SUMMARY OF CHANGES

NCI Protocol #: 9825
Local Protocol #: 16-700
Protocol Version Date: May 24, 2019
Protocol Title: A Phase 2 Study of olaparib and cediranib for the treatment of recurrent ovarian cancer

#	Section	Change
1.	Header	Protocol version date in header changed from December 31, 2018 to May 24, 2018.
2.	Title Page 2	Protocol version date changed from December 31, 2018 to May 24, 2018.

3.	7.1.1.1	Revision of the Protocol CAEPR:
		
		Protocol Section(s) for Insertion of Revised CAEPR (Version 2.4, April 24, 2019): 7.1.1.1
		Page Number(s): 70-72
		
		• Increase in Risk Attribution:
		  • Changed to Less Likely from Also Reported on Olaparib Trials But With Insufficient Evidence for Attribution: Platelet count decreased; White blood cell decreased
		
		• Provided Further Clarification:
		  • A new note has been added to the CAEPR; "**NOTE:** New Primary Malignancies other than MDS/AML New primary malignancies have been reported in <1% of patients. There were other contributing factors/potential alternative explanations for the development of the new primary malignancy in all cases, including documented BRCA mutation, treatment with radiotherapy and extensive previous chemotherapy including carboplatin, taxanes, anthracyclines and other alkylating and DNA damaging agents. Most are not attributed to olaparib."

4.	ICF	Protocol version date in header changed from 12/31/2018 to 5/24/2018.

5.	ICF	Revision of the ICD as Specified Below:
		
		• Increase in Risk Attribution:
		  • Changed to Occasional from Also Reported on Olaparib Trials But With Insufficient Evidence for Attribution: Bruising, bleeding
		
		• Provided Further Clarification:
		  • Infection (under Occasional) is now reported as Infection, especially when white blood cell count is low (under Occasional).

NCI Protocol #: 9825

DF/HCC Protocol #: 16-700

TITLE: A Phase 2 Study of olaparib and cediranib for the treatment of recurrent ovarian cancer

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NCI-Supplied Agents:
Cediranib (NSC 732208; [redacted] supplied by CTEP
Olaparib (NSC 747856; [redacted] supplied by CTEP

Study Sponsor: CTEP

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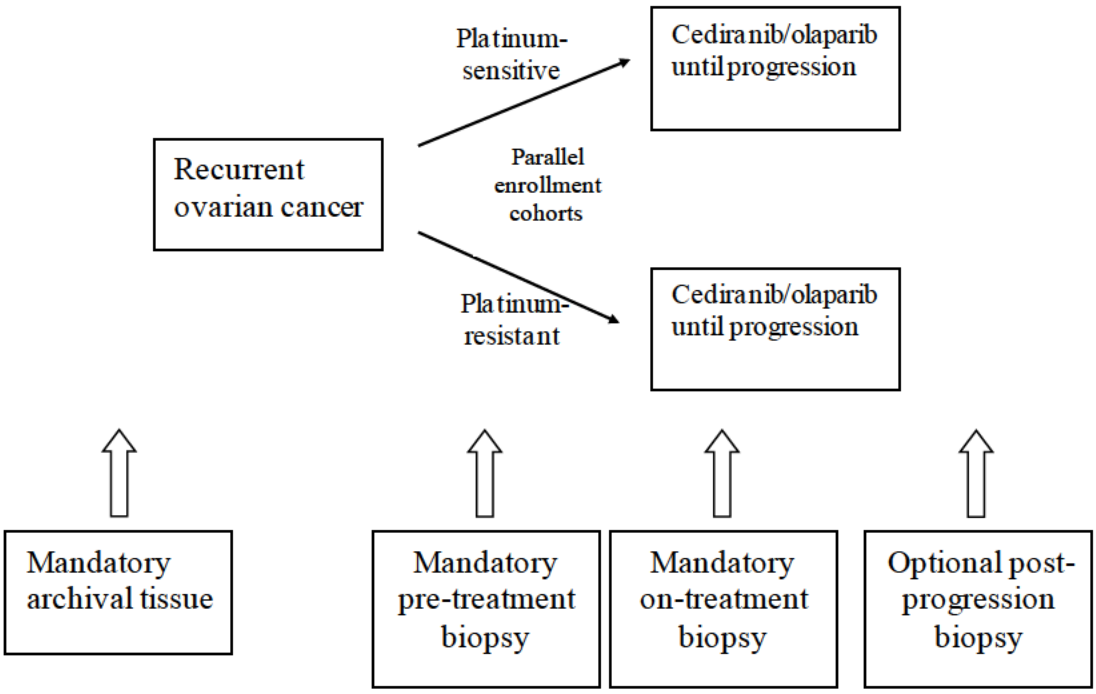
SCHEMA


Platinum-sensitive
Cediranib/olaparib until progression
Recurrent ovarian cancer
Parallel enrollment cohorts
Platinum-resistant
Cediranib/olaparib until progression
Mandatory archival tissue
Mandatory pre-treatment biopsy
Mandatory on-treatment biopsy
Optional post-progression biopsy

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1. OBJECTIVES

1.1 Study Design

The purpose of this study is to test the clinical activity and safety of the combination of olaparib and cediranib in both patients with platinum resistant as well as platinum sensitive ovarian cancer and to evaluate integrated biomarkers as predictors of response to this regimen.

1.2 Primary Objectives

1. To evaluate the association of BROCA-HR with the clinical activity of cediranib/olaparib, as measured by progression-free survival (PFS), in women with recurrent platinum-sensitive ovarian cancer.
2. To assess the clinical activity of cediranib/olaparib, as measured by objective response, in women with recurrent platinum-resistant ovarian cancer.

1.3 Secondary Objectives

1. To assess overall survival (OS), objective response, and clinical benefit (SD or response ≥ 16 weeks) in women with platinum-sensitive ovarian cancer, and PFS, OS, and clinical benefit in women with platinum-resistant ovarian cancer
2. To assess the safety of cediranib/olaparib in women with recurrent platinum-sensitive and -resistant ovarian cancer
3. To evaluate the association of circulating endothelial cells at baseline and day 3 with the clinical activity of cediranib/olaparib, as measured by PFS, in women with platinum-sensitive and –resistant ovarian cancer.
4. To evaluate changes in BROCA-HR status between archival and pre-treatment biopsy samples.
5. To evaluate the associate of BROCA-HR with the clinical activity of cediranib/olaparib as measured by PFS, in women with platinum-resistant ovarian cancer.
6. To characterize genomic alteration by whole exome sequencing in women with platinum-sensitive and -resistant ovarian cancer.
7. To identify biomarker signatures that correlate with the clinical activity of cediranib/olaparib in women with recurrent platinum-sensitive and -resistant ovarian cancer, including changes in gene expression or acquired mutations in on-treatment tumor biopsies that are associated with clinical activity, and changes in gene expression or acquired mutations in post-progression biopsies that are associated with clinical resistance.
8. To explore changes in biomarker signatures and candidate angiogenic markers from pre-treatment to post-progression in women with platinum-sensitive and -resistant ovarian cancer.

9. To evaluate the population PK of the combination of cediranib and olaparib (tablets) in platinum-sensitive and -resistant ovarian cancer.

1.4 Exploratory Objectives

1. To determine the feasibility of a mobile phone app (eCO) to collect patient-generated blood pressure and symptom data based upon study protocol recommendations.
2. Assess patient and health care professional perceived usability and satisfaction of the eCO app (for patients) and of a connected web portal (for health care providers).
3. Assess the number of generated alerts to the study team (via the web portal and email "high" alerts) based on pre-determined severity levels

2. BACKGROUND

2.1 Study Disease(s): Ovarian cancer

Ovarian cancer remains the leading cause of death from gynecologic malignancy in the United States. Ovarian cancer will be diagnosed in 21,980 women in the United States in 2014 (Siegel et al 2014); the majority of patients are diagnosed with advanced FIGO stage III or IV cancer and will eventually develop cancer recurrence following initial platinum- and taxane-based chemotherapy (Bookman et al, 2009 and McGuire et al 1996). Recurrences are defined by the duration of time between receipt of last platinum and evidence of cancer recurrence which is called the platinum-free interval (PFI). Platinum doublets are standard of care for treatment of patients with platinum sensitive recurrence (> 6 month PFI) (Pfisterer et al, 2006 and Pujade-Lauraine et al 2010). Strategies to improve progression free survival (PFS) for patients with platinum sensitive recurrence are to add agents to chemotherapy and/or used as maintenance following completion of chemotherapy (Ledermann et al 2012 and Aghajanian et al 2012) as well as to devise new targeted agent combinations (Liu et al 2014). Also importantly, the realization that ovarian cancer is composed of several different subtypes with different molecular profiles, improved understanding of the genomics of these subtypes and eligibility restriction to specific histologic subtypes are all being employed in rational clinical trial design for ovarian cancer in order to improve patient outcomes (Liu et al 2014).

2.2 IND Agent(s)

2.2.1 Cediranib (AZD2171)

Cediranib (AZD2171, Recentin™; 4-[(4-fluoro-2-methyl-1*H*-indol-5-yl)oxy]-6-methoxy-7-(3-pyrrolidin-1-ylpropoxy) quinazoline maleate; AZD2171 maleate) is a member of an emerging class of novel orally (PO) -administered small molecule vascular endothelial growth factor (VEGF) receptor tyrosine kinase (TK) inhibitors with anti-angiogenic properties (Hennequin *et al.*, 1999; Wedge *et al.,* 2005).

Mechanism of Action
VEGF is a key angiogenic factor, and has been implicated in tumor blood vessel formation and in disease progression in a range of solid tumor malignancies (Hicklin and Ellis, 2005). Two high-affinity VEGF transmembrane receptors (VEGFRs) with associated TK activity have been identified on human vascular endothelium, VEGFR-1 (also known as fms-like tyrosine kinase 1 or Flt-1) and VEGFR-2 (also known as kinase insert domain-containing receptor or KDR) (Ferrara *et al*., 2003). VEGFR-1 and VEGFR-2 signaling help mediate tumor progression. Cediranib has been developed as a potent inhibitor of VEGFR-1 and VEGFR-2 (Wedge *et al*., 2005). Cediranib also has activity against VEGFR-3 and c-Kit (Jurgensmeier *et al*., 2005). Cediranib is expected, with chronic oral dosing, to inhibit VEGF-driven angiogenesis and as a result prevent the progression and metastasis of solid tumors, and may have broad-spectrum clinical utility.

Nonclinical Efficacy
The effect of cediranib was studied in athymic *nu/nu* mice bearing established subcutaneous human tumor xenografts of diverse histologies [SW620 (colon), PC-3 (prostate), Calu-6 (lung), SKOV-3 (ovarian), and MDA-MB-231 (breast)]. Animals were administered cediranib PO at doses from 0.75-6 mg/kg/day (2.25-18 mg/m^2/day) in a constant volume of 0.1 mL/10 g body weight for 24-28 days. Cediranib produced a statistically significant inhibition of tumor growth in all human tumor types examined when dosed at 1.5 mg/kg/day (4.5 mg/m^2/day) or higher.

The murine renal cell carcinoma (RENCA) model, which rapidly (generally within 10 days) metastasizes to the lung and abdominal lymph nodes, has also been used for cediranib efficacy studies (Drevs *et al.*, 2004). In experiments incorporating a vehicle control, cediranib (at a dose of 6.3 mg/kg/day PO) reduced primary tumor growth, metastasis, and microvessel density more potently than any other previously-studied VEGF RTK inhibitor reported in the literature.

Using a transgenic mouse model in which multiple mammary tumors spontaneously develop after two pregnancies, investigators studied the temporal effects of cediranib administration (Klinowska *et al.*, 2004). When dosed with cediranib (0.75- 6 mg/kg/day PO) at the time early lesions start to develop, the number of tumor foci was not affected, but their growth was inhibited. When tumors were well-established before cediranib was given (at doses of 3 and 6 mg/kg/day), dose-dependent growth inhibition occurred as well as tumor regression.

Further details of the nonclinical efficacy of cediranib can be found in the Cediranib Investigator's Brochure (2011).

Nonclinical Pharmacology and Toxicology
Nonclinical pharmacology and toxicology company-sponsored studies have been conducted in rats, dogs, and cynomolgus monkeys (Cediranib Investigator's Brochure, 2011). In rats and dogs, oral bioavailability is high, but absorption is relatively slow, with C_{max} of the agent seen 4-6 hours after PO dosing. Plasma concentrations and exposure are generally linear over the dose ranges studied in rats. Cediranib is excreted

in the feces (>70% of the dose) of rats, dogs, and cynomolgus monkey after both PO and intravenous (IV) administration. Fecal excretion was the predominant route of elimination (>70% of the dose) in both rat, dog and cynomolgus monkey after both PO and IV administration. Elimination was rapid in rats and monkeys with over 75% of the dose being recovered in the first 48 hours; in dogs, excretion was slightly slower but again substantially complete by 7 days. Over the dose ranges examined in the rat, plasma concentrations and exposure generally increased in proportion to dose; however, in monkeys, plasma cediranib concentration-time profiles obtained following a single PO dose indicated that systemic exposure increased in a greater than dose-proportional manner over the dose range 0.05-2.5 mg/kg.

Protein binding of cediranib (90-95%) was relatively high across all species examined and was independent of concentration (range: 0.03-10 mcg/mL) and gender (Cediranib Investigator's Brochure, 2011). Cediranib was approximately 95% bound to human plasma proteins, with human serum albumin and α_1-acid glycoprotein accounting for most of this binding.

VEGF has three major biological activities in endothelial cells of rats and primates of the age groups used in the nonclinical studies (Cediranib Investigator's Brochure, 2011). It is an important angiogenic factor, a potent physiological mediator of vascular tone (specifically of vasodilation), and a potent modulator of capillary permeability inducing endothelial cell fenestrations. VEGF receptor inhibition was therefore considered to be the cause of many of the pathophysiological changes encountered. Vascular (myocarditis, choroid plexus) and renal (glomerulosclerosis and tubular degeneration) pathologies have been seen in rat, dog, and primate dosed with cediranib which are considered to be consistent with lesions induced by hypertension, although a direct effect by cediranib on these tissues cannot be excluded. Pathological findings were also seen in the adrenal glands (degenerative cortical changes), pancreas (acinar epithelial cell necrosis), thyroid (follicular epithelial cell atrophy), liver (hepatocyte necrosis), and biliary system (cholangitis and bile duct proliferation and bile duct cholangitis) of the rat. In addition in the primate, changes were seen in the gallbladder (mucosal hypertrophy) and bile duct (hyperplasia/hypertrophy).

Cediranib did not induce rat hepatic microsomal P450 activity but caused a 40-60% reduction in CYP1A activity at the 2.5 mg/kg dose level (Cediranib Investigator's Brochure, 2011). Inhibition studies *in vitro* using human hepatic microsomal protein gave IC_{50} values for cediranib against CYP2D6, CYP3A4 testosterone, and CYP3A4 midazolam of 32.9, 16.2, and 21.4 mcg/mL, respectively. For CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, and CYP2E1, the IC_{50} values were outside the concentration range of cediranib examined. As the clinically relevant plasma concentration of cediranib has not yet been determined, any possible effect on compound clearance and drug interaction is currently unknown.

Further details of the nonclinical pharmacology and toxicity of cediranib can be found in the Cediranib Investigator's Brochure (2011).

Clinical Pharmacology and Pharmacodynamics
Preliminary pharmacokinetics (PK) information indicates a time to maximum serum concentration (T_{max}) of 2 hours (range, 2-6 hours), a C_{max} of 107.8 ± 29.8 ng/mL, and a $t_{1/2}$ of 12.1 ± 2.2 hours (Sridhar *et al.*, 2008).

Preliminary information on blood biomarkers in glioblastoma patients indicates that plasma VEGF, placental growth factor (PLGF), and stromal cell-derived factor 1α (SDF1α) were increased after treatment, and plasma PIGF and VEGF decreased upon cediranib discontinuation. Plasma basic fibroblast growth factor (bFGF) and SDF1 α and viable circulating endothelial cells (CECs) increased when tumors escaped treatment with cediranib (Batchelor *et al.*, 2010).

Additional information on the relationship between clinical outcome and biomarkers has been reported for a DCTD-sponsored trial (Sorensen *et al.*, 2009). Changes in vascular permeability/flow as measured by magnetic resonance imaging (MRI) methods (K^{trans}), microvessel volume, and circulating collagen IV levels were determined. Of the 30 patients in the trial, all three parameters were reliably measured in 28. A greater reduction in K^{trans} after one dose of cediranib was seen in patients with increased PFS (P=0.0015) and overall survival (OS) (P=0.0039). A greater increase in the calculated blood volume (CBV) of tumor microvessels after one dose of cediranib was seen in glioblastoma patients with extended OS (P=0.0056). A greater increase in collagen IV levels in plasma was detected in patients with extended PFS (P=0.0010). Peripheral blood was evaluated serially for VEGF concentration and CECs in another trial (Ramalingam *et al.*, 2008). A stark increase in CECs was noted at progression in several patients

Adverse Events and Recommended Dose
The most frequently reported AEs for cediranib on company-sponsored trials were fatigue, diarrhea, nausea, vomiting, hoarseness, hand-foot syndrome, and hypertension (Cediranib Investigator's Brochure, 2011). Hypertension is an expected pharmacologic effect of agents that inhibit VEGF, and is one of the most common adverse events (AEs) reported in trials of cediranib. Dose-related increases in thyroid stimulating hormone (TSH) and decreases in total thyroxine have been observed at doses of 30 mg and above, and are most marked at 60 mg. The recommended dose for cediranib monotherapy is 30 mg/day; the recommended dose in combination with chemotherapy agents is 20 mg/day, although exceptions to these doses may be appropriate in other studies, depending on age, patient population, tumor type, or agent(s) given in combination with cediranib.

Clinical Experience
AstraZeneca has sponsored a total of 15 phase 1 studies of cediranib (single-agent or in combination with gefitinib, either FOLFOX, irinotecan [±cetuximab], pemetrexed or docetaxel, etoposide/cisplatin, or lomustine), 8 phase 2 studies (single-agent, or in combination with fulvestran, FOLFOX, or paclitaxel/carboplatin), one phase 2/3 study (cediranib plus bevacizumab), and two phase 3 studies (cediranib plus FOLFOX or XELOX and cediranib plus lomustine). Details of the studies, responses, and safety assessments are summarized in the Cediranib Investigator's Brochure (2011).

Cediranib has been administered to patients in 38 DCTD, NCI-sponsored clinical trials.

CRs and PRs have been reported in clinical trials of cediranib in solid tumors such as NSCLC (Gadgeel *et al*., 2011), renal cell carcinoma (RCC) (Sridhar *et al*., 2008), prostate (Dahut *et al*., 2013), mesothelioma (Garland *et al*., 2011), and gynecologic tumors (Hirte *et al*., 2008; Matulonis *et al*., 2009).

The MTD for cediranib in combination with 75 mg/m^2 temozolomide and radiation was established at 30 mg/day in patients with newly-diagnosed glioblastoma, with no dose-limiting toxicities (DLTs) observed (Gerstner *et al*., 2012). Cediranib was then administered at 45 mg/day in a post-radiation setting, and in addition to the expected AEs of hypertension, fatigue and palmar/plantar erythema, one patient discontinued due to grade 3 transaminase elevation and one patient required dose reduction to 15 mg/day due to proteinuria. Median PFS was 288 days (95% CI 240–∞) and median OS was 786 days (95% CI 411–∞); these values were improvements over historical controls. Best radiographic response in patients who completed chemoradiotherapy was CR in two patients, PR in 20 patients, and SD in 15 patients. Patients with increased tumor perfusion during chemoradiotherapy survived nearly 1 year longer (mean OS 611 days) than patients with decreased perfusion (mean OS 269 days).

Among 31 patients in a phase 2 trial of cediranib in recurrent glioblastoma, radiographic PRs (>50% volume reduction) were reported in 17 patients, and minor responses (25-50% volume reduction) in an additional 6 patients (Batchelor *et al*., 2010). Median PFS was 117 days, and median OS was 227 days. Additionally, cediranib alleviated brain edema, a major cause of morbidity in glioblastoma patients (Batchelor *et al*., 2007). DLTs were observed in 9 of the 16 patients with hypertension; fatigue and diarrhea were seen most often.

Two phase 2 trials of cediranib at two different dose levels (30 mg/day and 45 mg/day) in patients with unresectable locally advanced or metastatic hepatocellular carcinoma (HCC) yielded no objective responses (Zhu *et al*., 2012; Alberts *et al*., 2012). Grade 3 AEs were observed in 93% of patients receiving 45 mg/day (Alberts *et al*., 2012). Fatigue, hypertension, and anorexia accounted for the majority of the AEs.

Response information for 45 of 46 patients on a trial of cediranib in malignant pleural mesothelioma reported PR by RECIST in 4/47 patients (9%), including 2 patients with bulky disease who had 56% and 91% tumor shrinkage; and 16/47 (34%) had SD (Garland *et al*., 2011). Median PFS was estimated at 2.56 months, median OS at 9.5 months. The most common nonhematologic AEs were hypertension (70%), fatigue (64%), and diarrhea (64%).

