaire in a timely fashion. 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 participant took it away from the clinic before completion. Enter the participant's responses into the SPROUT system once received back.

6. Waiving the Quality of Life and Health Utility Components

The only time that we will not require a participant to complete the quality of life (and/or health utility) questionnaires is if s/he cannot comprehend 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 the questionnaire/SPROUT system.

7. Unwillingness to Complete Quality of Life and Health Utility Questionnaires

If a participant 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 s/he is NOT eligible and should NOT be put on study.

8. Inability to Complete Quality of Life and Health Utility Questionnaires (for reason other than illiteracy in English or French)

An eligible participant may be willing but physically unable to complete the questionnaires, because of blindness, paralysis, etc. If the participant is completing the QOL and health utility assessments 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 participant 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 participant 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 participant. Whichever method is used, it should be recorded on the questionnaire.

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

9. Electronic and Paper Versions of the Quality of Life, Health Utility, and Social Determinants of Health Questionnaires

Participants should complete the FACT-P, FACT-Taxane, FACT-BP, EQ-5D-5L, and Social Determinants of Health questionnaires within the SPROUT system. See the Electronic Patient Reported Outcome User Guide, posted on the trial webpage, which provides both the URL for accessing SPROUT, as well as step-by-step instructions for the completion of the electronic questionnaire. However, as it is possible that access through an electronic device may not be possible (e.g. system down), or that the participant may decline electronic means of completion, under these rare circumstances the participant may complete the questionnaire on paper. *If needed*, please obtain the properly formatted paper copy of the FACT-P, FACT-Taxane, FACT-BP, EQ-5D-5L, and Social Determinants of Health Questionnaire for this study from the trial webpage and, after the participant completes it, please enter the responses into the SPROUT system.

In the pages that follow, the FACT-P, FACT-Taxane, FACT-BP, EQ-5D-5L, and Social Determinants of Health questionnaires that will be used in this study have been provided in its paper version. The question content of the electronic and paper versions is identical.

Quality of Life Questionnaire – ENGLISH

CCTG Trial: **PR.25**

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 enrollment

During chemotherapy:

☐ Day 1 Cycle 3 ☐ Day 1 Cycle 5 ☐ Day 1 Cycle 7 ☐ Day 1 Cycle 9 ☐ Day 1 Cycle ___

Off Treatment - prior to progression:

☐ End of Treatment Visit ☐ Every 6 weeks after End of Treatment Visit

Disease progression during treatment or after end of treatment:

☐ Progression

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 PARTICIPANT FOR QUESTIONNAIRE COMPLETION.

CCTG use only

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

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

FACT-P (Version 4)
FACT-Taxane (Version 4)
FACT-BP (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please go on to next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

Please go on to next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C2	I am losing weight	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
P1	I have aches and pains that bother me	0	1	2	3	4
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
P3	My pain keeps me from doing things I want to do	0	1	2	3	4
P4	I am satisfied with my present comfort level	0	1	2	3	4
P5	I am able to feel like a man	0	1	2	3	4
P6	I have trouble moving my bowels	0	1	2	3	4
P7	I have difficulty urinating	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
P8	My problems with urinating limit my activities	0	1	2	3	4
BL5	I am able to have and maintain an erection	0	1	2	3	4
NTX 1	I have numbness or tingling in my hands	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet	0	1	2	3	4
NTX 3	I feel discomfort in my hands	0	1	2	3	4
NTX 4	I feel discomfort in my feet	0	1	2	3	4
NTX 5	I have joint pain or muscle cramps	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
NTX 6	I have trouble hearing	0	1	2	3	4
NTX 7	I get a ringing or buzzing in my ears	0	1	2	3	4
NTX 8	I have trouble buttoning buttons	0	1	2	3	4