Among 47 evaluable patients receiving cediranib in a trial in ovarian, primary peritoneal serous, or fallopian tube cancer, the clinical benefit rate was 30%; eight patients had a PR and six had SD; there were no CRs (Matulonis *et al*., 2009). Median PFS was 5.2 months, and median OS had not been reached after a median follow-up time of 10.7

months. Grade 4 AEs included CNS hemorrhage, lipase, and hypertriglyceridemia/ hypercholesterolemia/elevated lipase, and dehydration/elevated creatinine. Grade 3 AEs include hypertension, fatigue, and diarrhea. Hypertension occurred in 87% of the patients by the end of the study; in 43%, it was grade ≥3 (Robinson *et al.*, 2010). Grade 2 hypothyroidism occurred in 43% of patients.

Preliminary information from 60 patients in a phase 2 trial of cediranib in persistent ovarian, peritoneal, or fallopian tube cancer has been reported (Hirte *et al.*, 2008). Patients were divided into those whose disease was found to be platinum-resistant and those whose disease was platinum-sensitive in a prior therapy regimen. Response and prolonged SD rate was 41% for platinum-sensitive and 29% for platinum-resistant patients, respectively. In the platinum-sensitive group, there were two confirmed PRs and one unconfirmed PR, while one unconfirmed PR was observed in the platinum-resistant arm. Median time to progression (TTP) and median survival for all patients was 4.1 months and 11.9 months, respectively, with no significant differences between the platinum-sensitive and -resistant groups. The most frequent AEs were fatigue, diarrhea, hypertension, and anorexia, while hypertension and fatigue were the most frequent grade 3 or higher AEs. Sixteen patients required dose reduction to 30 mg and 20 mg.

Information on 59 patients in a trial of cediranib in metastatic androgen-independent prostate cancer has been reported (Dahut *et al.*, 2013). A total of 59 patients were enrolled, of whom 67% had received two or more previous chemotherapy regimens. Six of 39 patients with measurable disease had confirmed PRs and one had an unconfirmed PR. At 6 months, 43.9% of patients were progression-free; the median PFS and OS periods for all patients were 3.7 months and 10.1 months, respectively. Decreases in lymph node metastases as well as in lung, liver, and bone lesions were observed. Grade 3 AEs included vomiting, prolonged QTc interval, muscle weakness, weight loss, dehydration, fatigue, hypoxia, renal failure, transaminitis, and anorexia.

Thirty-two of 43 patients enrolled in a trial of cediranib in renal cell carcinoma (RCC) are evaluable for response (Sridhar *et al.*, 2008). PRs were observed in 12 patients, SD in 15, and PD in 5. Median PFS was 8.7 months and the 6-month progression-free proportion was 63%. Treatment-related grade 3 or higher AEs included hypertension, fatigue, joint pain, abdominal pain, and dyspnea.

Cediranib was administered in a phase 2 trial in small cell lung cancer (SCLC), in which one unconfirmed PR and eight SD were noted (Ramalingam *et al.*, 2008). Salient AEs were fatigue (four grade 3, two grade 4), and grade 3 diarrhea, skin rash, proteinuria, transaminitis, muscle weakness, and hypertension. However, the original 45 mg/day dose was not tolerable in the patient population, and the modest activity seen at 30 mg/day did not support the use of cediranib as monotherapy for SCLC.

A combination trial of cediranib plus docetaxel, doxorubicin, and cyclophosphamide in advanced breast cancer accrued only two patients, and was closed due to systolic dysfunction that occurred with concurrent cediranib and doxorubicin (Denduluri *et al.*, 2007).

Another combination trial of cediranib plus pemetrexed in NSCLC divided patients into two arms—those who had not received bevacizumab in prior chemotherapy regimens (Cohort A), and those who had (Cohort B) (Gadgeel *et al*., 2011). The confirmed response rate was 16% (10% Cohort A, 25% Cohort B), and the disease control rate (CR/PR/SD) was 71% (74% Cohort A, 67% Cohort B). Grade 3/4 AEs included neutropenia, febrile neutropenia, fatigue, diarrhea, hypertension, anorexia, cardiac ischemia, bronchopleural fistula, and esophagitis. Of the 17 patients who received cediranib for 4 cycles, 71% required dose reduction from 30 mg/day, and of the 18 patients who received pemetrexed for 4 cycles, 22% required dose reduction.

Additional information on clinical trials conducted with cediranib is summarized in Lindsay *et al*. (2009).

Safety Profile
As of August 2009, 582 patients on DCTD, NCI-sponsored clinical trials of cediranib had been evaluated for AEs. The most common grade 3/4 AEs were hypertension, fatigue, anorexia, diarrhea, and metabolic (ALT/SGPT and AST/SGOT).

Hypothyroidism was observed in 14/21 pediatric patients with CNS tumors administered cediranib, including one with a prolonged elevated TSH and thyroxine (T4) that went untreated. Proteinuria has been seen in seven patients, including two grade 3 events in Cycle 1 and Cycle 2, respectively. Hypertension has been observed in 18/21 patients who received more than a few days of therapy. Of the 18 cases, 10 experienced grade 2 hypertension as the highest reported grade and 8 reported grade 3 hypertension. Reversible posterior leukoencephalopathy syndrome (RPLS) shortly after initiation of Cycle 2 of therapy was seen in one patient who had been appropriately managed for grade 3 hypertension

In a phase 2 trial of cediranib in 46 patients with epithelial ovarian, fallopian tube, or peritoneal cancer, 31 patients (67%) developed hypertension by Day 3 of treatment, and 87% had developed hypertension by the end of the study (Robinson *et al*., 2010). Fourteen women developed proteinuria, seven within the first 2 weeks of treatment. Only 7 of the 20 women who developed grade 3 hypertension developed proteinuria.

In a phase 2 study of cediranib in patients with solid tumors, patients (n=126) were assigned to cediranib dose groups of either 45 or 30 mg/day with or without antihypertensive prophylaxis (Langenberg *et al*., 2009). Severe hypertension occurred in one patient receiving prophylaxis *versus* 18 in the nonprophylaxis groups. Antihypertensive prophylaxis did not result in fewer dose reductions or interruptions. Increases in blood pressure, including moderate and severe readings of hypertension, were seen in all groups and successfully managed.

Hypertension and kidney toxicity (*i.e.,* proteinuria) are commonly observed AEs seen in the class of angiogenesis inhibitor agents (Izzedine *et al*., 2007; Launay-Vacher and Deray, 2009). Indeed, many of the AEs observed in human clinical trials of cediranib

have been described in studies of other angiogenesis inhibitors (Herbst, 2006; Kappers *et al.,* 2009). A number of mechanisms have been described that account for AEs such as impaired wound healing, gastrointestinal perforation, hemorrhage and thrombosis, cardiac impairment, endocrine dysfunction, and RPLS (Kamba *et al*., 2007).

2.2.2 **Olaparib (AZD2281)**

Olaparib (AZD2281, KU-0059436, CO-CE 42, 4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2*H*)-one) is a potent and well-tolerated oral inhibitor of polyadenosine 5'-diphosphoribose [poly-(ADP-ribose)] polymerization (PARP)-1 and PARP2. Olaparib is an active monotherapy in tumors with defective components of homologous recombination repair (HRR), which includes those with BRCA1/2 mutations. A first-in-man phase 1 dose escalation trial of single agent olaparib in a patient cohort enriched for patients with BRCA germline mutations indicated substantial PARP inhibition in surrogate tissues and anti-tumor activity in 40% of ovarian cancer patients with germline BRCA mutations, using combined RECIST and GCIG CA-125 criteria (Fong *et al*., 2010).

Mechanism of Action
Preclinically, olaparib displays antitumor activity against a variety of tumor cell lines and this sensitivity of the cells is believed to depend upon components of a defective HRR capability (Olaparib Investigator's Brochure, 2013). As a major example of this selective activity, both BRCA1- and 2-deficient ($^{-/-}$) tumors are sensitive to PARP inhibition. Early studies indicated that PARP inhibition in BRCA1/2 homozygous null cells, but not the isogenic BRCA heterozygous cells, led to cell death. BRCA1 and 2 are proteins necessary for proper function of HRR, the high fidelity repair system that addresses DNA double-strand breaks (DSBs). The backup repair system to HRR is base-excision repair (BER), which requires PARP function and primarily addresses single-strand breaks (SSBs). However, the system works both ways in that repair of SSBs in BER can lead to stalled replication forks that strain the system and cause double strand breaks, resulting in a situation that requires intact HRR and BRCA1 or BRCA2. Thus, HRR dysfunction sensitizes cells to PARP inhibition leading to further chromosomal instability, cell cycle arrest and apoptosis (Farmer *et al*., 2005). This sensitivity is suggested to result in a large therapeutic window for PARP inhibition in mutation carriers. Pre-clinical studies support these findings showing that other BRCA mutant, but not wild-type, human cell lines are highly sensitive to olaparib (Menear *et al*., 2008).

Nonclinical Pharmacology and Efficacy
Olaparib has demonstrated cellular activity in the low nM range with a cellular dose for 50% inhibition (IC_{50}) of 2 nM in HeLa cells (Olaparib Investigator's Brochure, 2013). The effective concentration for inhibiting cellular PARP activity in cancer cells by >90% is approximately 30 nM to 100 nM olaparib in several tumor cell lines including ovarian A2780, breast MCF-7, and colorectal SW620. These concentrations lead to significant ablation of PARP activity (based on the inhibition of PAR formation), with maximal PARP-1 inhibition occurring at around 100 nM. Consistent with this, maximal

potentiation of an appropriate DNA SSB-inducing chemotoxic agent (MMS) was also seen *in vitro* at 100 nM, which equates to 43.4 ng/mL.

An analysis of the correlation of olaparib response with several standard-of-care (SOC) chemotherapies in a panel of breast cancer cell lines has demonstrated a strong correlation with both carboplatin (0.84, p=0.0006) and camptothecin (0.8, p=0.0018) (Olaparib Investigator's Brochure, 2013). This is consistent with what is known about the types of DNA damage they induce (intra-strand and inter-strand cross-links for platinum and trapped topoisomerases-DNA adducts for camptothecins, both of which result in DNA DSB formation in replicating cells) and the DDR pathways that deal with them (primarily HRR in cells undergoing DNA replication). The same does not hold for a mechanistically unrelated chemotherapy, such as paclitaxel (-0.11) whose mechanism of action is unrelated to the induction of DNA damage.

The analysis of olaparib and platinum response was extended to additional tumor indications where platinum treatment is SOC and included ovarian, non-small cell lung cancer (NSCLC) and head and neck squamous cell carcinoma cell lines (Olaparib Investigator's Brochure, 2013). Consistent with the breast cancer cell line data, the strong correlation between platinum response and olaparib response was observed. These *in vitro* data have been extended further into *in vivo* patient-derived tumor explant (PTX) models of both breast and NSCLC and again the correlation is seen between platinum sensitivity and olaparib sensitivity.

In vitro combination studies demonstrate that olaparib is able to potentiate the cytotoxicity of DNA-damaging agents, including the monomethylating agent temozolomide (melanoma, glioblastoma, colorectal), topoisomerase-1 inhibitors such as camptothecin, irinotecan, and topotecan (ovarian, pancreatic, colorectal), and platinum-based agents such as cisplatin and carboplatin (breast) (Olaparib Investigator's Brochure, 2013). Studies with BRCA1-deficient orthotopically-transplanted *in vivo* mouse mammary tumor models showed that, in addition to single agent activity of olaparib, sequential treatment of mice with olaparib following a single dose of platinum agent increased the time to progression on treatment and extended OS. These data support the idea that olaparib can extend the antitumor effect of platinum agents when given as a maintenance treatment.

Following single oral doses, absorption was rapid (maximum plasma concentration [C_{max}] <2 hours in mice, rats and dogs) while bioavailability was <60% in male and female mice, <20% in male and female rats and ~79% in male dogs (Olaparib Investigator's Brochure, 2013). Low oral bioavailability in rat may have been due to poor absorption or rapid first pass metabolism. Distribution of olaparib is in the gastrointestinal tract and in tissues associated with the metabolism and elimination of foreign compounds. Further investigations are still ongoing. Excretion is primarily via the feces and, to a lesser extent, the urine.

Investigations in human *in vitro* systems indicated metabolism of olaparib was CYP mediated and that CYP3A4 and 3A5 were the dominant metabolic enzymes (Olaparib

Investigator's Brochure, 2013). Similar studies indicated flavin mono-oxygenase-3 was not able to metabolize olaparib. In *in vitro* direct inhibition assays, olaparib (100 μM) had only limited effect against CYP3A (up to 46% inhibition) and less effect against other CYPs tested. In time dependent inhibition assays, olaparib had only very minor effects against CYP3A and no effect against other CYPs. Clinically significant direct inhibition of intestinal CYP3A is possible but significant effects against hepatic CYP3A are less likely. The CYP induction potential of olaparib was investigated in cultures of human hepatocytes. At the highest olaparib concentration (30 mcM), minor induction of CYP2B6 activity was observed (<40% positive control) and smaller effects on CYPs 2C9 and 2C19 activities were noted. These changes were unlikely to be of clinical significance. A small decrease in CYP3A activity was noted, which may suggest time-dependent inhibition, however, this was not explored further.

In studies using Madin-Darby Canine Kidney (MDCK) II cells transfected with multidrug resistance 1 (MDR1; Pgp), BCRP or MRP-2 drug efflux transporters, olaparib was shown to be a substrate of MDR1 but not BCRP or MRP-2 (Olaparib Investigator's Brochure, 2013). In the same systems, olaparib was an inhibitor of BCRP and MRP-2 but had little or no inhibitory effect on MDR1.

In isolated human hepatocytes, olaparib was a substrate for organic anion transport proteins. In the same system, olaparib was shown to be an organic cation transporter 1 (OCT1) inhibitor (IC_{50} 11.9 μM) (Olaparib Investigator's Brochure, 2013). In HEK-293 cells transfected with OATP1B1, olaparib functioned as an inhibitor and IC_{50} values of 20.3 mcM and 27.1 mcM were derived (substrate dependent). Using the criteria defined in the European Medicines Agency (EMA) guidelines on the investigations of drug interactions (EMA 2013), it is possible olaparib may precipitate an interaction via hepatic drug uptake transporters, particularly OCT1.

SimCYP population PK simulations of the separate effect of co-administration of itraconazole and rifampicin (clinically relevant CYP3A inhibitor and inducer, respectively) on olaparib PK in humans, when administered at the recommended human dose, were performed (Olaparib Investigator's Brochure, 2013). The itraconazole (200 mg twice daily [BID] x 7 days) simulation indicated olaparib (400 mg bd x 7 days) steady state C_{max} and area under the concentration-time curve (AUC) would increase by 2.8 and 3.5 fold, respectively. The rifampicin simulation (600 mg x 6 days) indicated olaparib (400 mg BID x 6 days) steady state C_{max} and AUC in the presence of rifampicin would be reduced to 33% and 29%, respectively, of the values in the absence of rifampicin.

Nonclinical Toxicology

Olaparib has been tested in dogs and rats (Olaparib Investigator's Brochure, 2013). There were no noted effects on the cardiovascular or respiratory parameters of an anesthesized dog or any behavioral, autonomic, or motor effects in the rat. Toxicology studies indicate that the target organ of toxicity is the bone marrow. *Ex vivo* work has confirmed that olaparib is also active against human marrow. The cytotoxic effect becomes evident at a higher concentration than required to fully ablate PARP activity. 28-day dog and rat studies demonstrate a reversible myelotoxic effect that is mild to

moderate. Platelets are first affected, followed by white blood cells. In 26-week repeat-dose studies in rats, doses were well-tolerated in male rats, with hematological effects and increased spleen weights observed at all dosages. In female rats, doses of 15 mg/kg/day resulted in significant reduction in body weight. Hematological effects and increased spleen weights were again observed at all dosages. The difference between sexes was considered to be due to the fact that females had greater plasma exposure levels than males. In 26-week repeat-dose studies in dogs, olaparib was well-tolerated. Hematological changes were observed, characterized by pancytopenia.

Clinical Pharmacology

Olaparib is rapidly absorbed following capsule oral dosing in cancer patients (Olaparib Investigator's Brochure, 2013). Mean volume of distribution was 40.3 L, mean plasma clearance was 4.55 L/h, and the estimated terminal half-life ($t_{1/2}$) was between 5 and 12 hours. Exposure increased proportionally with dose at doses up to 100 mg but increased in a less than proportional fashion at higher doses. On multiple dosing, there was no evidence of time dependency of the PK and no marked accumulation. There was no evidence of ethnic difference in olaparib PK between Japanese and Caucasian patients. Recovery of administered radiolabelled olaparib dose was >94% in four patients and approximately 60% in a further two with the lower recoveries apparently due to slower fecal excretion of dosed material by these two patients. Drug-related material was eliminated in the urine (35-50%) and in the feces (12-60%) with 6-20% of the dosed material recovered in the urine as unchanged drug. Plasma concentrations of olaparib were similar to those of total radioactivity up to 6 or 8 hours after dosing but the profiles diverged thereafter indicating the presence of circulating metabolites. Metabolite identification in plasma and the excreta is ongoing.

Studies of the relative single-dose bioavailability of capsule vs. tablet formulations showed that at the two lower tablet doses, the C_{max} with the tablet formulation tended to be slightly higher and the AUC was similar (Olaparib Investigator's Brochure, 2013). However, at the highest tablet dose (250 mg), the exposure delivered by the tablet formulation (both C_{max} and AUC) was higher than that delivered by the 400 mg capsule. The tablet and the capsule formulations cannot therefore be considered to be bioequivalent. Further details regarding PK comparisons between the capsule and tablet formulations may be found in the 2013 Olaparib Investigator's Brochure.

Table 1.2.1.3-1. Systemic Exposure of Olaparib Tablet vs. Capsule Formulations

Parameter	25 mg tablet vs. 50 mg capsule	50 mg tablet vs. 100 mg capsule	250 mg tablet vs. 400 mg capsule
C_{max} ratio 90% CI	1.29 1.10, 1.52	1.53 1.11, 2.11	2.49 1.87, 3.31
AUC ratio 90% CI	1.03 0.85, 1.24	0.99 0.69, 1.42	1.74 1.36, 2.23

C_{max} = maximum plasma concentration, AUC = area under the concentration-time curve, CI = confidence interval

Clinical Efficacy

The first clinical study in man of olaparib (KU-36-92) was a dose-escalation study in patients with advanced solid tumors (Olaparib Investigator's Brochure, 2013). Preliminary data demonstrated that olaparib is generally well-tolerated at doses up to and including the MTD of 400 mg BID in patients with various solid tumors. As of October 2, 2013, approximately 2103 patients with ovarian, breast, pancreatic, melanoma, and other advanced solid tumors have received olaparib, either as monotherapy or in combination with other chemotherapy agents. AEs considered to be associated with olaparib included anemia (mild to moderate), neutropenia (mild to moderate), and thrombocytopenia (generally mild to moderate, sometimes severe), nausea and vomiting (mild to moderate), and fatigue (mild to moderate).

Olaparib has also been studied in an expansion phase in BRCA-deficient ovarian cancer at a dose of 200 mg BID. Fifty patients were treated, including 48 with BRCA-deficient germline mutations and two patients of unknown status or significance. Twenty (40%) patients achieved complete response (CR) or partial response (PR) by RECIST and/or GCIG-CA125 criteria. An additional three patients experienced stable disease (SD) for more than four cycles (Fong *et al.*, 2010). A multicenter phase 2 study enrolled two sequential cohorts of women with known germline BRCA2 or BRCA2 mutations and recurrent advanced ovarian cancer to receive olaparib continuously at a dose of 400 mg BID (Cohort 1) or 100 mg BID (Cohort 2) (Audeh *et al.*, 2010). Responses were observed in 33% (11 of 33) patients enrolled in the 400mg BID cohort and 13% (3 of 24) patients enrolled in the 100 mg BID cohort. A phase 2 study of olaparib in advanced serous ovarian cancer and triple-negative breast cancer included a cohort of 46 ovarian cancer patients who were known not to carry a germline BRCA mutation, in which an overall response rate (ORR) of 23.9% was observed (Gelmon *et al.*, 2010).

Additional studies of olaparib as monotherapy or in combination with a platinum reagent for treatment of metastatic BRCA-deficient ovarian cancer are ongoing. Results from a phase 2 trial investigating olaparib as maintenance therapy following platinum-based therapy for platinum-sensitive serous ovarian cancer demonstrated a significant progression-free survival (PFS) benefit (8.4 vs. 4.8 months, $P<0.001$), with subgroup analyses demonstrating evidence of benefit regardless of BRCA status (Ledermann *et al.*, 2012). Lee and Kohn and colleagues have examined olaparib with carboplatin in two schedules in BRCA1/2 mutation carriers with breast and/or ovarian cancer and women with high grade serous ovarian cancers (Lee *et al.*, 2011). They also see activity with over 80% of ovarian cancer patients attaining either SD or PR lasting up to 18+ months. Additional phase 1 and 2 trials in both BRCA-deficient and BRCA-competent ovarian cancer are currently ongoing.

Olaparib was granted accelerated approved by the FDA in the United States as monotherapy in women with advanced ovarian cancer associated with germline BRCA mutation in the companion diagnostic test BRACAnalysis CDx and who have received at least 3 prior lines of therapy for ovarian cancer on December 19, 2014.

2.2.3 **Pre-clinical rationale for combination cediranib and olaparib**

Several lines of preclinical evidence support the combination of a PARP inhibitor and anti-angiogenic therapy.

While the role of DNA damage repair pathways in tumors treated with anti-angiogenic therapies is not well understood, the hypoxic state is known to result in genetic instability and mutagenesis. It is known that hypoxia triggers a DNA damage response, resulting in p53 accumulation and eventual apoptosis; p53-deficient tumors suppressed the apoptotic effect, promoting tumor survival in spite of the hypoxic state (Graeber *et al.*, 1996). However, despite the presence of DSB markers such as histone γH2AX, there is little evidence of DNA damage during the hypoxic state, and γH2AX staining is atypical (diffuse rather than punctate), though severe hypoxia may result in aberrant replication complexes, SSBs, and regions of single-stranded DNA (Hammond *et al.*, 2002). After re-oxygenation, DSBs are noted to accumulate, and tumor survival is dependent upon intact DNA repair complexes (Hammond *et al.*, 2004). Thus, post-hypoxic tumor cells which rely upon angiogenic signaling may also be vulnerable to PARP inhibition.

Human breast (MCF-7) and lung adenocarcinoma (A549) cell lines grown under hypoxic conditions exhibit severely reduced levels of BRCA1 and RAD51 due to transcriptional downregulation (Bindra *et al.*, 2004; Bindra *et al.*, 2005). Subsequent work determined that chemical PARP inhibitors displayed increased cytotoxicity against A549, RKO (colon), and H460 (lung) cell lines under hypoxic conditions, compared to normoxic conditions (Hegan *et al.*, 2010). Exposure to PARP inhibitors or PARP-1 RNAi downregulated BRCA1 and RAD51 expression in a dose-dependent manner, regardless of oxygenation, and the addition of hypoxic conditions to PARP inhibition enhanced the downregulatory effect.

In addition, studies in primary human umbilical vein endothelial cells (HUVECs) and immortalized human endothelial cell lines demonstrate a connection between hypoxia-driven angiogenesis and DNA repair, and show that inhibition of DNA repair pathways can inhibit endothelial cell proliferation. In HUVECs treated under a hypoxic state, γH2AX foci are found primarily in proliferating endothelial cell populations (positive staining for proliferative cell nuclear antigen) where they co-localize with replication protein A, suggesting a replication stress-related origin of hypoxia-induced γH2AX foci (Economopoulou *et al.*, 2009). Small interfering RNA (siRNA) knockdown of the replication stress-induced ataxia teleangiectasia mutated kinase (ATM)- and Rad3-related kinase (ATR) pathway, but not the ATM pathway, inhibited γH2AX formation, and siRNA knockdown of γH2AX significantly decreased growth factor-induced proliferation and fetal calf serum-induced HUVEC proliferation under hypoxic conditions. PARP inhibition (via the specific small-molecule inhibitor GPI 15427) inhibited angiogenesis in matrigel *in vitro* (Tentori *et al.*, 2007). At drug levels that did not affect endothelial cell proliferation (0.1-1 mcM), PARP inhibition reduced the formation of tube-like structures and inhibited platelet-derived growth factor (PlGF)- and VEGF-induced endothelial cell migration. At 1 mcM, GPI 15427 did not inhibit hypoxia-inducible factor 1α (HIF-1α) induction by the hypoxia mimetic agent $CoCl_2$, indicating that PARP inhibition's effects

on migration were not exerted through influencing HIF-1α function.

Collectively, the evidence indicates that anti-angiogenic therapy may complement PARP inhibition, particularly in the context of DNA repair-deficient tumors. These results also suggest that the combination of cediranib and olaparib may synergize not only with regard to direct antitumor activity but also with regard to their anti-angiogenic effect on tumor vasculature.

Nonclinical Efficacy

Limited nonclinical data exist regarding the specific combination of olaparib and cediranib. Olaparib (100 nM) and cediranib (5 nM) have potentially synergistic activity in *in vitro* microvascular cell tube growth assays (Figure 1), inhibiting cell tube growth and branching in a greater than additive fashion (Jung Min Lee, unpublished data) Olaparib (10 nM) and cediranib (50 nM) individually reduced tumor cell invasion, and the combination of both agents nearly completely abolished invasion compared to the control (Figure 2).

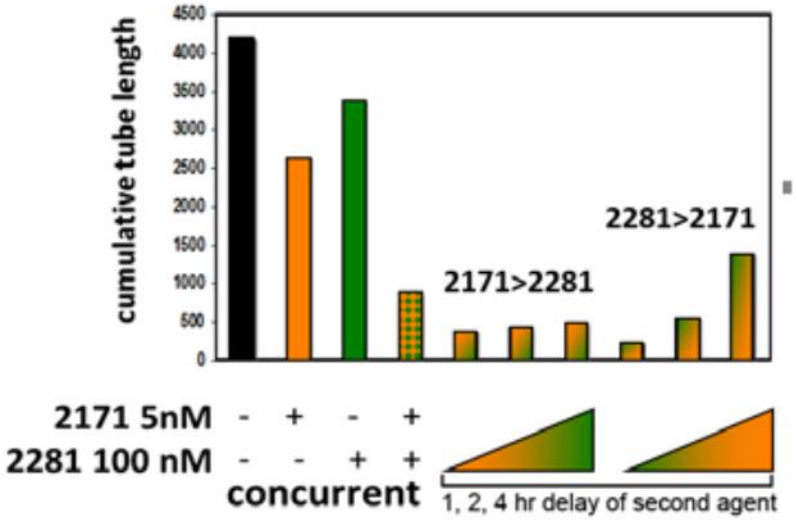


Figure 1. Microvascular cell tube formation assay.

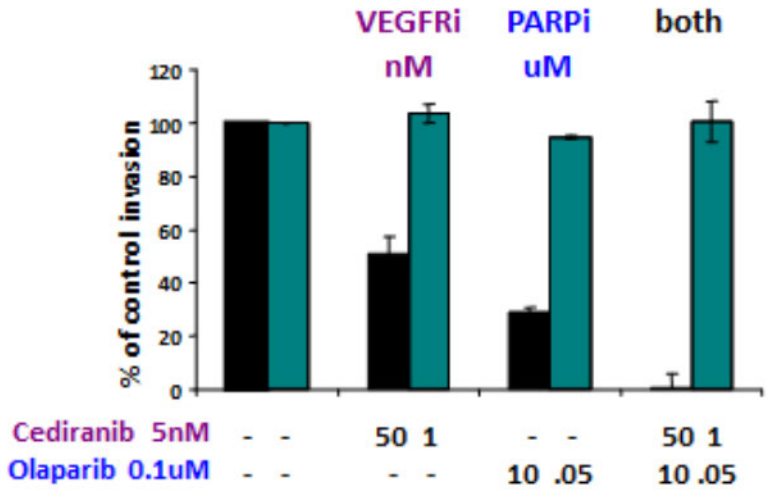


Figure 2. Tumor invasiveness assay.

2.2.4 **Clinical Background**

2.2.4.1 Phase 1 experience with cediranib and olaparib

NCI protocol 8348 included a Phase 1 component that established the recommended Phase 2 dosing (RP2D) of cediranib in combination with olaparib in the capsule formulation. This Phase 1 enrolled a total of 28 patients (20 ovarian, 8 breast). (Liu *et al*., 2013)

At the highest dosing level of cediranib 30 mg daily (QD) and olaparib 400 mg BID, two DLTs were observed (grade 4 neutropenia and thrombocytopenia), and the recommended phase 2 dose (RP2D) was declared to be cediranib 30 mg QD and olaparib 200 mg BID (Liu *et al*., 2013). Only one additional grade 4 adverse event (AE) (neutropenia) was observed. Fatigue (93%), diarrhea (86%), nausea (57%), and hypertension (45%) were the most commonly observed AEs, consistent with previously reported toxicities of cediranib and olaparib. Fatigue, which has been observed with both cediranib and olaparib in single-agent studies, may have been more prominent due to overlapping toxicity. Diarrhea was generally controllable with loperamide, although several patients required dose reduction. Hypertension, a well-documented toxicity of cediranib, was manageable with aggressive anti-hypertensive therapy; of note, only one patient required dose reduction for hypertension. Although all three grade 4 AEs observed were hematologic, in general, the combination was well-tolerated with primarily grade 1/2 hematologic toxicities.

Twenty-five patients (18 ovarian, 7 breast) from the phase 1 portion were evaluable for response by Response Evaluation In Solid Tumors (RECIST) criteria, version 1.1 (Liu *et al*., 2013). The two ovarian cancer patients not evaluable by RECIST 1.1 were followed by Gynecologic Cancer InterGroup (GCIG) CA125 criteria. The non-evaluable breast cancer patient experienced clinical progression within the first cycle of treatment and

therefore did not undergo comparative imaging. There was one confirmed CR and seven confirmed PRs among the 18 evaluable ovarian patients, for an ORR of 44%. An additional three patients had SD for at least 24 weeks, for an overall clinical benefit rate of 61%. Both ovarian patients followed by CA125 had SD, with one patient having SD for ≥24 weeks. In the 11 evaluable ovarian patients with known BRCA mutation, there was one CR and four PRs, for an ORR of 45%. None of the breast cancer patients met RECIST 1.1 criteria for clinical response. Two patients had SD for ≥24 weeks. The median PFS was 8.7 months for ovarian cancer patients and 3.7 months for breast cancer patients.

Dose escalation of cediranib in combination with olaparib in the tablet formulation has been completed in NCI protocol 8348 through a Phase 1-T component. Six doses of cediranib and olaparib tablets were explored (number of patients on each dose level in parentheses):

- Cediranib 20mg daily / Olaparib 200mg BID (3)
- Cediranib 20mg daily / Olaparib 250mg BID (3)
- Cediranib 20mg daily / Olaparib 300mg BID (6)
- Cediranib 30mg daily / Olaparib 150mg BID (3)
- Cediranib 30mg daily / Olaparib 200mg BID (6)
- Cediranib 30mg daily / Olaparib 250mg BID (3)

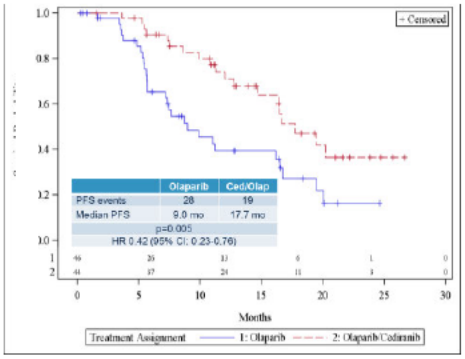
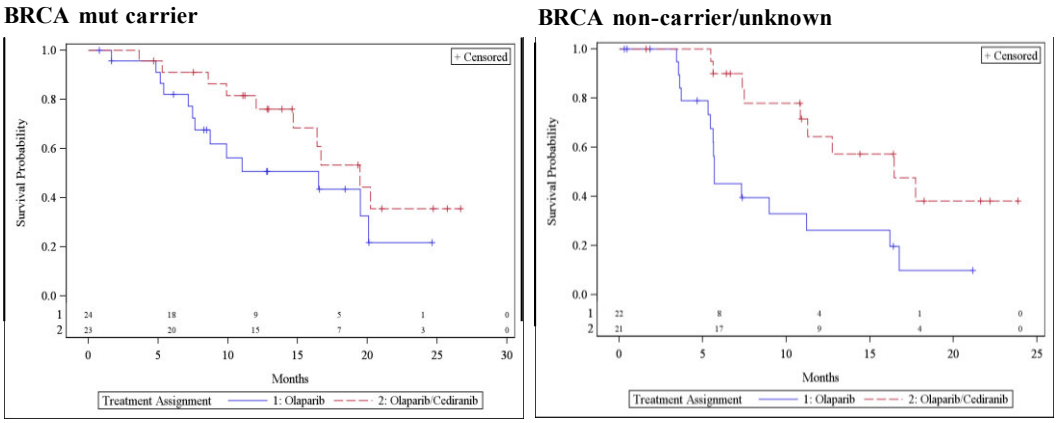


Fig 3: Kaplan-Meier PFS curves in patients treated on olaparib and cediranib/olaparib in Phase 2 trial.

Three DLTs were observed across all patients enrolled to 8348 Phase 1-T; one DLT in the six patients on cediranib 30mg/olaparib 200mg, and two DLTs in the two patients on cediranib 30mg/olaparib 250mg. The recommended phase 2/3 dosing was therefore concluded to be cediranib 20mg daily and olaparib tablets 300mg BID or cediranib 30mg daily and olaparib tablets 200mg BID. Six responses (CR or PR) were observed in the 24 patients on the study; these included one CR in the six patients on the cediranib 20mg/olaparib 300mg dosing and one CR and two PRs in the six patients on the cediranib 30mg/olaparib 200mg dosing. To preserve uniformity of cediranib dosing with prior clinical trial experience, the dose of cediranib 30mg daily and olaparib tablet 200mg BID will be further explored in this study.

2.2.4.2 Phase 2 experience with cediranib and olaparib combination

A multi-center open-label randomized Phase 2 trial comparing the activity of the cediranib and olaparib combination to olaparib alone in platinum-sensitive recurrent ovarian cancer randomized 90 patients in a 1:1 ratio to either the combination or single-agent olaparib (capsule formulation) (Liu *et al.*, 2014). Eligibility criteria for this trial included platinum-sensitive disease recurrence, with platinum-sensitivity defined as recurrence occurring greater than or equal to 6 months after the last platinum-containing regimen. Patients were allowed to receive an unlimited number of platinum-based lines



	BRCA Mutation Carrier		BRCA Non-carrier/Unknown	
	Olaparib	Ced/Olap	Olaparib	Ced/Olap
PFS events	13	10	15	9
Median PFS	16.5 mo	19.4 mo	5.7 mo	16.5 mo
	p=0.16		p=0.008	
	HR 0.55 (95% CI: 0.24-1.27)		HR 0.32 (95% CI: 0.14-0.74)	

Fig 4: Kaplan-Meier PFS curves in gBRCAm and BRCA non-carrier/unknown patients.

of therapy, and up to one non-platinum-based regimen in the recurrent setting. No anti-angiogenics in the recurrent setting were allowed; no prior PARP-inhibitors were allowed.

The combination of cediranib and olaparib significantly extended both PFS and overall response rate (ORR) compared to olaparib alone in this patient population, with a median PFS of 9.0 months for olaparib alone and 17.7 months for cediranib/olaparib (HR 0.418, 95% CI 0.229-0.763, p = 0.005) (Figure 3). There were 2 complete responses (CR) and 20 partial responses (PR) in patients on olaparib alone (48% ORR) and 5 CRs and 30 PRs in patients on cediranib/olaparib (80% ORR, p = 0.002).

Forty-seven of the 90 patients enrolled to the Phase 2 cediranib/olaparib vs. olaparib trial were known BRCA mutation carriers (25 olaparib; 23 cediranib/olaparib). A post-hoc subset analysis of PFS by BRCA mutation status (carrier vs. non-carrier/unknown) is shown in Figure 4 (next page). In BRCA mutation carriers, the median PFS was 16.5 months on the olaparib alone arm and 19.4 months on the cediranib/olaparib arm (HR 0.55, 95% CI 0.24-1.27, p = 0.16). In BRCA non-carrier/unknown patients, the median PFS was 5.7 months on the olaparib alone arm, and 16.5 months in the cediranib/olaparib arm (HR 0.32, 95% CI 0.14-0.74, p = 0.008).

Differentially occurring grade 3 or 4 toxicities attributed to study treatment included fatigue (27% cediranib/olaparib vs 11% olaparib, p = 0.06), diarrhea (23% vs 0%, p = 0.0004), and hypertension (41% vs 0%, p < 0.0001). There were two Grade 4 events, both in the cediranib/olaparib arm: 1 grade 4 hypertension in a patient who was not fully compliant with blood pressure monitoring and 1 grade 4 myelodysplastic syndrome (MDS). The patient with MDS had two prior lines of therapy and had been on study for approximately 1 year when she was diagnosed with MDS. Four patients on the cediranib/olaparib arm withdrew from study treatment secondary to toxicity (1 each due to weight loss, MDS, recurrent avascular necrosis in the setting of prior history of avascular necrosis, and vaginal fistula formation). Otherwise, AEs were manageable

with a combination of symptom management and dose holds and/or reductions, and removal from the study for reasons other than a PFS event was balanced between the arms (2 withdrawal of consent, 1 investigator decision, 5 clinical progressions on cediranib/olaparib vs. 3 withdrawal of consent, 1 investigator decision, and 6 clinical progressions on olaparib alone).

2.2.4.3 **Rationale for trial design**

The combination of cediranib and olaparib may offer a novel treatment regimen for women with recurrent ovarian cancer utilizing combination biologic agents as an alternative to standard cytotoxic chemotherapy. However, unanswered questions exist regarding the activity of this regimen in the platinum-resistant population, as well as whether particular biomarkers may predict for more robust response to this regimen.

The trial is designed to allow assessment of activity and BROCA-HR as a predictor of activity in two separate cohorts of women with recurrent ovarian cancer, either in the platinum-sensitive or platinum-resistant setting. Women will be stratified to one of the two cohorts depending on their platinum-resistance status at the time of enrollment.

Due to the findings in the Phase 2 randomized study of cediranib/olaparib versus olaparib, where the observed response rate in 44 women with platinum-sensitive ovarian cancer who received cediranib/olaparib was 80% with a median PFS of 17.7 months (detailed in Section 2.2.4.2), no interim futility is designed for this cohort.

Data regarding the activity of the cediranib/olaparib combination in platinum-resistant patients is less robust. Six patients in the Phase 1 study had platinum-resistant disease, of whom 3 had a response. In preliminary results from a bridging Phase 1 study of cediranib together with olaparib in the tablet formulation, 4 of 14 patients with RECIST measurable disease had a partial or complete response. Therefore, in the platinum-resistant cohort, a Simon two-stage design will be utilized.

2.2.4.4 **Rationale for on-study biopsies**

Pre-clinical studies suggest that synergy between cediranib and olaparib is mediated through induction of a more HR-deficient state. However, it currently remains unknown whether a particular biomarker might predict for a more robust response to the cediranib/olaparib combination. In prior clinical experience with PARP-inhibitors, the response to PARP-inhibitors appears to be most robust in patients with germline *BRCA1* or *BRCA2* mutations (Gelmon *et al.*, 2011). However, certain patients without a gBRCA mutation may also benefit from PARP-inhibitor (Gelmon *et al.*, 2011). In the Phase 2 study, benefit with cediranib and olaparib was observed in both women with and without gBRCA mutation.

A pre-treatment biopsy is included in this trial as the tumor may be evolve between the time of collection of an archival sample and the time of initiating on study treatment. Recent data reported by McNeish et al. demonstrated that changes in a signature of HR-

deficiency can be seen between archival and pre-treatment biopsies, and that the signature of HR-deficiency in pre-treatment biopsies can predict activity of the PARP-inhibitor rucaparib (McNeish *et al.*, 2015). In this study, ARIEL2, patients with gBRCAmt had a median PFS of 9.4 months on rucaparib. In comparison, patients who were gBRCAwt but had a HR-deficient signature on their pre-treatment biopsy had a median PFS of 7.1 months, while those who were gBRCAwt but lacked a signature for HR-deficiency had a PFS of only 3.7 months. BROCA-HR will be assessed as the primary biomarker for HR-deficiency in the pre-treatment biopsy, and BROCA-HR assessment will be correlated with activity of the cediranib/olaparib combination in patients, as assessed by PFS. As exploratory analyses, we will also compare BROCA-HR in the pre-treatment biopsy to the archival sample.

An on-treatment biopsy is being performed to assess for interval change in biomarkers that will be critical for understanding the mechanism of cediranib/olaparib synergy as well as potential mechanisms of resistance. It has been hypothesized that the mechanism of synergy between cediranib and olaparib is the induction of a more HR-deficient state in the setting of hypoxia from anti-angiogenics. In the on-treatment biopsy, gene expression analysis will ask whether proteins involved in HR are being downregulated after initiation of cediranib and olaparib. Additionally, how this downregulation correlates with overall activity of the cediranib/olaparib combination would be explored. BROCA-HR will also be utilized to understand whether early mutations within elements of HR occur in response to challenge to cediranib/olaparib, and how such occurrences correlate with clinical activity.