Please go on to next page

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

NTX 9	I have trouble feeling the shape of small objects when they are in my hand	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4
Tax1	I feel bloated	0	1	2	3	4
Tax2	My hands are swollen	0	1	2	3	4
Tax3	My legs or feet are swollen	0	1	2	3	4
Tax4	I have pain in my fingertips	0	1	2	3	4
Tax5	I am bothered by the way my hands or nails look	0	1	2	3	4
BP1	I have bone pain	0	1	2	3	4
BP2	It hurts when I put weight or pressure on the place where I have bone pain	0	1	2	3	4
BP3	I have bone pain even when I sit or lie still	0	1	2	3	4
BP4	I need help doing my usual activities because of bone pain	0	1	2	3	4
BP5	I am forced to rest during the day because of bone pain	0	1	2	3	4
BP6	I have trouble walking because of bone pain	0	1	2	3	4
BP7	Bone pain interferes with my ability to care for myself (bathing, dressing, eating, etc.)	0	1	2	3	4
BP8	Bone pain interferes with my social activities	0	1	2	3	4
BP9	Bone pain wakes me up at night	0	1	2	3	4
BP 10	I am frustrated by my bone pain	0	1	2	3	4
BP 11	I feel depressed about my bone pain	0	1	2	3	4
BP 12	I worry that my bone pain will get worse	0	1	2	3	4
BP 13	My family has trouble understanding when my bone pain interferes with my activity	0	1	2	3	4
Q7	In how many places in your body have you felt bone pain?	0	1	2	3	4+

Health Utilities Questionnaire – ENGLISH

CCTG Trial: **PR.25**

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 enrollment

During chemotherapy:

☐ Day 1 Cycle 3 ☐ Day 1 Cycle 5 ☐ Day 1 Cycle 7 ☐ Day 1 Cycle 9 ☐ Day 1 Cycle ___

Off Treatment - prior to progression:

☐ End of Treatment Visit ☐ Every 6 weeks after End of Treatment Visit

Disease progression during treatment or after end of treatment:

☐ Progression

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 PARTICIPANT FOR QUESTIONNAIRE COMPLETION.

CCTG use only

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

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

EQ-5D-5L Questionnaire

CCTG : PR.25

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

We would like to know how good or bad your health is TODAY.

This scale is numbered from 0 to 100.

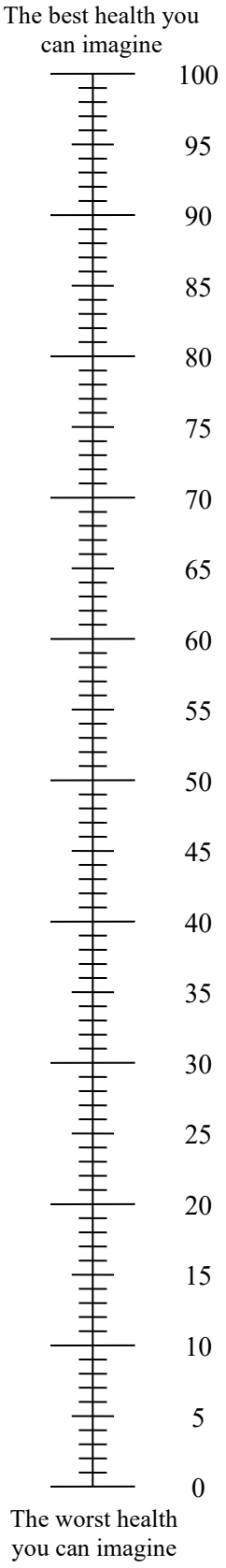
100 means the best health you can imagine.

0 means the worst health you can imagine.

Mark an X on the scale to indicate how your health is TODAY.

Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Please check to make sure you have answered all questions.

Thank you.

Social Determinants of Health – ENGLISH

CCTG Trial: **PR.25**

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 enrollment

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 PARTICIPANT FOR QUESTIONNAIRE COMPLETION.

CCTG use only

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

This box to be completed by the clinical research associate: Pt. Serial #: _____ Pt. Initials: ____ ____ ____

Background: As part of this clinical trial, researchers are interested in learning more about trial participants, such as yourself. This questionnaire will ask you about the conditions and places in which you live, learn, work, and play. This information will help us better understand who participates in clinical trials, so that we can identify potential inequities in access to these trials and better learn how non-medical factors may impact health outcomes. We plan on using the data collected to design new approaches that will make clinical trials more effective, inclusive, accessible and equitable for all.

Importantly, this questionnaire is entirely voluntary. Your decision to complete (or not complete) this questionnaire will not impact your participation on this clinical study or your overall care. If you choose to participate, this questionnaire should take about 5 minutes to complete.