An optional off-treatment biopsy is being requested of patients at the time of progression. Resistance to PARP-inhibitors has been clearly documented in women with ovarian cancer. Various mechanisms of resistance to PARP-inhibitors have been reported, including the development of "reversion mutations", where the original germline mutated *BRCA1* or *BRCA2* in a patient's tumor back-mutates into a functional version of the gene, leading to restoration of HR deficiency (Edwards *et al.*, 2008; Sakai *et al.*, 2008), loss of 53BP1 (Jaspers *et al.*, 2013), stabilization of BRCA1 (Johnson *et al.*, 2013), or expression of certain miRNAs that may regulate HR-related genes (Moskwa *et al.*, 2011). Molecular characterization from these off-treatment biopsies would be compared to the pre- and on-treatment biopsies to understand changes in gene expression or development of novel mutations/back-mutations that would allow for insight into mechanisms of resistance.

The findings from these biomarker studies would identify biomarkers for patients most likely to derive clinical benefit from cediranib/olaparib, as well as those patients who are unlikely to respond to the combination. Given the potential toxicities of this regimen, identification of patients who are more likely or less likely to respond would allow for future stratification of patients based upon a molecular signature to receive or not receive the cediranib/olaparib combination for treatment of their ovarian cancer.
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2.3 Correlative Studies Background

2.3.1 BRCA1 and BRCA2

BRCA1 and BRCA2 (BRCA1/2) are tumor suppressor genes, in which inherited loss-of-function mutations confer a high lifetime risk of breast and ovarian carcinoma. BRCA1/2 are key components of the BRCA-Fanconi anemia (FA) pathway, which is critical to homologous combination-mediated DNA repair. Germline BRCA1/2 mutations (gBRCAm) are the prototype molecular alterations that confer HRD, and PARPi's demonstrate synthetic lethality in cells deficient in BRCA1/2 (Bryant *et al.*, 2005; Farmer *et al.*, 2005). Clinically, BRCA1/2 mutation carriers with recurrent ovarian cancer have had an approximate 40% response rate to PARPi alone (Audeh *et al.*, 2010; Kaye *et al.*, 2012).

Myriad Genetics has been chosen as the partner for BRCA1 and BRCA2 testing in this study due to its extensive experience of BRCA1 and 2 mutation detection. Myriad keeps the most comprehensive database on BRCA1/2 gene mutations and their clinical relevance. Furthermore, Myriad has an established laboratory infrastructure which supportshigh volume testing with turnaround times that can meet the needs of a clinical trial.

2.3.2 BROCA-HR

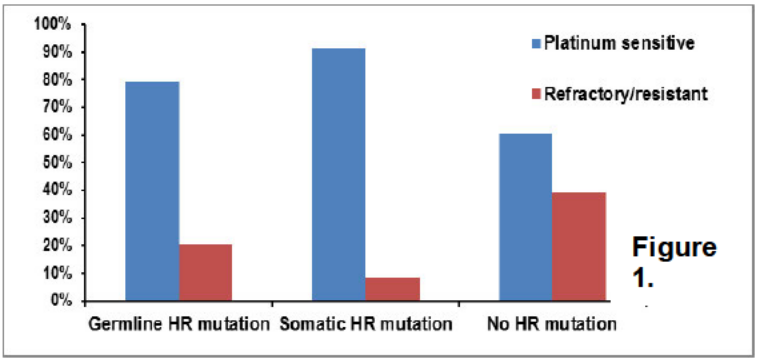


Figure 1.

The University of Washington group has previously published the methodology and validation experiments for targeted capture and massively parallel sequencing of cancer genes (Nord *et al.*, 2011; Walsh *et al.,* 2011; Walsh *et al.*, 2010; Pritchard *et al.,* 2012; Pennington *et al.,* 2012). BROCA is a targeted massively parallel sequencing assay that is capable of identify all classes of mutations including gene rearrangements. Using BROCA, Walsh et al demonstrated that nearly one-fourth of women with ovarian carcinoma have germline loss of function mutations in at least one of the 12 genes (Walsh *et al.,* 2011). Furthermore, most of these genes are in the BRCA-FA pathway. After *BRCA1/2*, the most common genes mutated in women with ovarian cancer are *BRIP1 (FANCJ), RAD51D, RAD51C (FANCO),* and *PALB2 (FANCN)* (Walsh *et al.,* 2011; Wickramanayake *et al., 2012).* Pennington et al applied BROCA to detect somatic mutations in tumor DNA from 363 women with ovarian carcinoma. Combining germline and somatic mutations increased the fraction of cases identified with HRD to 31%, including 23% with germline and 9% with somatic mutations in FA/HR genes (and 1% with both somatic and germline mutations) (Pennington *et al.*, 2014). The presence of either a germline or somatic FA/HR

mutation is highly predictive of an improved primary response to platinum chemotherapy (P<.0005, **Figure 1**) and longer overall survival (P=.001, Pennington *et al.*, 2014, **Figure 2**). Germline and somatic loss of function mutations were identified in all of the 13 FA/HR genes evaluated.

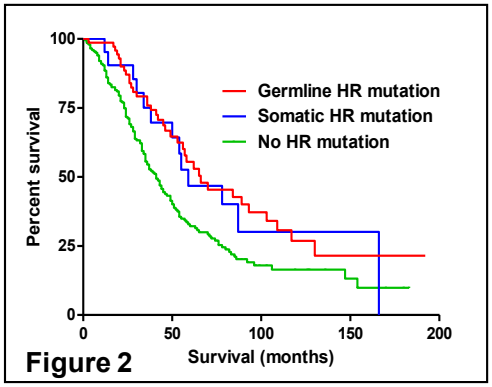


Figure 2

Dr. Swisher's laboratory has designed a new version of BROCA (BROCA-HR) that includes many additional DNA repair genes (75 total genes) as well as 3000 single nucleotide polymorphisms (SNPs). Similar sequencing accuracy and sensitivity sequencing DNA is obtained from formalin fixed paraffin embedded (FFPE), fresh blood and flash frozen specimens. BROCA-HR includes genes that are targets of both somatic and germline mutations. The BROCA-HR includes genes that regulate homologous recombination or NHEJ that, if mutated, could mediate resistance to PARPi such as *TP53BP1* (Johnson *et al.*, 2013; Bunting *et al.*, 2010; Bouwman *et al.*, 2010). The BROCA design is flexible and can be altered to include any genes of research interest. The current design for BROCA-HR includes the following genes:

BROCA-HR gene list (n=65)

a. BRCA-FA homologous recombination pathway: *ATM, ATR, BABAM1, BAP1, BARD1, BLM, BRCA1, BRCA2 (FANCD1), BRIP1 (FANCJ), BRCC3, BRE,, CHEK1, CHEK2, ERCC1, ERCC4 (FANCQ), FAM175A (abraxas), FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG (XRCCC9), FANCI, FANCL, FANCM, GEN1, MRE11A, NBN, PALB2 (FANCO), RAD50, RAD51C (FANCO), RAD51D, RBBP8 (CtIP), SLX4 (FANCP), UIMC1 (RAP80), XRCC2,*

b. DNA mismatch repair (Lynch syndrome) *MLH1, MSH2 (*and *EPCAM), MSH6, PMS2*

c. Other DNA repair or surveillance genes : *CDK12, CDH4, HELQ, NEIL1, PPM1D, POLD1, POLE, RIF1,TP53, ID4, PAXIP1, POLQ, RINT1, TP53BP1, USP28, WRN, XRCC3*

d. NER genes: *ERCC2, ERCC3, ERCC4, ERCC5, ERCC6, DDB1, XPA, SPC,*

e. NHEJ pathway genes*: DCLRE1C, LIG4, PARP1, PRKDC, TOPBP1, XRCC4, XRCC5, XRCC6*

f. PI3K pathway: *PTEN, PIK3CA*

2.3.3 Plasma Angiome

To date, the effort to identify candidate predictive blood-based markers for anti-angiogenic inhibitors has been challenging for many reasons. These include biological complexity, limitations of available reagents, limited sample collection in most trials, and a lack of randomization, which is needed to deal with the potential confounding of prognostic and predictive markers. Many of these barriers have now been overcome. Compared to tissue-based biomarkers, blood-based biomarkers have the significant

advantages of low cost, universal applicability, and the ability to be followed over the course of a patient's treatment. By focusing on soluble factors of known biological relevance, further scientific, diagnostic, and therapeutic efforts are greatly facilitated

The application of multiplex ELISA approaches in clinical samples is rapidly evolving, having only recently shown positive results. The design of the Duke multiplex panel array to interrogate diverse biologies related to angiogenesis is novel. Many of the analytes in our multiplex array were developed and optimized for performance in plasma and serum samples from cancer patients. The Duke plasma angiome approach utilizes the Searchlight™ platform from Aushon BioSystems Inc, and the panel has been developed in tandem with the team at Aushon for over 7 years to develop multiple new assays and optimize the performance of our specific panel design (see Table 3).

Table 3: Plasma-based marker identification

Soluble Angiogenic Factors		Matrix-Derived Factors	Markers of Vascular Activation and Inflammation
ANG-2	PDGF-BB	sEndoglin	CRP
bFGF	PlGF	Osteopontin	ICAM-1
HGF	VEGF-A	TGFβ1	IL-6
IGFBP1	VEGF-D	TGFβ2	PAI-1 Active
IGFBP2	sVEGFR1	TGFβRIII	PAI-1 Total
IGFBP3	sVEGFR2	TIMP1	SDF-1
PDGF-AA	sVEGFR3	TSP2	VCAM-1

This approach is technically robust and readily adaptable to clinical practice. Because this data will be derived from patients, even preliminary data may significantly improve our understanding of how angiogenesis and tumor growth factors are regulated in cancer patients. Promising findings can be followed up in future clinical studies and in preclinical models. Because the Duke angiome lab serves as the core lab for multiplex ELISA analyses within the Alliance, the current ovarian cancer profiling can be compared to the profiles seen in other phase III studies, helping to optimize future profiling approaches and provide the disease specific context needed for clinically meaningful companion diagnostics. Given the results of this prior work and the work of others, we anticipate being able to identify and validate or refute candidate markers of benefit that are specific for anti-angiogenic agents.

2.3.4 Circulating endothelial cells/circulating endothelial progenitor cells (CEC/CEP)

The presence of CECs has been recognized as a potential biomarker of vascular damage (Bertolini *et al.,* 2006). Elevated numbers of CEC have been described in lymphoma, melanoma, and other solid tumors including ovarian cancer, reflecting the perturbation of vascular endothelium (Goon *et a,,* 2006). CECs have been examined in early clinical trials using anti-angiogenics (Ning *et al*,. 2010, Park *et al.,* 2013, Kummar *et al*., 2011).

In the phase II study of bevacizumab, thalidomide, docetaxel, and prednisone in metastatic prostate cancer (Ning *et al*, 2010), the numbers of post-treatment CEC correlated with PSA response; patients with ≥ 75% PSA decline had an increase in CEC levels compared with those who had < 75% PSA decline (p=0.02).

As part of the Phase 2 cediranib/olaparib vs. olaparib study, a self-selected subset of eligible patients who had been randomized to receive either olaparib or cediranib/olaparib underwent correlative studies. Blood samples were collected at baseline and day 3 to measure circulating endothelial cells (CEC: nucleated CD133-CD146+CD31+CD45-), and circulating endothelial progenitor cells (CPC: viable nucleated CD133+, CD146-, CD31+ CD45 - or dim). 10 patients had paired correlative CEC/CPC studies. The increase of CEC pretreatment to day 3 was correlated with PFS>6mo in 6 pts on O+C (p=0.011, 95%CI 0.47-0.99, R2=0.91). The increase of CEC pretreatment to day 3 correlated with PFS>6mo in 5 patients on cediranib and olaparib (P=0.011, 95%CI 0.47-0.99, R^2=0.91, Lee *et al*. manuscript in preparation). These findings support the hypothesis that cediranib and olaparib combination may yield greater inhibition in tumor vascularity and these changes may correlate with response rate and result in survival benefit. We hypothesize a risk classifier by Flow Cytometry, including CECs, may correlate with clinical response to olaparib and cediranib combination in recurrent ovarian cancer.

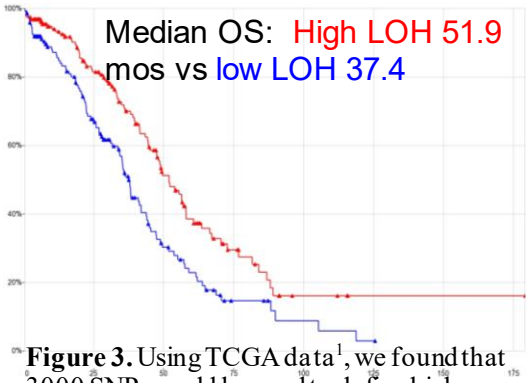


Figure 3. Using TCGA data[1], we found that 3000 SNPs could be sued to define high genomic LOH, which is associated with significantly longer survival.

2.3.5 Genomic scarring

A common characteristic of genomic scarring is large (>15Mb) but sub-chromosomal deletions. Therefore, fine mapping of LOH is not necessary to identify the HRD genomic scar. We tested the theoretical ability of 3000 SNPs to define "genomic scarring" in existing TCGA data (Figure 3, unpublished data). Indeed, using only 3000 SNPs can define cases with high LOH which have better prognosis. Combining the BRCA mutational status and the LOH profile (Figure 4, unpublished data) provides additional prognostic information. In this trial, we will assay 3000 SNPs in the same BROCA-HR assay at no additional cost which will provide an LOH profile to assess genomic scarring as an exploratory biomarker.

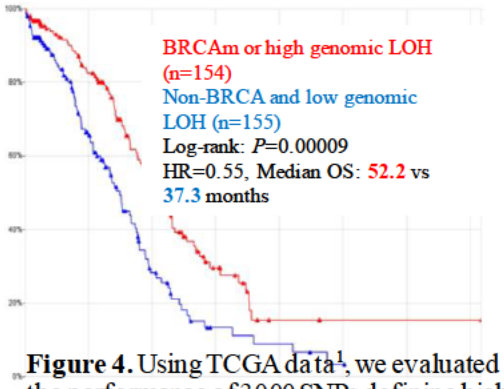


Figure 4. Using TCGA data[1], we evaluated the performance of 3000 SNPs defining high genomic LOH in combination with BRCAm

Combining the mutation information from BROCA sequencing with the LOH profile will also allow us to test performance of a combined biomarker as outlined in Figure 5, with the prediction that HR proficient cancers would achieve no significant benefit from the addition of PARPi

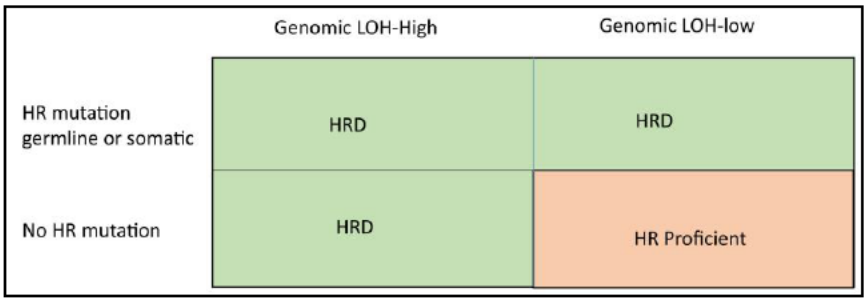


Figure 5

2.3.6 Whole exome sequencing (WES)

The Broad Institute in Cambridge MA has a long experience with whole exome sequencing, and invented one of the most commonly used approaches available today[6]. The protocol involves generating tens of thousands of 120-mer oligonucleotides on solid arrays, cleaving them from the array and converting them into single-stranded, biotin-labeled RNA 'baits' to drive hybridization through high concentration. This protocol was licensed to Agilent, and this method has now been used in >500 publications.

2.3.7 RAD51 assay

Homologous recombination mediated DNA damage repair (HR) is a pathway that accurately repairs DNA double strand breaks. This is a multi-step process and one of the key steps in the pathway is the loading of RAD51 on single stranded DNA generated at double-strand breaks following resection by nucleases. RAD51 is an ATP-driven recombinase that is deposited on the single stranded DNA which results in the formation of a proteo-nucleo filament. These filaments can be detected as sub-nuclear

foci using antibodies specific to RAD51. In addition, expression of many genes involved in HR mediated DNA double-strand break repair, including RAD51, is restricted to the S/G2 phases of the cell cycle. Presence of RAD51 sub-nuclear foci is a surrogate measure of HR proficiency of the tumor sample.

The D'Andrea Lab and the Center for DNA Damage and Repair at Dana-Farber Cancer Institute in Boston MA have developed an immunohistochemistry based assay that can identify RAD51-foci on pathology samples (unpublished data).

Multiple studies have established the synthetic-lethal relationship between HR deficiency and sensitivity to inhibitors of Poly-ADP-ribose polymerase (PARP). Therefore, presence of RAD51-foci is expected to correlate with PARP inhibitor resistance. Conditions for the assay have been developed and validated in a panel of 14 patient-derived xenograft (PDX) models of high-grade serous ovarian cancer, where 10 samples were BRCA1/2 wild-type and 4 samples carried mutations in BRCA1. In-vivo testing of Olaparib response of these models showed that 13 models were resistant to Olaparib, including the BRCA1 mutant models, while a BRCA1/2 wild-type model, DF83, was sensitive. Genomic analysis of DF83 revealed that the promoter of another HR pathway gene, RAD51C, was hyper-methylated resulting in HR-deficiency and PARP inhibitor sensitivity. In correlation with PARP inhibitor response, all models except DF83 had sub-nuclear RAD51-foci (Figure 6).

PDX model	Subtype	BRCA_status	Cycles_chemo	HR_status by RAD51	Olaparib_response
DF09	HGSOC	wild type	0	Proficient	resistant
DF14	HGSOC	wild type	5	Proficient	resistant
DF20	HGSOC	wild type	0	Proficient	resistant
DF59	HGSOC	BRCA1 5385InsC	7	Proficient	resistant
DF68	HGSOC	BRCA1 Q563X	5	Proficient	resistant
DF83	HGSOC	wild type	4	Deficient	sensitive
DF86	HGSOC	BRCA1 del exons 21-214	5	Proficient	resistant
DF101	HGSOC	BRCA1 187delAG	2	Proficient	resistant
DF106	HGSOC	wild type	1	Proficient	resistant
DF118	HGSOC	wild type	1	Proficient	resistant
DF149	HGSOC	wild type	0	Proficient	resistant
DF172	Mixed	wild type	2	Proficient	resistant
DF181	HGSOC	wild type	7	Proficient	resistant
DF216	Adenocarcinoma	wild type	2	Proficient	resistant

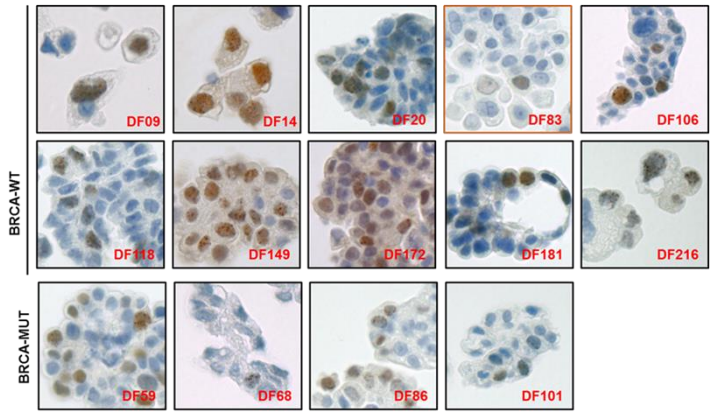


Figure 6. Presence of RAD51 foci tracks with PARP inhibitor response in ovarian cancer models. Sensitivity to olaparib, a PARP inhibitor, and the presence of RAD51 foci was determined in a cohort of 14 PDX models derived from ovarian cancers. Characteristics of eadch PDX model are shown in the table and images of RAD51 in the FFPE sections of ascites-derived cells is shown. Note that DF83 is the only model that was sensitive to olaparib, and this model lacks RAD51 foci

2.4 eCediranib-Olaparib (eCO) Application

2.4.1 Rationale for developing an application for toxicity reporting

The combination of cediranib and olaparib has been studied in several clinical trials, as outlined earlier. Primary toxicities associated with cediranib include hypertension and diarrhea, which can be serious if not aggressively identified and managed and may require discontinuation of the drug. These toxicities can be managed with symptom management, dose reductions, study drug "holidays" and use of clinical guidelines for management (Raja, 2011; Liu, 2015). For example, in patients participating in the ICON6 study, which studied the combination of cediranib with chemotherapy followed by cediranib maintenance, the discontinuation rate due to diarrhea in the arm where cediranib was administered concurrently with chemotherapy with subsequent cediranib maintenance was 10.8% (Data on file, AstraZeneca). Thus, consistent reporting and clinical management are key to successfully managing toxicities on the cediranib-olaparib combination.

As part of the planned study, participants are required to monitor blood pressure at home 2 times/day (or 1 time/day if stable after 8 weeks) and contact the study team if hypertension develops. Paper diaries for self-blood pressure monitoring are kept by the patient and reviewed with the study team at each study visit. However, intervention for any hypertensive event relies upon the patient contacting the study team to report an elevated blood pressure. Reliability of self-monitoring of blood pressure has been previously demonstrated to be present certain challenges via use of paper diaries which are subject to under-reporting, over-reporting and incorrect entries (Mengden, 1998).

Similarly, for diarrhea management, patients are educated about the occurrence of diarrhea and diarrhea management, including the use of loperamide and instructions for use based on the change in the number of stools from baseline. Self-management instructions including initiation of a BRAT (bananas, rice, applesauce, toast) diet are also provided verbally by the study team. Patients are informed when to contact the study team should diarrhea symptoms not be controlled using these strategies. At each study visit, the patient is interviewed and the number and severity of diarrhea events are documented. Again, however, interventions for diarrhea management rely on the patient contacting the study team when these events occur.

The development of an app that might allow for better data reporting of hypertension and diarrheal events could therefore significantly improve early and successful management of these toxicities.

2.4.2 Background on mobile health technology

Over the past several years, the field of digital health has been rapidly growing. Mobile health technologies are being utilized in a number of diseases for supporting patients and health care professionals including medication titration, symptom management, education and remote monitoring (Weaver, 2007; Kearny, 2009).

Use of mobile health in oncology has been increasing in the past few years. In an early

pilot of use of mobile phone technology for symptom management in patients with colon cancer (QUASAR 2) symptoms and temperature were entered using the keypad by answering questions based on CTCAE criteria which were displayed on a pre-loaded mobile phone. Amber and red alerts were automatically sent from the server to a dedicated pager with response time required within 30 minutes. Clinical algorithms for management were utilized to assure quality and standardization. Red alerts were also generated if patients didn't enter data >24 hours. Data entry compliance was 98% and all patients reported positive experiences with use of the mobile phone (Weaver, 2007). An advanced symptom management system (ASySM©) has been evaluated in several clinical trials evaluating the impact of a mobile-phone based system to assess incidence, severity and distress related to six chemotherapy symptoms (nausea, vomiting, fatigue, mucositis, hand-foot syndrome and diarrhea) in patients with lung, breast of colorectal cancer. These studies have shown that this technology can support symptom management, provide a more accurate reflection of chemotherapy related toxicity, provide a better means of monitoring in practice and were well received by patients (Kearny, 2009; Maguire, 2008; McCann, 2009). Evaluations of telemonitoring, telehealth including video conferencing, text messages and mobile phone technology in oncology have been completed or are currently underway (Kroenke, 2010; Mooney, 2014; Agboola, 2014).

2.4.3 Background on eCO application development

Therapeutic software, or companion software, is a new area of digital health providing a link between mobile technology and therapies. Voluntis, a digital health company headquartered in Paris, France with offices in Cambridge, MA, is a pioneer in the development of therapeutic companion software medical devices. In collaboration with the National Cancer Institute and Dana Farber Cancer Institute and supported by Astra Zeneca, the developer of cediranib and olaparib, Voluntis has developed eCO (e Cediranib-Olaparib), a mobile and web software application for use by healthcare providers and their adult female patients with recurrent ovarian cancer who are being treated with the investigational drug combination of cediranib and olaparib. Since treatment with cediranib is frequently associated with hypertension and diarrhea, eCO provides patients with a means of capturing these symptoms on a mobile device and will convey, symptom management guidance to the patient, as required. This guidance is the same as detailed in the NCI #9825 study protocol. eCO provides secure capture, storage and transmission of blood pressure and diarrhea data as well as other symptom-related data to aid in remote monitoring of these symptoms by health care professionals. The system captures symptom data through manual entry by the patient using icons and also includes wireless connectivity capability to measure a patient's blood pressure and capture the data through a Bluetooth enabled monitor. eCO supports symptom monitoring by HCPs via a secure web portal that reports and analyzes patient data entered in the eCO app. The use of the app can provide reproducible, reliable, and immediate feedback to the patient and their healthcare team, consistently reinforcing self-management recommendations including when to contact the study team. Additionally, the app can assist with adherence to the study protocol for blood pressure monitoring providing a means for the study team to be notified if

blood pressure values are outside of acceptable range or if monitoring is not being done according to the protocol recommendations. Updated diarrhea and blood pressure data collection protocols are incorporated into the eCO app (see Appendix H). This additional data collection does not change any treatment recommendations detailed in the study protocol.

The recommendations communicated by the app are the same as those detailed in the study protocol, therefore, study subjects using the app will receive the same symptom management guidance as those not using the app. Study subjects who will not be using the eCO app will follow usual study procedures which include a paper diary for blood pressure monitoring and reporting of symptoms using guidelines provided by the study team

Usability of the eCO app will be assessed as part of the pilot evaluation with the support of User-Centered Design, Inc., a Human Factors Engineering consulting firm headquartered in Ashburn, VA. User-Centered Design staff include psychologists, interaction designers, and developers who focus on improving the user experience.

2.4.4 Description of the eCO Mobile Application and Web Portal

eCO is a software medical device which is considered to be non-significant risk and will be used within the 9825 study under an Investigational Device Exemption (IDE). eCO consists of a mobile application for patients and a web software application for the study team. The eCO app and web portal have been evaluated by User-Centered Design, Inc. This human factors engineering/usability evaluation included a heuristic review and in-lab assessment with users similar to those who will participate in the pilot study.

When enrolled in the pilot study, the patient will be entered into eCO via the study team web portal (see Figure 9). Once the enrollment is completed a registration email will be sent to the patient which includes a temporary login and password. Once this information is entered, the patient creates a 4-digit access code which is needed each time eCO is opened (Figure 6). During the set-up process, the patient also provides an answer to a security question which needs to be answered correctly in case of a forgotten access code. Patients are also recommended to passcode protect her phone using the "Passcode" feature for the iPhone. No data is stored in the app or on the phone; all data is stored in a secure, HIPPA compliant cloud server. Each phone will have a label placed on the outside (cover) with the User Support number in case of a lost or misplaced phone.

2.4.5 eCO Mobile Application (for patients)

The eCO App will be used by patients to:

- Record self-monitored blood pressure automatically through a blue-tooth enabled blood pressure monitor (A&D Connected Blood Pressure Device UA651-BLE).
- Manually record a self-monitored blood pressure as needed.

- Receive recommendations to recheck blood pressure within a specified timeframe or contact the study team based on pre-determined severity levels.
- Record diarrhea based on number of bowel movements per day compared with baseline (pre-entered).
- Receive self-management recommendations for loperamide (Imodium®) dosing and BRAT diet which are the same as provided to study patients who are not using the eCO app.
- Contact the study team for hypertension and diarrhea events, as needed, based on pre-determined severity levels. The "Contact" screen will allow the patient with one "tap" to call directly from the mobile phone using phone numbers entered by study staff at each study site.

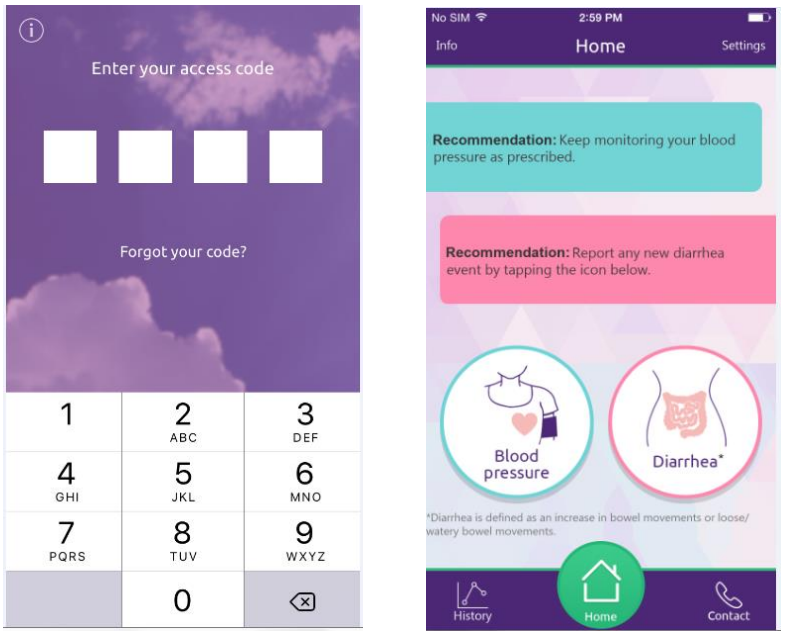


Figure 6. eCO mobile app login and home screens. *"Login" screen which requires entry of a personalized 4-digit access code (shown on the left). "Home" screen (shown on the right) which is used to enter a blood pressure or a diarrhea event. The patient also can view summary graphs of her blood pressure and reported diarrhea as well as access phone numbers to contact the study team, if needed.*

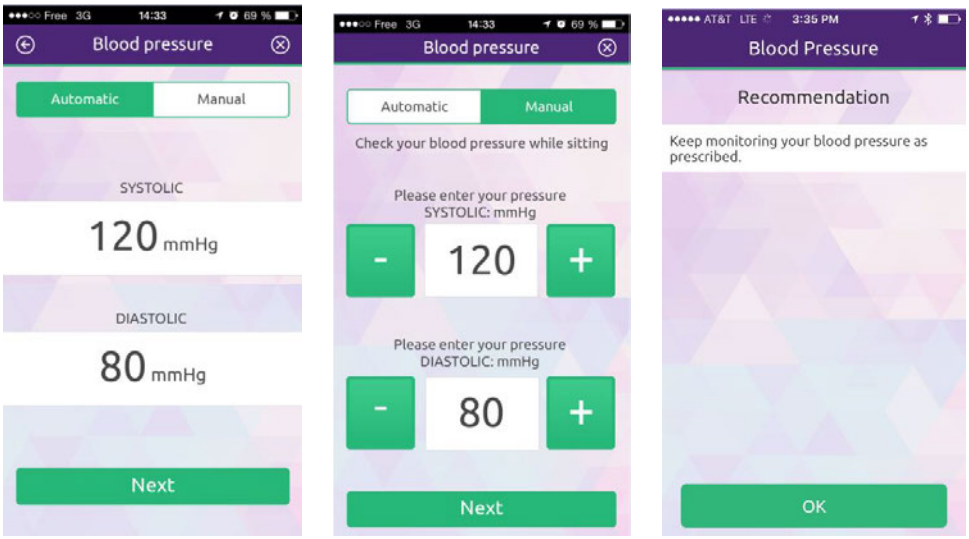


Figure 7: **eCO mobile app screens for blood pressure monitoring.** *Blood pressure (BP) can be entered into eCO automatically using the blue-tooth connected A&D BP monitor (shown on the left) or by manual entry using the +/- buttons (shown in the middle). Patients will be asked to enter any BP related symptoms. Based on these entries recommendations, using pre-determined severity levels, will be sent to the patient. These recommendations include continue checking blood pressure as prescribed, recheck BP within a specified time frame or contact the study team (shown on the right).*

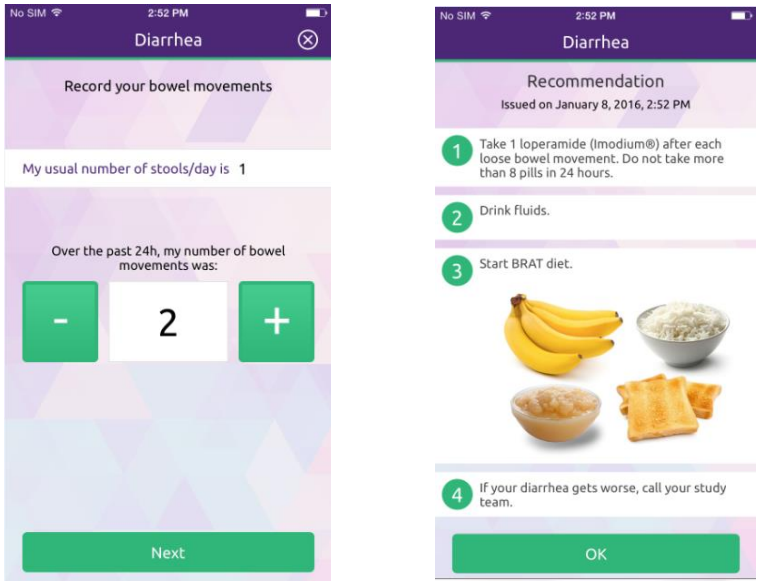


Figure 8. eCO mobile app screens for recording diarrhea. *Baseline usual number of bowel movements per day is entered by the study team at the first study visit. When experiencing diarrhea, the patient is asked to enter the number of bowel movements per day which is compared against baseline and any symptoms that are entered. Using the patient entries, the app will provide recommendations, based on pre-determined severity levels. These recommendations include use of loperamide and start BRAT diet or contact the study team.*

See the Appendix for full-size screenshots of the eCO app. eCO will be available for use on the Apple iOS platform with iPhone models starting from the 4S through the current model. Patients who currently use an iPhone will be asked to install the eCO app on their phone. Patients who use an Android phone or do not currently use a smartphone will be provided with an iPhone 6 which has the eCO app preloaded and includes a data plan for calling and receiving calls from the study team (intended for study use only).

eCO User Support will be utilized to track any app malfunctions that occurred during the pilot study. Adverse event reporting will be done according the 9825 clinical trial protocol using the study approved eCRFs. Adverse events (device-related injury) that could be related to the investigational device (eCO app) will be recorded using CTEP procedures and reported to Voluntis, Inc., the legal manufacturer of eCO.

Data collected via the eCO app will not be used for grading of adverse events nor used for primary study analysis.

2.4.6 **eCO Healthcare Professional Web Portal**

Each study center will be added to the eCO system by a back office administrator with assigned rights to add new study centers. Each study center will have an identified staff person who will be responsible for identifying the health professionals (HCP) who are involved in the study at the site. Upon adding study team members to eCO, a registration email will be sent to the HCP which includes a temporary login and password. During the first sign in, the study team member will reset the password and answer a secret question which will be required to reset a password. Each study team member will have his/her own personal account.

The eCO Healthcare Professional Web Portal will be used by the study team to:

- Add patients to the web portal who are participating in the pilot study. Adding a patient to the eCO web portal will generate an email to the patient with a temporary login ID and password.
- Set frequency of blood pressure reminders (twice daily or once daily) based on the study protocol.
- Monitor patients who are participating in the pilot study at their site including patients on the "Patient Watchlist" who are considered in a "BP event" with close monitoring.
- Specify the team (Oncologist and Research Nurse) who will be receiving email alerts for BP >180/110 mmHg and systolic BP $\leq$ 90 mmHg.
- Monitor patients who have entered or are continuing in a "diarrhea event" with severity indicated by number of flag icons (1-4).
- Review the individual patient profile which includes patient demographics, summary of BP values, reported diarrhea events, notifications and recommendations.
- Enter "Action recommendations" using a drop down list of actions for hypertension and diarrhea based on an individual BP or diarrhea entry.

- Review notifications received on individual patients based on pre-defined criteria. Notifications history will be maintained in the specific patient file on the web portal.
- Inactivate patients who are no longer participating in the pilot study.
- Have access to sections of the 9825 study protocol pertaining to hypertension and diarrhea management which have been uploaded into the web portal.

Interventions for hypertension management or study drug holds will be done per protocol by the study team and documented as required in the study eCRFs and/or medical record.

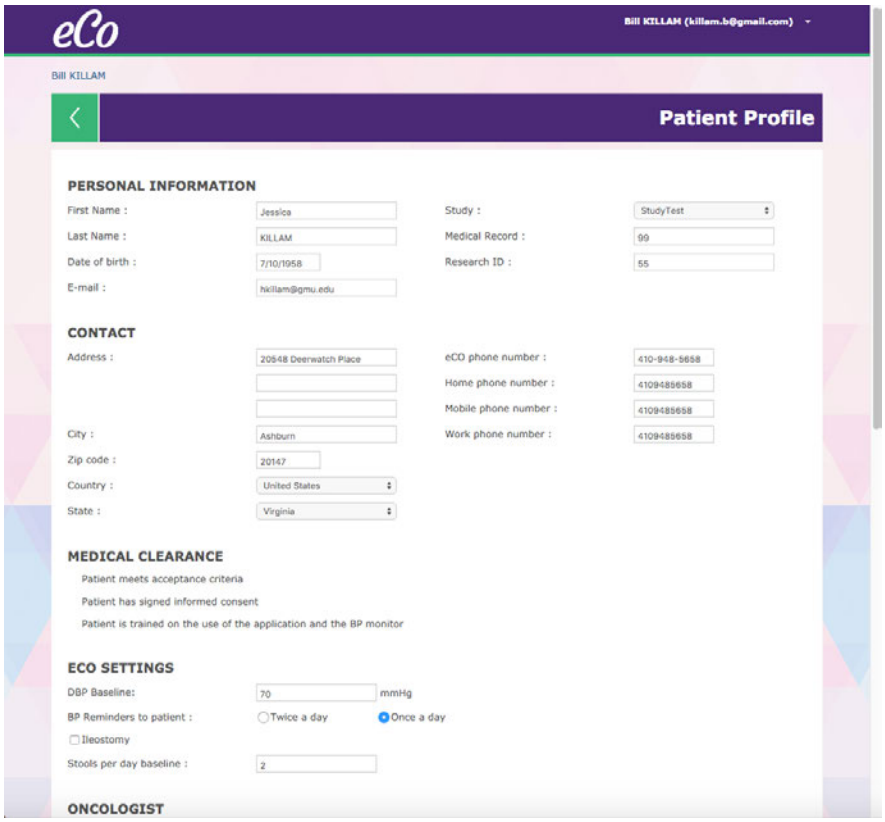


Figure 9. Adding a new patient profile into the eCO web portal. *This screen shows some of the key information entered by the study team to add a new patient. At the first study visit, the study team enters required information for the eCO app including baseline diastolic blood pressure, frequency of BP reminders and baseline number of stools per day.*

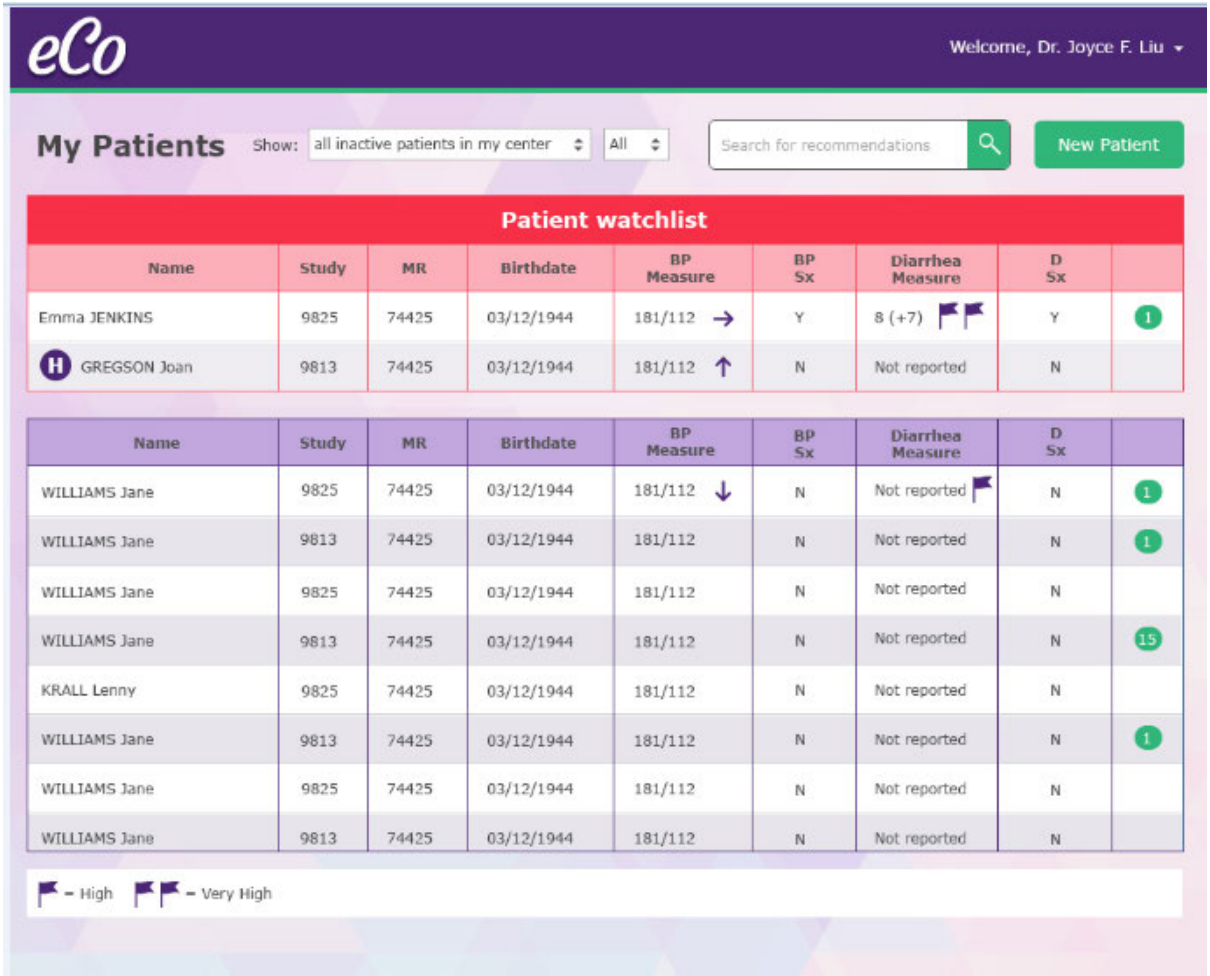


Figure 10. eCO HCP Web Portal. *Example of the home screen for the web portal includes a list of active patients and a summary of key data which can be used by the study team to monitor their patients. The "Patient Watchlist" in red includes those patients who are currently being more closely monitored for a "BP event". Those patients who are currently considered in a "Diarrhea event" are indicated by a flag (number of flags indicate severity).*