Instructions: Please answer all the questions by indicating the response that best applies to you. We tried to provide a wide range of response options so you can accurately describe yourself. If you do not feel that you are accurately reflected in the response options provided, please select "Other" and enter your response. You do not have to answer any questions that make you feel uncomfortable. Your responses to these questions will not impact your participation on this clinical study or your overall care.

1. If available, would you prefer your healthcare appointments offered in another language?
(Check one only.)

□ Yes
□ No
□ Do not know
□ Prefer not to answer

1a. If yes, which language?
(Check one only.)

□ American Sign Language	□ Arabic	□ Bengali
□ Dari	□ English	□ French
□ German	□ Greek	□ Gujarati
□ Haitian Creole	□ Hindi	□ Indigenous languages
□ Inuktitut	□ Iranian Persian	□ Italian
□ Korean	□ Portuguese	□ Mandarin
□ Malayalam	□ Polish	□ Russian
□ Punjabi	□ Romanian	□ Spanish
□ Serbian	□ Serbo-Croatian	□ Tagalog
□ Tamil	□ Turkish	□ Ukrainian
□ Urdu	□ Vietnamese	□ Yue (Cantonese)
□ Other (Please specify) _____	□ Do not know/Unsure	□ Prefer not to answer

2. Were you born in Canada?

□ Yes
□ No
□ Do not know
□ Prefer not to answer

2a. If no, when did you arrive?

□ Less than 5 years ago
□ 5 to 9 years ago
□ 10 years ago or more

3. Do you currently experience any of the following due to a severe and persistent physical or mental condition? (*Check all that apply.)*

□ Difficulty seeing (e.g. severe vision impairment)
□ Difficulty hearing (e.g. severe hearing loss)
□ Difficulty with walking or climbing (e.g. severe mobility issues)
□ Difficulty remembering or with concentration (e.g. severe memory loss or disorientation)
□ Difficulty with personal hygiene (e.g. physically unable or lack motivation to shower)
□ Difficulty with activities for daily living (e.g. physically unable or lack motivation to: e.g. eat, get out of bed, work)
□ Difficulty with communicating (e.g. severe speech impairment, trouble generating words)
□ Difficulty with comprehension (e.g. severe learning disability, trouble understanding words)
□ None of the above
□ Do not know
□Prefer not to answer

4. What is your gender identity?

□ Woman
□ Man
□ Transgender man
□ Transgender woman
□ Gender fluid or non-binary
□ Two-spirit (a term by and for Indigenous peoples)
□ Prefer to self-describe _____
□ Do not know
□ Prefer not to answer

5. Which category(ies) best describe your sexual orientation?
(Check all that apply.)

□ Asexual or Aromantic
□ Bisexual
□ Demisexual
□ Homosexual or Gay
□ Heterosexual or Straight
□ Lesbian
□ Pansexual
□ Queer
□ Two-Spirit (a term by and for Indigenous peoples)
□ Prefer to self-describe _____
□ Do not know
□ Prefer not to answer

6. What is your current level of education?
(Check one only.)

□ No formal schooling
□ Grade school (grade 1-8)
□ Some high school, but did not graduate
□ High school or high school equivalency certificate (grade 9-12)
□ Completed Registered Apprenticeship or other trades certificate or diploma (or ongoing)
□ College, CEGEP or other non-university certificate or diploma (or ongoing)
□ Undergraduate degree or some university
□ Postgraduate degree or professional designation (e.g. Master's, PhD, MD)
□ Do not know
□ Prefer not to answer

7. Do you currently have difficulty paying for basic needs?

□ Yes
□ No
□ Not applicable, I do not have to pay for my basic needs
□ Do not know
□ Prefer not to answer

8. In the past 12 months, were you unable to get medicine or medical supplies, or did you do anything to make them last longer because of the cost?