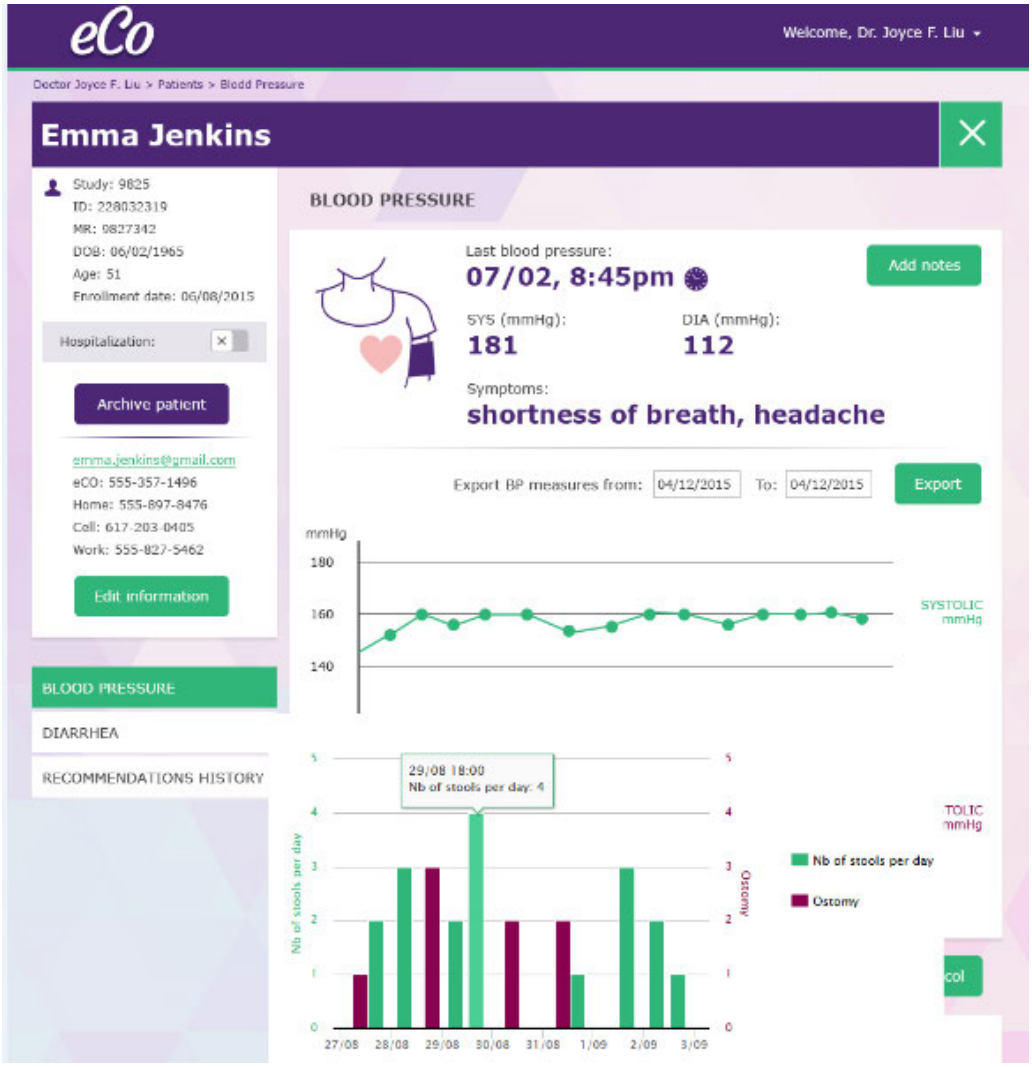


Figure 11: Patient profile from the eCO Web Portal. *Example of a patient profile which includes current and historical data on that patient for BP monitoring and diarrhea event reporting, notifications and hospitalization status.*

2.4.7 Cybersecurity Risk Controls

Cybersecurity is the protection of information systems from theft or damage to the hardware, the software, and to the information on them, as well as from disruption or misdirection of the services they provide. It includes controlling physical access to the hardware, as well as protecting against harm that may come via network access, data and code injection, and due to malpractice by operators, whether intentional, accidental, or due to them being tricked into deviating from secure procedures.

eCO has undergone a risk assessment/analysis and risk controls measures for cybersecurity. This Risk Management process is based on ISO 14971 (Application of Risk Management to Medical Devices, a nine-part standard which first establishes a

framework for risk analysis, evaluation, control, and management, including a specified a procedure for review and monitoring during production and post-production). The EBIOS approach is used to express the security needs and identify the security objectives. It is compliant with standards ISO 27000 (Information technology -- Security techniques -- Information security management systems -- Overview and vocabulary), ISO 15408 (Information technology – Security techniques – Evaluation criteria for IT security) and ISO 17799 (Information technology -- Security techniques -- Code of practice for information security management).This process is based on the analysis of the context of the application and defining the scope of the information system on which the risk assessment is performed (intended use, software requirements, critical functions, data workflow, architecture if the information system) in order to obtain a detailed and prioritized list of events that may affect the application. The security needs are based on availability, integrity, confidentiality and auditability, as well as the potential impacts of a cybersecurity breach. For each potential threat, a list of vulnerabilities is established depending on the equipment, architecture and software (example: web portal authentication, attacked obtains a user password via a server-side brute force attack). Then, a risk analysis is performed to define the risk level, corresponding to the highest threat a security breach could lead to, as well as the likelihood (probability of harm that could occur to a user of the application). Mitigations are then identified for each risk in order to eliminate or reduce to an acceptable level the identified risks.

2.4.8 Participating Study Sites and Enrollment

The 9825 main study plans to enroll 70 patients in 12 centers who are part of the ETCTN network. Subjects who are eligible for enrollment in the 9825 study will be offered the opportunity to participate in the pilot. Subjects previously enrolled in the study prior to the eCO app start date can choose to use the eCO app to track blood pressure and diarrhea, although this data will not be used for the pilot study analysis.

Subjects who are willing to participate in the pilot will complete the informed consent form during a routine visit with their study coordinator.

The pilot study intends to enroll a minimum of 12 patients and up to 20 patients. Accrual is anticipated to be 1-2 patients/month.

Subjects who currently use an iPhone will have the option of installing the eCO app on their personal phone and use it during the study or will be provided with an iPhone 6 for use during the study. Subjects who currently use an Android phone or who do not have a smartphone will be provided with an iPhone 6 at the first study visit. The iPhones provided will have the eCO app preinstalled as well as a limited data plan and will be restricted to study use only. A label will be applied to the outside of each phone with the User Support number in case of technical issues or lost or misplaced phone. Phones provided by the study will also be labeled with an inventory number which has been assigned to the patient.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Participants must have histologically or cytologically confirmed ovarian cancer, peritoneal cancer or fallopian tube cancer and must have a histological diagnosis of either high grade serous or high grade endometrioid cancer based on local histopathological findings. Participants with a deleterious BRCA-mutation on a commercial CLIA assay with other high-grade histologies are also eligible.

Due to the long acceptance of BRCA testing through Myriad, Myriad testing will be accepted as documentation of a deleterious mutation. If testing for BRCA is done by other organizations, documentation from a qualified medical professional (e.g., ovarian cancer specialty physician involved in the field, high risk genetics physician, genetics counselor) listing the mutation and confirming that the laboratory results show a recognized germline deleterious *BRCA1* or *BRCA2* mutation or *BRCA* rearrangements is required to document the presence of a deleterious mutation. Please collect a copy of Myriad or other BRCA mutational analysis (positive or VUS or negative) reports.

3.1.2 Participants must have measurable disease via RECIST 1.1, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm with conventional techniques or as ≥10 mm with spiral CT scan, MRI, or calipers by clinical exam. See Section 11 for the evaluation of measurable disease.

3.1.3 Prior therapy

3.1.3.1 Patients may not have received prior PARP inhibitors

3.1.3.2 Patients may have received but may not have progressed on prior anti-angiogenic therapy in the upfront setting

3.1.3.3 For platinum sensitive cohort

1) Cancer that has not progressed within 6 months of the last receipt of platinum-based chemotherapy.
2) No limit on the number of platinum-based lines
3) No more than one prior non-platinum based line of therapy in the recurrent setting

3.1.3.4 For platinum-resistant or -refractory cohort

1) Disease that has progressed within 6 months of the last receipt of platinum-based chemotherapy
2) No more than 1 prior line of therapy in the platinum-resistant/-refractory setting.
3) No limit on number of prior lines received in the platinum-sensitive

setting prior to development of platinum-resistance (defined as disease progression within 6 months of platinum-based chemotherapy).

Hormonal therapies used as single agents (i.e. tamoxifen, aromatase inhibitors) will not count towards line limit considerations.

3.1.4 Age ≥18 years of age. Because no dosing or adverse event data are currently available on the use of cediranib or olaparib in patients under the age of 18, children are excluded from this study.

3.1.5 ECOG performance status ≤2 (see Appendix A)

3.1.6 Participants must have normal organ and marrow function as defined below:

– Leukocytes	≥3,000/mcL
– Absolute neutrophil count	≥1,500/mcL
– Hemoglobin	≥10 g/dL
– Platelets	≥100,000/mcL
– Total bilirubin	≤1.5 x the institutional upper limit of normal (ULN)
– AST(SGOT)/ALT(SGPT)	≤3 × institutional upper limit of normal
– Creatinine	less than or equal to the institutional upper limit of normal OR
– Creatinine clearance	≥60 mL/min/1.73 m^2 for participants with creatinine levels above institutional normal.
– Proteinuria	less than or equal to 1+ proteinuria on two consecutive dipsticks taken no less than week apart, **or** a urine protein:creatinine (UPC) ratio of ≤1.
– Coagulation parameters (INR, aPTT)	≤ 1.25 × ULN institutional limits, except where a Lupus anti-coagulant has been confirmed

3.1.7 Presence of biopsiable disease and willingness to undergo pre-treatment and on-treatment biopsy

3.1.8 The effects of olaparib and cediranib on the developing human fetus are unknown. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and up to 3 months after end of treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

3.1.9 Adequately controlled thyroid function, with no symptoms of thyroid dysfunction and TSH less than or equal to the upper limit of normal.

3.1.10 Patients must be able to tolerate oral medications and not have gastrointestinal illnesses that would preclude absorption of cediranib or olaparib.

3.1.11 Ability to understand and the willingness to sign a written informed consent document.

3.1.12 Willingness to release and confirmed availability of archival tissue sample for research purposes.

3.1.13 Willingness and ability to check and record daily blood pressure readings. Blood pressure cuffs will be provided to patients. Please refer to sections 5.4, and Appendix C (blood pressure diary).

3.2 Exclusion Criteria

3.2.1 Participants may not have had chemotherapy or RT within 3 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study and must have recovered to ≤ grade 1 from adverse events due to agents administered more than 3 weeks earlier. Patients should not have received hormonal therapy for treatment of their cancer within 2 weeks of study entry.

3.2.2 Participants should not have received any other investigational agents nor have participated in an investigational trial within the past 4 weeks.

3.2.3 Participants may not have had prior use of PARP inhibitors. Patients may not have received prior treatment affecting the VEGF pathway in the recurrent setting, including but not limited to thalidomide, bevacizumab, sunitinib, or sorafenib.

3.2.4 Participants may not have any evidence of ongoing inadequately controlled hypertension (defined as a systolic BP of >140 mmHg or a diastolic BP of >90 mmHg). Patients with hypertension may not be on more than three antihypertensive medications for management of their blood pressure (medications that combine two anti-hypertensives into one are considered as two medications). It is strongly recommended that patients who require three antihypertensive medications for baseline management of pre-existing hypertension be actively followed by a cardiologist or blood pressure specialist for management of BP while on protocol.

3.2.5 Participants may not have had any prior history of hypertensive crisis or hypertensive encephalopathy.

3.2.6 Participants may not have had history of abdominal fistula or gastrointestinal perforation. Patients with a history of abdominal fistula will be considered eligible if the fistula has healed or was surgically repaired, there has been no evidence of fistula for at least 6 months, and patient is deemed to be at low risk of recurrent fistula.

3.2.7 Participants may not have had a history of intra-abdominal abscess within the past 3 months.

3.2.8 Participants may not have current signs and/or symptoms of bowel obstruction or signs and/or symptoms of bowel obstruction within 3 months prior to starting study drugs

3.2.9 Participants may not have a dependency on IV hydration or TPN.

3.2.10 Participants with any concomitant or prior invasive malignancies are ineligible with the following exceptions:

- Treated limited-stage basal cell or squamous cell carcinoma of the skin
- Carcinoma in situ of the breast or cervix
- Primary endometrial cancer meeting the following conditions: Stage not greater than IA, grade 1 or 2, no more than superficial myometrial invasion, without vascular or lymphatic invasion; no poorly differentiated subtypes, including papillary serous, clear cell, or other FIGO grade 3 lesions.
- Prior cancer treated with curative intent with no evidence of recurrent disease 3 years following diagnosis and judged by the investigator to be at low risk of recurrence.

3.2.11 Participants with any of the following:
- History of myocardial infarction within six months
- Unstable angina
- NYHA classification of III or IV

3.2.12 If cardiac function assessment is clinically indicated or performed: participants will be ineligible if left ventricular ejection fraction (LVEF) is less than normal per institutional guidelines, or <55%, if the threshold for normal is not otherwise specified by institutional guidelines.

Patients with any of the following risk factors should have a baseline cardiac function assessment:
- Prior treatment with anthracyclines
- Prior treatment with trastuzumab
- Prior central thoracic radiation therapy (RT), including RT to the heart
- History of myocardial infarction within 6 to 12 months (Patients with history of myocardial infarctin within 6 months are excluded from the study
- A NYHA classification of II controlled with treatment (see Appendix E)

- Prior history of impaired cardiac function

3.2.13 Participants may not have had a history of a stroke or transient ischemic attack within six months

3.2.14 Participants should not have clinically significant peripheral vascular disease or vascular disease (including aortic aneurysm or aortic dissection).

3.2.15 Participants may not have a major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to starting cediranib.

3.2.16 Participants should not have any uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.17 Patients with untreated brain metastases, spinal cord compression, or evidence of symptomatic brain metastases or leptomeningeal disease as noted on computed tomography (CT) or magnetic resonance imaging (MRI) scans are ineligible. Screening imaging to rule out brain metastases is not required for screening, but should be performed prior to study enrollment if clinically indicated. Patients with treated brain metastases must demonstrate stable post-therapeutic imaging and resolution of any associated symptoms and must be stably off steroids with no symptoms for at least 6 months following therapy prior to starting study drug.

3.2.18 Participants may not have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to cediranib or olaparib.

3.2.19 Participants receiving any medications or substances that are *strong* inhibitors or inducers of CYP3A4 or *moderate* inhibitors of CYP3A4 are ineligible (see Appendix D). The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product. Dihydropyridine calcium-channel blockers are permitted for management of hypertension. Appendix D (Patient Drug Information Handout and Wallet Card) should be provided to patients.

3.2.20 Pregnant women are excluded from this study because olaparib and cediranib have the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with olaparib and cediranib, breastfeeding should be discontinued if the mother is treated with cediranib and olaparib. These potential risks may also apply to other agents used in this study.

3.2.21 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with cediranib or olaparib. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.2.22 Participants should not have evidence of coagulopathy or bleeding diathesis. Therapeutic anticoagulation for prior thromboembolic events is permitted.

3.2.23 Current use of a prohibited medication. The following medications or non-drug therapies are prohibited:

- Other anti-cancer therapy while on study treatment.
- Prophylactic use of bisphosphonates in patients without bone disease, except for the treatment of osteoporosis.
- Because the composition, PK, and metabolism of many herbal supplements are unknown, the concurrent use of all herbal supplements is prohibited during the study (including, but not limited to, cannabis, St. John's wort, kava, ephedra [ma huang], ginkgo biloba, dehydroepiandrosterone [DHEA], yohimbe, saw palmetto, or ginseng).
- Raloxifene is allowed for patients taking it for bone health.

3.2.24 Participants may not have any features suggestive of myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML) on peripheral blood smear or bone marrow biopsy, if clinically indicated.

3.3 Inclusion of Women and Minorities

Because only women can develop ovarian cancer, only women are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN or RAVE or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined

in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

4.2 Site Registration

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

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the 9825 protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select LAO-MA036, and protocol #9825
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

4.2.2 Submitting Regulatory Documents

Requirements For 9825 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human

Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission

When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

4.2.3 Checking Site Registration Status

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

For trials with slot reservation requirements, OPEN will connect to IWRS at enrollment initiation to check slot availability. Registration staff should ensure that a slot is available and secured for the patient before completing an enrollment.

Once a slot reservation request has been made, the following source documentation should be faxed to the Lead Institution or designee for confirmation of eligibility.

- Copy of required laboratory tests:
  - CBC with differential
  - Serum chemistries (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, albumin, calcium, phosphorus, AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin)
  - TSH, free T4
  - Urinalysis (2 measures at least 1 week apart) or urine protein:creatinine ratio
  - CA125
- Signed informed consent form
- HIPAA authorization form (if separate from the informed consent document)
- EKG
- MUGA or ECHO (if indicated)
- CT scan (chest, abdomen, pelvis)
- Pathology report
- Screening or most recent clinic visit note (including documentation of oncologic history, past medical history, concomitant medications)
- BRCA test report, if BRCA testing has been performed
- Documentation of availability of archival tissue
- Documentation of the presence of biopsiable disease
- Documentation of patient's willingness and ability to check and record daily blood pressure readings.

The Lead Institution or designee may then approve the slot reservation to allow completion of enrollment.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

4.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients or request slot reservations: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type. If a DTL is required for the study, the registrar(s) must also be assigned the OPEN Registrar task on the DTL.
- To approve slot reservations or access cohort management: Be identified to Theradex as the "Client Admin" for the study.
- Have regulatory approval for the conduct of the study at their site.

Prior to accessing OPEN/IWRS, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- If applicable, all patients have signed an appropriate consent form and HIPAA authorization form.

4.3.3 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://theradex.com/CTMS/Downloads.aspx. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk: 609-619-7862 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 14 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. TREATMENT PLAN

5.1 Treatment Regimen

Treatment will be administered on an outpatient basis. The cycle length is 28 days, and patients will undergo cancer assessment per RECIST 1.1 criteria after every 2 cycles of therapy.

Expected toxicities and potential risks as well as dose modifications for cediranib and olaparib are described in Section 6 (Expected Toxicities and Dosing Delays/Dose Modifications). No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Toxicity assessments will be done using NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 until March 31, 2018. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. 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 web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Regimen Description					
Agent	**Dosing Instructions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Olaparib	Olaparib will be given BID at the same times each day.	200 mg	PO	Twice daily and continuously	28 days (4 weeks)
Cediranib	Orally each morning on an empty stomach, either 1 hour before or 2 hours after breakfast.	30 mg	PO	Daily and continuously	

The participant will be required to maintain an accurate medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each cycle.

5.2 Pre-treatment Criteria

5.2.1 Screening Visit

Patients must meet criteria at screening as outlined in Section 3.1

5.2.2 Hematologic Parameters for Treatment

Patients must meet the following absolute neutrophil count (ANC) and hematologic parameters for treatment. Additionally, dosing parameters for hematologic AEs in Section 6.2 should be observed.

- Cycle 1, Day 1: ANC $\geq 1500/mm^3$

- Cycle 1 Day 15:
  - ANC ≥ 1000/mm^3
  - Platelets ≥ 100,000/mcL
  - Hemoglobin ≥ 8 mg/dL

- Cycles 2 and beyond, Day 1:
  - ANC ≥ 1000/mm^3
  - Platelets ≥ 100,000/mcL
  - Hemoglobin ≥ 8 mg/dL

5.2.3 All Cycles, Day 1

Patients must meet the following parameters on day 1 of each cycle to proceed with treatment. Patients who do not meet these criteria may resume treatment later in the cycle once criteria are met. Cycles and days are numbered continuously regardless of any dose holds or delays in resumption of treatment.

- Adequate blood pressure control, as detailed in Section 6.3
- Serum creatinine ≤ 1.5 x the institutional upper limit of normal
- Liver function tests (AST and ALT) ≤ 3 x the institutional upper limit of normal
- ECOG performance status of 0, 1 , or 2
- No evidence of life-threatening medical problems
- Urine protein:creatinine ratio OR urine dipstick protein as detailed in Section 6.5

5.2.4 Pre-Cycle 1 Therapy: Translational Component

All patients are required to participate in the translational component of the trial. The presence of biopsiable disease should be determined before patients sign the informed consent based upon assessment of prior imaging studies. If a patient previously deemed to be biopsiable is subsequently found to not have safely biopsiable disease, the patient is not prejudiced from receiving treatment. Biopsiability should be re-determined at the time of each mandatory biopsy; if the patient does not have disease that can be safely biopsied at that time, the planned biopsy should be waived. Drug therapy will be initiated after acquisition of initial translational components and dispensed for the 28-day cycle. Translational component sample acquisition will occur as detailed in Section 9.

5.3 Agent Administration

5.3.1 Cediranib

Cediranib at the appropriate dose level will be given orally continuously each morning on an empty stomach, either 1 hour before or 2 hours after breakfast. Subjects should not "make up" a missed dose or a dose that was vomited. Subjects should take cediranib with a glass of water.

Cediranib will be dispensed at the start of each cycle. Patients will be provided with a pill diary for each drug (Appendix B), instructed in its use, and asked to bring it with them to each appointment.

Frequent blood pressure monitoring is important in patients receiving cediranib. Clinical trials of cediranib demonstrate that increases in blood pressure may occur following dosing with cediranib for a number of weeks and that these increases may occur relatively quickly when starting the drug. Patients will be asked to record twice-daily blood pressure readings (Appendix C). If two successive systolic readings are >140 mmHg OR two successive diastolic readings are >90 mmHg OR any combination of elevated systolic and diastolic blood pressure are observed, patients will be instructed to contact their physician as soon as possible. Patients should seek medical advice if their BP exceeds 180 mmHg (systolic) or 105 mmHg (diastolic) at any time and should also be encouraged to contact their physician if they are concerned about any symptoms that may be associated with high blood pressure (*e.g.*, headache). Section 6 includes specific guidelines on the management and, if appropriate, dose modifications for treatment-emergent hypertension.

5.3.2 Olaparib (tablet formulation)

Olaparib at the appropriate dose level will be given orally continuously twice daily, with doses taken at the same times each day approximately 12 hours apart. The correct number of 100mg or 150mg tablets comprising the appropriate dose should be taken at the same times each day with approximately 240 mL of water. The morning dose may be taken approximately 1 hour after the cediranib dose, following a light meal/snack. The evening dose may be taken with a light meal/snack. The olaparib tablets should be swallowed whole and not chewed, crushed, dissolved, or divided.

Olaparib will be dispensed at the start of each cycle. Patients will be provided with a pill diary (Appendix B), instructed in its use, and asked to bring it with them to each appointment.

If vomiting occurs shortly after the olaparib tablets are swallowed, the dose should only be replaced if all of the intact tablets can be seen and counted. Should any patient enrolled on the study miss a scheduled dose, the patient will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If greater than 2 hours after the scheduled dose time, the missed dose should not be taken, and the patient should take their allotted dose at the next scheduled time. Subjects should avoid grapefruit juice while on study, due to P450 interactions.

5.4 General Concomitant Medication and Supportive Care Guidelines

Cediranib demonstrated minimal inhibitory effects on the activity of CYP3A4 (testosterone and midazolam) *in vitro*, although the IC_{50} was far in excess of the clinically relevant concentrations. Based on *in vitro* and clinical exposure data, olaparib is considered unlikely to cause clinically significant drug interactions through inhibition or induction of cytochrome P450 enzyme activity. However, *in vitro* data have also shown that the principal enzyme responsible for the

formation of the 3 main metabolites of olaparib is CYP3A4. Given these data, potent inhibitors or inducers of CYP3A4 as outlined in Appendix D must not be used during this study for patients receiving olaparib. Moderate inhibitors of CYP3A4 should be avoided. If the inhibitor cannot be avoided, the olaparib tablet should be reduced by 50% during the duration that the patient remains on the moderate CYP3A4 inhibitor, as per below the table below. Dihydropyridine calcium-channel blockers are allowed for management of hypertension.

Olaparib tablet dose	**Olaparib tablet dose on moderate CYP3A inhibitor**
200mg BID	100mg BID
150mg BID	150mg daily (patient should take AM dose)
100mg BID	100mg daily (patient should take AM dose)

Because of the potential for interaction of cediranib with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies.

Patient should receive general concomitant and supportive care medications based on best medical practice. Neupogen and other bone marrow-supportive agents, including erythropoiesis-stimulating agents, are not allowed during treatment.

Other anti-cancer therapy while on study treatment is not permitted.

Prophylactic use of bisphosphonates in patients without bone disease is not permitted, except for the treatment of osteoporosis.

The use of any natural/herbal products or other "folk remedies" is not allowed on study. All medications must be recorded in the case report form and be reviewed by the treating physician at each visit.

Frequent **blood pressure monitoring** is important in patients receiving cediranib. Experience to date suggests that increases in blood pressure may occur following dosing with cediranib for a number of weeks and that these increases may occur over a relatively short time frame. It is imperative that the investigator institute appropriate measures to control BP. This may necessitate changes to existing antihypertensive medication, addition of new medication(s), and/or interruption/withdrawal of cediranib. Patients will be provided blood pressure cuffs and must be able and willing to monitor their blood pressure on a twice daily basis.

Supply and Distribution: Blood pressure cuffs will be supplied by VWR. Each kit contains a blood pressure monitor (which includes standard size cuff), an adaptor and a large size cuff. Kits will be shipped in the original manufacturer's packaging.

Ordering Instructions: No starter supplies are available. Sites are permitted to order a maximum of 10 Blood Pressure kits at a time for enrolled patients. To obtain the kits, please complete the "Blood Pressure Kit Order Request Form" and email it to the VWR staff listed on the form. The form is available on the CTSU website.

Section 6 includes specific guidelines on the management and, if appropriate, dose modifications for treatment-emergent hypertension.

Because of the rapid changes in blood pressure that can occur and the potential for severe life-threatening complications if hypertension is not appropriately managed, patients should check their blood pressure twice daily for at least the first 8 weeks after starting study drug, or, if anti-hypertensive management is required, until a stable anti-hypertensive regimen has been established, even if this requires more than 8 weeks. After 8 weeks or once a stable regimen has been achieved, blood pressure monitoring may be reduced to once daily. Twice daily monitoring should be re-implemented after any cediranib hold/dosing delay for two weeks or until the patient is re-established on a stable anti-hypertensive regimen, whichever takes longer. Patient blood pressures should be reviewed with the study team on a weekly basis for the first 8 weeks of study treatment to ensure that blood pressure guidelines are being correctly followed.

Cediranib can impair healing. For this reason, cediranib should be held two weeks prior to any surgical procedures and may be restarted when the surgical wound is healed. Patients who have had major surgical procedure, open biopsy, or significant traumatic injury within 28 days of starting cediranib are not eligible for the study, as per Section 3.2.16.

5.5 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue on until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

5.6 Duration of Follow Up

Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. All participants' vital status may be followed after removal from the study treatment using publically available databases.

5.7 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. 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 web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

6.1 Olaparib and Cediranib Dose Modification Tables

The dose levels and the general approach to dose modification of olaparib and cediranib combination therapy are shown below. AEs should be treated with the appropriate maximum supportive care, and dose reductions should be clearly documented in the case report form.

Dose Level	Olaparib tablets
-2	100 mg twice daily
-1	150 mg twice daily
1	200 mg twice daily

Dose level	Cediranib tablets
-2	15 mg daily
-1	20 mg daily
1	30 mg daily

6.2 General Management of Adverse Events

The management of general adverse events not otherwise specified will be as per the table below. Management of specific toxicities, including hypertension, proteinuria, decreased in

LVEF, diarrhea, fever and neutropenia, nausea and vomiting, thyroid toxicities, reversible posterior leukoencephalopathy syndrome (RPLS), and gastrointestinal perforation will be as further outlined in specific sections 6.3-6.11.

General Management of Adverse Events (Non-Hematologic)

Observation	Action
AE resolves promptly with supportive care	Maintain dose level
Any grade 2 non-hematologic AE (excluding hypertension or other AEs with specific management instructions outlined in the sections below, or easily correctable asymptomatic grade 2 laboratory abnormalities) related to cediranib or olaparib that persists despite maximal support.	Hold study drug(s)[1] for up to 14 days until toxicity resolves to ≤ grade 1. Treatment may be restarted at one dose level lower for the drug(s) causing the toxicity, as per the dose reduction levels in Section 6.1, at the treating investigator's discretion.[2] The overall PI of the study should be informed regarding all dose modifications. Patients whose toxicity has not resolved after 14 days will be removed from study. Patients experiencing persistent Grade 2 fatigue that is felt to be acceptable by both patient and treating investigator may continue on study drug without dose hold or reduction at the treating investigator's discretion.
Any ≥grade 3 non-hematologic (excluding grade 3 hypertension or easily correctable asymptomatic grade 3 laboratory abnormalities)	Hold study drug(s)[1] for up to 14 days until toxicity resolves to ≤ grade 1. Treatment may be restarted at one dose level lower for the drug(s) causing the toxicity, as per the dose reduction levels in Section 6.1, at the treating investigator's discretion.[2] The study PI of the study should be informed regarding all dose modifications.
1. Grade 3 or 4 non-hematologic AE related to cediranib and olaparib combination that does not resolve to grade 0-2 within 14 days despite maximum supportive care after treating patient at the lowest reduced dose level.[3] 2. Grade 3 or 4 non-hematologic AE related to cediranib/olaparib lasting >14 days despite maximum supportive care and treatment being	Remove patient from study.

held.	

[1]At the discretion of the investigator, the study drugs may be held or dose modified independently if the observed toxicity is attributed to only one of the drugs, while the patient continued to receive the drug not associated with the observed toxicity. The time a given drug is held should not exceed 14 days.
[2]Patients who are at the lowest reduced dose level may have their drug resumed at that dose level after discussion with the overall PI.
[3]Excluding hypertension. For thromboembolic events, treatment may be resumed at the discretion of the investigator once patient is asymptomatic.

General Management of Adverse Events (Hematologic)

Observation	Action
Absolute neutrophil count ≥1000/mcL **AND** Platelets ≥100,000/mcL **AND** Hemoglobin ≥8 mg/dL	Maintain dose level.
Absolute neutrophil count <1000/mcL **OR** Platelets <100,000/mcL **OR** Hemoglobin <8 mg/dL	Hold treatment for up to 14 days until absolute neutrophil count ≥1000/mcL, platelets ≥100,000/mcL, and hemoglobin ≥8 mg/dL. Treatment may be restarted at one dose level lower for the drug(s) causing the toxicity, as per the dose reduction levels in Section 6.1, at the treating investigator's discretion. The study PI of the study should be informed regarding all dose modifications.[1] Patients whose counts have not recovered to absolute neutrophil count ≥1000/mcL, platelets ≥100,000/mcL, and hemoglobin ≥8 mg/dL after 14 days should be removed from study.
Grade 4 hematologic AE related to cediranib or olaparib that does not resolve to absolute neutrophil count ≥1000/mcL, platelets ≥100,000/mcL, and hemoglobin ≥8 mg/dL despite maximum supportive care after 14 days.	Remove patient from study.

[1]At the discretion of the investigator, the study drugs may be held or dose modified independently if the observed toxicity is attributed to only one of the drugs, while the patient continued to receive the drug not associated with the observed toxicity. The time a given drug is held should not exceed 14 days.

For AEs that are unrelated to the study drugs, study drug may be held for up to 14 days at the discretion of the treating investigator. Drug holds of greater than 14 days for unrelated AEs where the patient is experiencing ongoing clinical benefit may be considered after discussion with the overall PI.

Patients experiencing ongoing clinical benefit who experience a related AE where continuation of one of the drugs is considered, in the judgment of the treating investigator AND overall PI, to be potentially life-threatening or with the potential for long-term harm to the patient, may be allowed to continue on the unrelated drug after discussion with the overall PI.

6.3 Hypertension

Increases in BP and cases of hypertension have been associated with many drugs acting on the VEGF pathway. The proposed mechanism for this increase is through inhibition of VEGF-induced peripheral vasodilation. Hypertension following cediranib treatment has been seen in animal studies as well as clinical trials.

Only doses of cediranib will be modified for hypertension; olaparib doses will not be reduced unless other toxicities are experienced. Patients receiving cediranib will be provided with blood pressure monitors for home use and will check and record their blood pressures at least twice daily while on study treatment.

See the table below for guidelines on hypertension management and Appendix G for suggested antihypertensive medications by class.

Note:

- If patients require a delay of >2 weeks for management of hypertension, management should be discussed with the overall PI and may require discontinuation from protocol therapy
- Patients may have up to 4 drugs for management of hypertension prior to any dose reduction in cediranib.
- Hypertension should be graded using the NCI CTCAE v4.0 until March 31, 2018. CTCAE version 5.0 should be utilized beginning April 1, 2018. Patients with baseline hypertension who require the addition of new medications for hypertension management while on study drug may not have an increase in CTCAE grade, but a change in attribution should be noted.
- Note: Stopping or reduce the dose of cediranib is expected to cause a decrease in BP. The treating physician should monitor the patient for hypotension and adjust the number and dose of antihypertensive medications accordingly.

Table 6.3: Hypertension Monitoring and Management
• See Appendix G for suggested antihypertensive medications by class • Abbreviations: Angiotensin Converting Enzyme (ACE) Inhibitors, Angiotensin II Receptor Blockers (ARB), selective beta blockers (BB), Dihydropyridine calcium channel blockers

(DHP-CCP)

- If patients require a delay of >2 weeks for management of hypertension, discontinuation of cediranib or protocol therapy may be considered after discussion with the Study Chair.
- Patients may have up to 4 drugs for management of hypertension prior to any dose reduction in cediranib
- Hypertension should be graded using the NCI CTCAE v4.0 until March 31, 2018. CTCAE version 5.0 will be utilized beginning April 1, 2018. Please note: patients may have baseline hypertension meeting CTCAE grading criteria on study entry. Should patients require increase in dosing of BP medication or increased number of medications, they should then be noted to have hypertension related to study drug, with grading as per CTCAE v4.0 criteria until March 31, 2018. CTCAE version 5.0 should utilized beginning April 1, 2018. Baseline grade of hypertension should also be recorded in the patient's record.
- Note: Stopping or reduce the dose of cediranib is expected to cause a decrease in BP. The treating physician should monitor the patient for hypotension and adjust the number and dose of antihypertensive medications accordingly.

Event	Definition	Antihypertensive Therapy	Blood Pressure Monitoring	Cediranib Dose Modification
Grade 1	Asymptomatic transient (<24 hours) increase by >20 mmHg diastolic or to ≥ 140/90 mmHg if previously WNL	Consider early initiation of BP medication for BP > 140/90 mmHg that is confirmed on a second reading. Cediranib can cause rapid escalation in BP, and early initiation of BP management can reduce likelihood of HTN-related complications.	Continue standard BP monitoring per treating MD and confirm resolution of BP to <140/90 mmHg within 24 hours.	None
Grade 2	Recurrent or persistent (>24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to ≥ 140/90 mmHg if previously WNL Monotherapy may be indicated	Initiate BP medication for first line treatment. *Suggestions:* ACE-inhibitor Escalate dose of medication in step-wise fashion until BP is controlled or at a maximum dose If BP is not controlled to < 140/90 mmHg with one drug regimen, then add a	Increase frequency of monitoring until stabilized to BP <140/90 mmHg	Do not hold cediranib unless otherwise clinically necessary

		second agent. **Study drug does not need to be held unless otherwise clinically necessary** *Consider renal consult*		
Grade 3	Requiring more than one drug or more intensive therapy than previously.	Maximize 2 drug regimen • *Suggestions:* ACE-inhibitor + BB Escalate doses of existing medication until BP is controlled or at a maximum dose. If BP is not controlled to < 140/90 mmHg with two drug regimen, then add a third agent. **Study Drug will not be held during trial of two drug combinations. Additional anti-hypertensive drugs, up to a total of 4, may be maximized for blood pressure control.** *Consider consult with a blood pressure management specialist if greater than 3 drugs are required for BP control.*	Increase frequency of monitoring until stabilized to BP <140/90 mmHg	Do not hold cediranib or other study drugs unless BP is not decreased to less than 150/100 mmHg 48 hours after multi-drug therapy is instituted or if clinical symptoms worsen (e.g. headache). If BP is not controlled to less than 150/100 mmHg with maximal therapy or if clinical symptoms worsen, then hold cediranib (up to 14 days) until maximum effect of the anti-hypertensive agents is achieved. If BP is reduced to less than 140/90 within 14 days, cediranib may be resumed at prior dose.

Grade 4	If threatening consequences OR SBP ≥ 180mmHg OR DBP ≥ 110mmHg	Initiate treatment Hospitalize patient for ICU management, IV therapy as necessary 14 days are allowed to maximize the full effect of anti-hypertensive agents.	Intensive BP monitoring (hospitalization if necessary)	**Hold cediranib.** If BP is reduced to less than 140/90 within 14 days, cediranib may be resumed at a reduced dose after discussion with the Study PI and/or sponsor.

6.4 Diarrhea

Diarrhea is often observed with cediranib, and active and early management of diarrhea is recommended even with grade 1 diarrhea. Management as follows:

Management of Diarrhea

Toxicity	Management/Modifications
Initial grade 1 or 2 diarrhea:	Patients can take loperamide (per standard practice) and continue to take loperamide until patients are free from diarrhea for at least 12 hours. The dose of loperamide should not exceed 16 mg in a 24-hour period.
	If diarrhea persists despite 24 hours of loperamide treatment, hold cediranib for a maximum of 7 days, continue loperamide, and maintain hydration. Cediranib may be restarted at the same dose once patients have been free from diarrhea for 12 hours.
For either persistent grade 2 diarrhea or grade 3 or 4 diarrhea:	Follow 6.2

6.5 Proteinuria

Proteinuria has been observed in cediranib studies. Patients with a urine protein to creatinine ratio (UPC) of greater than 1.0 at entry are ineligible. Increases in proteinuria may occur during treatment and should be managed as follows:

Management of Proteinuria

Proteinuria Value if following by U/A	Monitoring	Dose modification
Greater than 2+ on urine dipstick or U/A **AND** Creatinine ≤1.5x ULN	Perform UPC.	Continue study drugs at planned dose.
Greater than 2+ on urine dipstick or U/A **AND** Creatinine >1.5x ULN	Perform UPC.	**HOLD cediranib** until results of UPC are known, and see below
Based on results of the UPC†:		
UPC ≤ 1.0	Continue monitoring prior to each cycle as per previous.	Continue study drugs at planned dose
UPC > 1.0 and ≤ 3.5 **AND** Creatinine ≤1.5x ULN	Perform UPC prior to each cycle.	Continue study drugs at planned dose.
UPC > 3.5 **OR** Creatinine >1.5x ULN	Perform UPC prior to each cycle.	**Hold cediranib** for up to 7 days and repeat UPC and Creatinine assessment. If UPC resolves to <3.5 and Creatinine to ≤1.5x ULN, resume cediranib with reduction in cediranib by one dose level. Consider consultation with nephrologist.
†If UPC is <1.0 and creatinine >1.5x ULN, AE management should be followed as per Table 6.2.		

6.6 Decrease in LVEF

Patients who have any of the following should undergo an echocardiogram (ECHO) or multi-gated acquisition (MUGA) scan at baseline and every four cycles while on study:

1. Prior treatment with anthracyclines
2. Prior treatment with trastuzumab
3. A NYHA classification of II controlled with treatment (see Appendix E)
4. Prior central thoracic RT, including RT to the heart
5. History of myocardial infarction within the prior 12 months.

The decision to continue or hold cediranib/olaparib is based on the LVEF as it relates to the institution's lower limit of normal (LLN) **and** change in ejection fraction from screening (LVEF as measured at registration) according to the following table. If the institution's LLN is not specified, an LVEF of 55% should be considered the LLN threshold:

Management and Monitoring of Decreased LVEF

Relationship of LVEF to Institution's LLN	LVEF Decrease <10%	LVEF Decrease 10-15%	LVEF Decrease ≥16%
Normal	Continue	Continue	Continue and repeat MUGA/ECHO within 1-2 cycles. If LVEF decrease persists, remove from protocol therapy.

Participants with symptomatic decrease in LVEF attributed to study drugs should be removed from protocol therapy.

6.7 Fever and Neutropenia

Patients who develop fever and neutropenia will be managed via standard medical practice and American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) guidelines. Patients will need to recover from fever and active infectious issues prior to resuming therapy. Growth factors such as Neupogen or Neulasta may not be used.

6.8 Nausea and Vomiting

Olaparib: Events of nausea and vomiting are known to be associated with olaparib treatment. They are generally mild to moderate (CTCAE Grade 1 or 2) severity, intermittent and manageable on continued treatment. No routine prophylactic anti-emetic treatment is required at the start of study treatment; however, patients should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local treatment practice guidelines.