□ Yes
□ No
□ Not applicable, I did not have to get any medicine or medical supplies in the past 12 months
□ Do not know
□ Prefer not to answer

9. What is your current housing situation?

□ A place you or your family owns
□ A place you or your family rents
□ Social housing, Subsidized housing, or Rent-geared-to-income
□ Supportive housing or Group Home
□ Long-term care facility
□ Correctional facility
□ Staying in someone else's place because you have no alternative
□ Experiencing homelessness (e.g. shelter, living in a public place or vehicle)
□ Other (Specify)_____
□ Do not know
□ Prefer not to answer

10. Who do you live with?

(Check all that apply.)

□ Parent(s) or Guardian(s)
□ Spouse or Partner
□ Child(ren)
□ Grandparent(s)
□ Sibling(s)
□ Other family
□ Friends or Roommates
□ Paid caregiver
□ Alone
□ Other (Specify) _____
□ Do not know
□ Prefer not to answer

11. In the past 12 months, was there a time when you were not able to pay the mortgage or rent on time?

□ Yes
□ No
□ Not applicable, I do not have to pay rent or mortgage
□ Do not know
□ Prefer not to answer

12. In the past 12 months, has lack of transportation kept you from medical appointments, meetings, work, or from getting things needed for daily living?

(Check all that apply.)

□ Yes, it has kept me from medical appointments or getting medicines
□ Yes, it has kept me from non-medical meetings, appointments, work, or getting things that I need
□ No
□ Not applicable, I did not need transportation for these activities in the past 12 months
□ Do not know
□ Prefer not to answer

13. In the past 12 months, did you miss making a payment on any utility bills (e.g. electric, gas/oil, water) because of cost?

□ Yes
□ No
□ Not applicable, I did not have to pay utility bills in the past 12 months or utilities already included in rent
□ Do not know
□ Prefer not to answer

14. Do you feel you have people who you can open up to or confide in?

□ Yes, I always or sometimes have someone
□ No, I don't have anyone
□ Do not know
□ Prefer not to answer

15. Do you have people to rely on if you needed help?

□ Yes, I always or sometimes have someone
□ No, I don't have anyone
□ Do not know
□ Prefer not to answer

16. Are you currently employed (this includes self-employed, full-time, part-time or other)?

□ Yes
□ No
□ Do not know
□ Prefer not to answer

16a. If no, are you currently looking for work?

□ Yes
□ No
□ Do not know
□ Prefer not to answer

16b. If yes, is your main job temporary or part-time (e.g. casual, contract, freelance, short-term, seasonal)

□ Yes
□ No
□ Do not know
□ Prefer not to answer

16c. If yes, do you feel that your current employment could be negatively affected if you raised concerns about your work (e.g. health, safety, rights)?

□ Yes
□ No
□ Do not know
□ Prefer not to answer

16d. If yes, in the past 12 months, did your income change a lot from month to month?

□ Yes
□ No
□ Do not know
□ Prefer not to answer

17. Roughly how many minutes does it take to travel from your home to this clinic?

(Please write number of hours/minutes.) Hours____ Minutes____
□ Do not know
□ Prefer not to answer

18. Do you have a primary care provider (e.g. nurse practitioner, general practitioner, family physician)? *(Check one only.)*

□ Yes
□ No
□ Other (please specify) _____
□ Do not know
□ Prefer not to answer

APPENDIX VI - 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 participants are permissible.

In these rare circumstances, minor deviations that do not impact participant 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).
- Participant 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 participants 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 participant 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 randomization.	Sara Rushton Clinical Trials Assistant, CCTG Email: SRushton@ctg.queensu.ca	613-533-6430	613-533-2941
STUDY SUPPLIES Forms, 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)	David Boren Study Coordinator, CCTG DBoren@ctg.queensu.ca	613-533-6430	613-533-2941
	or: Dr. Mariam Jafri Senior Investigator, CCTG MJafri@ctg.queensu.ca	613-533-6430	613-533-2941
STUDY CHAIR	Dr. Michael Kolisnsky Study Chair Michael.Kolinsky@albertahealthservices.ca		
SERIOUS ADVERSE EVENT REPORTING See protocol Section 9.0 for details of reportable events.	Dr. Mariam Jafri Senior Investigator, CCTG MJafri@ctg.queensu.ca	613-533-6430	613-533-2941
	or: David Boren Study Coordinator, CCTG DBoren@ctg.queensu.ca	613-533-6430	613-533-2941