6.9 Thyroid Toxicities

The use of cediranib has been associated with elevations of the TSH and patients should be managed as per the following schema and chart:

Monitoring and Management of Thyroid Toxicities

Result of TSH, T4, and T3	Action

Increases of TSH with normal T4/T3:	Monitor
Increases in TSH with normal T4/T3 and adverse events suggestive of incipient hypothyroidism:	Consider replacement thyroxine.
Increase in TSH with reductions in T4 and T3:	Consider replacement thyroxine

In all of the above cases, study treatment should continue unless clinically contraindicated. Referral to an endocrinologist should also be considered if thyroid abnormalities occur. Patients already on thyroid replacement hormone who require adjustment of their replacement regimen will be considered to have a drug-related toxicity.

6.10 Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Cases of MRI-documented posterior reversible encephalopathy syndrome (PRES), including RPLS, have been reported in patients receiving cediranib in clinical studies. Cediranib should be held in patients with symptoms/signs suggestive of RPLS, pending work-up and management, including control of blood pressure, if hypertension is present. Cediranib should be discontinued upon diagnosis of RPLS. After consultation with the PI and the NCI, consideration of restarting the study may be evaluated in light of any clinical benefit.

6.11 Gastrointestinal Perforation

Gastrointestinal perforation, sometimes associated with fistula formation, has been observed in patients receiving cediranib. Some events of gastrointestinal perforation have been fatal but causality could not be unequivocally assigned to cediranib.

Cediranib should be permanently discontinued in those patients who experienced gastrointestinal perforation or fistula. All events of gastrointestinal perforation are followed-up and an assessment should be made on their relationship to the underlying tumor.

6.12 Rotator Cuff Injury

A limited number of patients have experienced rotator cuff injuries while receiving the combination of cediranib and olaparib. Patients should therefore be monitored closely for the development of any shoulder pain or weakness.

Management of Rotator Cuff Symptoms			
Grade	Symptoms/Findings	Action	Dose modifications
1	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not	Limit heavy lifting or carrying of heavy objects, bags or backpacks.	None.

	indicated	Consider shoulder MRI if symptoms warrant.	
2	Moderate; minimal, local, or noninvasive intervention indicated; limiting age appropriate instrumental ADL	Obtain shoulder MRI if not previously obtained. If rotator cuff injury present on MRI, refer for physical therapy. Consider referral to orthopedics for evaluation as appropriate.	If deemed study-drug related, hold cediranib and olaparib for up to 14 days until symptoms resolve to Grade 1 or less. Cediranib and olaparib may then be resumed at a reduced dose level of each study drug. If patient is on the lowest dose level(s) of cediranib or olaparib, please contact the study PI to discuss dose modifications.
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Obtain shoulder MRI if not previously obtained. Refer to orthopedic surgeon for evaluation.	If deemed study-drug related, hold cediranib and olaparib for up to 14 days until symptoms resolve to Grade 1 or less. Cediranib and olaparib may then be resumed at a reduced dose level of each study drug after discussion with the overall PI.

6.13 Myelodysplastic Syndrome

Myelodysplastic syndrome (MDS) has been described in patients receiving olaparib. To monitor for any potential development of MDS, patients who have treatment held for hematologic toxicities should have blood counts and differentials checked at least weekly until recovery. If counts do not improve to CTCAE grade 1 or better despite drug cessation for 4 weeks, patients should be referred to a hematologist for further assessment. A bone marrow analysis should be considered per hematology assessment.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of

reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset of AEs, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. The SPEER is a list of events that are protocol-specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm for further clarification.

The CAEPR may not provide frequency data; if not, refer to the Investigator's Brochure for this information.

NOTE: The highest grade currently reported is noted in parentheses next to the AE in the SPEER. Report **ONLY** AEs higher than this grade expeditiously. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

7.1.1 CAEPRs for CTEP IND Agent(s)

7.1.1.1 CAEPR for Olaparib

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Olaparib (AZD2281, NSC 747856)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2073 patients.* Below is the CAEPR for Olaparib (AZD2281).

> **NOTE**: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, April 24, 2019[1]

Adverse Events with Possible Relationship to Olaparib (AZD2281) (CTCAE 5.0 Term) [n= 2073]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 4)***
GASTROINTESTINAL DISORDERS			

Adverse Events with Possible Relationship to Olaparib (AZD2281) (CTCAE 5.0 Term) [n= 2073]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Abdominal distension		
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		
Fatigue			***Fatigue (Gr 3)***
	Fever		
INFECTIONS AND INFESTATIONS			
	Infection[2]		
INVESTIGATIONS			
	Creatinine increased		
	Lymphocyte count decreased		
	Neutrophil count decreased		
	Platelet count decreased		
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy	
		Myelodysplastic syndrome	
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
		Pneumonitis	

NOTE: New Primary Malignancies other than MDS/AML
New primary malignancies have been reported in <1% of patients. There were other contributing factors/potential alternative explanations for the development of the new primary malignancy in all cases, including documented *BRCA* mutation, treatment with radiotherapy and extensive previous chemotherapy including carboplatin, taxanes, anthracyclines and other alkylating and DNA damaging agents. Most are not attributed to olaparib.

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting

PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATION SOC.

Adverse events reported on olaparib (AZD2281) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that olaparib (AZD2281) caused the adverse event:

CARDIAC DISORDERS - Cardiac disorders - Other (nodal rhythm); Chest pain - cardiac; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Tinnitus
ENDOCRINE DISORDERS - Hypothyroidism
GASTROINTESTINAL DISORDERS - Ascites; Colitis; Colonic obstruction; Dry mouth; Dysphagia; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intestinal perforation); Ileus; Jejunal perforation; Mucositis oral; Pancreatitis; Periodontal disease; Rectal hemorrhage; Small intestinal obstruction; Stomach pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Malaise; Non-cardiac chest pain
IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (systemic inflammatory response syndrome)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fracture; Gastrointestinal anastomotic leak; Injury, poisoning and procedural complications - Other (vena cava injury); Wound dehiscence
INVESTIGATIONS - Alanine aminotransferase increased; Aspartate aminotransferase increased; Blood bilirubin increased; GGT increased; Hemoglobin increased; Lipase increased; Serum amylase increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hypermagnesemia; Hypocalcemia; Hypokalemia; Hypomagnesemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Avascular necrosis; Bone pain; Generalized muscle weakness; Muscle cramp; Muscle weakness lower limb; Myalgia; Neck pain; Pain in extremity; Rotator cuff injury
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Amnesia; Ataxia; Cognitive disturbance; Concentration impairment; Encephalopathy; Intracranial hemorrhage; Peripheral sensory neuropathy; Stroke; Syncope; Transient ischemic attacks
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Delirium; Hallucinations; Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (decreased glomerular filtration rate); Renal and urinary disorders - Other (hydronephrosis); Urinary tract obstruction
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Oropharyngeal pain; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (chronic obstructive pulmonary disease)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Pruritus; Rash maculo-papular
VASCULAR DISORDERS - Flushing; Hot flashes; Hypertension; Hypotension; Thromboembolic event

Note: Olaparib (AZD2281) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.1.1.2 CAEPR for Cediranib

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Cediranib (AZD2171, NSC 732208)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or

potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1608 patients.* Below is the CAEPR for Cediranib (AZD2171).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.15, November 7, 2018[1]

Adverse Events with Possible Relationship to Cediranib (AZD2171) (CTCAE 5.0 Term) [n= 1608]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
		Hemolytic uremic syndrome	
		Thrombotic thrombocytopenic purpura	
CARDIAC DISORDERS			
		Heart failure	
		Left ventricular systolic dysfunction	
ENDOCRINE DISORDERS			
	Hyperthyroidism		
	Hypothyroidism		***Hypothyroidism (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
	Anal mucositis		***Anal mucositis (Gr 2)***
	Constipation		***Constipation (Gr 3)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dysphagia		***Dysphagia (Gr 2)***
		Gastrointestinal fistula[2]	
		Gastrointestinal perforation[3]	
	Mucositis oral		***Mucositis oral (Gr 3)***
Nausea			***Nausea (Gr 3)***
		Pancreatitis	
	Rectal mucositis		***Rectal mucositis (Gr 2)***
	Small intestinal mucositis		***Small intestinal mucositis (Gr 2)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
HEPATOBILIARY DISORDERS			
		Hepatic failure	
INFECTIONS AND INFESTATIONS			
	Infection[4]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Wound complication	

Adverse Events with Possible Relationship to Cediranib (AZD2171) (CTCAE 5.0 Term) [n= 1608]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 3)***
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 3)***
	Lymphocyte count decreased		
	Neutrophil count decreased		
	Platelet count decreased		
	Thyroid stimulating hormone increased		***Thyroid stimulating hormone increased (Gr 2)***
	Weight loss		***Weight loss (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Generalized muscle weakness		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 3)***
	Lethargy		
		Leukoencephalopathy	
		Reversible posterior leukoencephalopathy syndrome	
RENAL AND URINARY DISORDERS			
		Nephrotic syndrome	
	Proteinuria		***Proteinuria (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Laryngeal mucositis		***Laryngeal mucositis (Gr 2)***
	Pharyngeal mucositis		***Pharyngeal mucositis (Gr 2)***
	Tracheal mucositis		***Tracheal mucositis (Gr 2)***
Voice alteration			***Voice alteration (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Palmar-plantar erythrodysesthesia syndrome		***Palmar-plantar erythrodysesthesia syndrome (Gr 2)***
VASCULAR DISORDERS			
		Arterial thromboembolism	
Hypertension			***Hypertension (Gr 3)***
	Thromboembolic event		***Thromboembolic event (Gr 4)***
	Vascular disorders - Other (hemorrhage)[5]		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting

PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Gastrointestinal fistula includes Anal fistula, Colonic fistula, Duodenal fistula, Esophageal fistula, Enterovesical fistula, Gastric fistula, Gastrointestinal fistula, Ileal fistula, Jejunal fistula, Oral cavity fistula, Pancreatic fistula, Rectal fistula, and Salivary gland fistula under the GASTROINTESTINAL DISORDERS SOC.

[3]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

[4]Infections includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[5]Hemorrhage is a known consequence of VEGF/VEGFR signaling inhibition. The majority of hemorrhage events reported were mild; however, serious events, defined as symptomatic bleeding in a critical area or organ system (e.g., eye, gastrointestinal tract, genitourinary [GU] tract, respiratory tract, and nervous system) have been reported.

Adverse events reported on cediranib (AZD2171) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that cediranib (AZD2171) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Blood and lymphatic system disorders - Other (polycythemia); Bone marrow hypocellular; Febrile neutropenia
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac arrest; Cardiac disorders - Other (premature ventricular complexes); Cardiac disorders - Other (valvular heart disease); Chest pain - cardiac; Mobitz (type) II atrioventricular block; Myocardial infarction; Palpitations; Pericardial effusion; Pericarditis; Restrictive cardiomyopathy; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia
EAR AND LABYRINTH DISORDERS - Ear and labyrinth disorders - Other (ears feel full/plugged); Ear and labyrinth disorders - Other (viral labyrinthitis); Tinnitus; Vertigo
EYE DISORDERS - Blurred vision; Eye disorders - Other (blindness); Eye disorders - Other (visual disturbance); Papilledema; Photophobia; Retinal vascular disorder
GASTROINTESTINAL DISORDERS - Abdominal distension; Anal pain; Ascites; Bloating; Colitis; Colonic obstruction; Duodenal ulcer; Dyspepsia; Enterocolitis; Esophageal necrosis; Esophageal ulcer; Esophagitis; Flatulence; Gastric necrosis; Gastric ulcer; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (hydrops); Gastrointestinal disorders - Other (tongue sensitivity); Ileus; Oral pain; Periodontal disease; Peritoneal necrosis; Rectal pain; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema face; Edema limbs; Fever; Gait disturbance; Hypothermia; Malaise; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Cholecystitis; Gallbladder obstruction; Hepatic pain; Hepatobiliary disorders - Other (bile duct obstruction); Hepatobiliary disorders - Other (jaundice cholestatic)
IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Immune system disorders - Other (systemic inflammatory response syndrome)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Dermatitis radiation; Fracture; Injury, poisoning and procedural complications - Other (tracheostomy malfunction); Intestinal stoma leak; Venous injury; Wound dehiscence
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood bilirubin increased; Blood lactate dehydrogenase increased; CPK increased; Cardiac troponin I increased; Cardiac troponin T increased; Cholesterol high; Creatinine increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; GGT increased; Hemoglobin increased; INR increased; Investigations - Other (elevated ammonia level); Investigations - Other (increased blood erythropoietin); Lipase increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Metabolism and nutrition disorders - Other (failure to thrive)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Avascular necrosis; Back

pain; Bone pain; Chest wall pain; Muscle cramp; Muscle weakness lower limb; Muscle weakness upper limb; Myalgia; Myositis; Neck pain; Pain in extremity; Rotator cuff injury
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Central nervous system necrosis; Cognitive disturbance; Depressed level of consciousness; Dysarthria; Dysgeusia; Dysphasia; Encephalopathy; Hydrocephalus; Ischemia cerebrovascular; Memory impairment; Muscle weakness left-sided; Nervous system disorders - Other (coma); Nervous system disorders - Other (right hemiparesis); Olfactory nerve disorder; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Somnolence; Spinal cord compression; Stroke; Syncope; Transient ischemic attacks; Tremor
PSYCHIATRIC DISORDERS - Confusion; Delirium; Depression; Hallucinations; Insomnia; Suicide attempt
RENAL AND URINARY DISORDERS - Acute kidney injury; Chronic kidney disease; Cystitis noninfective; Hematuria; Urinary retention; Urinary tract obstruction
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation; Menorrhagia; Vaginal fistula
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Aspiration; Hypoxia; Pharyngolaryngeal pain; Pleural effusion; Pneumonitis; Pneumothorax; Pulmonary edema; Pulmonary fistula; Pulmonary hypertension; Sinus pain
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Nail loss; Pruritus; Purpura; Rash acneiform; Rash maculo-papular; Skin and subcutaneous tissue disorders - Other (petechiae); Skin and subcutaneous tissue disorders - Other (plantar warts); Skin ulceration; Urticaria
VASCULAR DISORDERS - Capillary leak syndrome; Flushing; Hypotension; Vasculitis

Note: Cediranib (AZD2171) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. 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 web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 7.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.
  - Other AEs for the protocol that do not require expedited reporting are outlined in section 7.3.4.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.

- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 7.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

7.3.2 CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

The Coordinating Center of the Corresponding Organization is responsible for submitting to the CTSU documentation of AEs that they deem reportable for posting on the CTSU protocol web page and inclusion on the CTSU bi-monthly broadcast.

7.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

7.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through**

CTEP-AERS must <u>also</u> be reported in routine study data submissions.

7.5 Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

7.6 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

7.7 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports or sentinel events that require reporting according to institutional policy.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agents administered in this study can be found in Section 7.1.

8.1.1 Olaparib (AZD2281) (NSC 747856)

Chemical Name: 4-[(3-{[4-(cyclopropylcarbonyl)piperazin-1-yl]carbonyl}-4-fluorophenyl)methyl]phthalazin-1(2*H*)-one

Other Names: AZD2281; KU-0059436; CO-CE 42

Classification: PARP inhibitor

CAS Registry Number: 763113-22-0

Molecular Formula: $C_{24}H_{23}FN_4O_3$

M.W.: 434.46

Approximate Solubility: 0.1 mg/mL pH independent solubility across physiologic range

Mode of Action: Olaparib is an inhibitor of subclasses 1, 2, and 3 of polyadenosine 5' diphosphoribose polymerase (PARP-1, PARP-2, and PARP-3). In tumors that are deficient in the homologous recombination DNA repair pathway (example, BRCA mutants), inhibition of PARP by olaparib causes accumulation of DNA double-strand breaks and genomic instability. Olaparib may also enhance the effects of DNA damage caused by ionizing radiation and chemotherapy.

Description: crystalline solid

How Supplied: AstraZeneca supplies and the CTEP, DCTD distributes olaparib as green, film-coated tablets in 100 mg and 150 mg strengths.

- 100 mg tablets are 14.5 mm x 7.25 mm oval-shaped
- 150 mg are 14.5 mm x 7.25 mm oval-shaped

Tablets are packaged in induction-sealed high-density polyethylene (HDPE) bottles with child-resistant closures. Each bottle contains 32 tablets with desiccant.

Tablet core components include active drug substance, copovidone, colloidal silicon dioxide, mannitol and sodium stearyl fumarate. Film coating contains hydroxypropyl methylcellulose (hypromellose), macrogol 400 (polyethylene glycol 400), titanium dioxide, iron oxide yellow and iron oxide black.

Storage: Store in a secure location below 30° C (86° F). Sites are not permitted to re-package tablets. Once the bottle is opened, olaparib tablets must be used within 3 months of the opening date; unused tablets should be discarded. Instruct patients not to open a bottle until they are ready to use it.

Stability: Shelf-life studies are ongoing. If a storage temperature excursion is identified, promptly return olaparib to < 30 °C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Route of Administration: Tablets can be taken by mouth with a light meal/snack.

Potential Drug Interactions: *In vivo* data indicate that CYP3A4/5 is important for olaparib metabolism and clearance in humans. For this reason, avoid concomitant administration of strong and moderate CYP 3A4/5 inducers and inhibitors. Consult the protocol document

or study investigator prior to making any dose adjustments related to potential drug-drug interactions.

In vitro data shows olaparib is a substrate for P-glycoprotein (P-gp), but not for organic anion-transporting polypeptides (OATP1B1 and OATP1B3), organic cation transporter 1 (OCT1), multi-drug resistance protein 2 (MRP-2) efflux transporter or breast cancer resistance protein (BCRP). Administration of strong P-gp inhibitors and inducers should be avoided with concurrent olaparib.

Based on *in vitro* data, olaparib inhibits CYP 3A4 and UGT1A1 enzyme systems and induces CYP 1A2, 2B6, and 3A4 and potentially induces CYP 2C9, 2C19 and P-gp. Therefore, avoid concomitant administration of sensitive substrates, particularly those with narrow therapeutic ranges.

Olaparib is also an inhibitor of P-gp, OATP1B1, OCT1, OCT2, OAT3, multi-drug and toxin extrusion proteins (MATE1 and MATE2K) and a weak inhibitor of BRCP, but not an inhibitor of OATP1B3 or MRP-2. *In vitro* studies suggest that olaparib may increase exposure of substrates of these transport systems, although the clinical relevance is not clear. The manufacturer recommends that statins, in particular, should be administered with caution when given concomitantly with olaparib.

Patient Care Implications: Pre-clinical data indicate that olaparib adversely affects embryofetal survival and development. Therefore, study participants and their partners who are of child-bearing potential should agree to use two (2) highly effective forms of contraception throughout their study participation and for three (3) months after the last dose of olaparib. It is recommended that olaparib be held 2 weeks prior to and 2 weeks after any major surgical procedures. Olaparib does not need to be held for simple procedures, such as tooth extraction, port placement, or biopsy.

Because the adverse events related to olaparib may include asthenia, fatigue and dizziness, patients should be advised to use caution while driving or using machinery.

Availability

Olaparib is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Olaparib is provided to the NCI under a Cooperative Research and Development Agreement (CRADA) between AstraZeneca Pharmaceuticals LP (the Pharmaceutical Collaborator) and the DCTD, NCI (see Section 12.3).

8.1.2 AZD2171 (NSC 732208)

Chemical Name: 4-[(4-Fluoro-2-methyl-1*H*-indol-5-yl)oxy]-6-methoxy-7-(3-pyrrolidin 1-ylpropoxy) quinazoline maleate

Other Names: Cediranib, AZD2171 maleate, Recentin™

CAS Registry Number: *288383-20-0 (for the free base)*

Molecular Formula: $C_{25}H_{27}FN_4O_3 \cdot C_4H_4O_4$

Molecular Weight: 566.59 as maleate salt (450.52 as free base)

Approximate Solubility: The aqueous solubility of AZD2171 is 0.0006 mg/mL for the free base (distilled water, pH 8.1 at 25°C) and 1.9 mg/mL for the maleate salt (distilled water, pH 4.4 at 25°C).

Mode of Action: AZD2171 is a highly potent inhibitor of vascular endothelial growth factor receptor (VEGFR) tyrosine kinase activity, which inhibits VEGF-dependent angiogenesis, neovascular survival and vascular permeability.

How Supplied: Astra-Zeneca supplies and CTEP, NCI, DCTD distributes AZD2171. The agent is available as beige film-coated tablets containing,15 mg and 20 mg of AZD2171 free base. The,15 mg and 20 mg tablets are,7 mm and 8 mm in diameter, respectively. Each bottle contains 35 tablets.

Tablet excipients include mannitol, dibasic calcium phosphate anhydrous, sodium starch glycolate, microcrystalline cellulose, and magnesium stearate with a film coat containing hypromellose 2910, polyethylene glycol 400, red iron oxide, yellow iron oxide, black iron oxide, and titanium dioxide.

Storage: Store intact bottles at controlled room temperature [20°C-25°C, (68-77°F)].

Stability: Stability studies are ongoing. Dispense AZD2171 tablets in their original containers. Alternatively, if exact quantity is dispensed in a pharmacy bottle, the supply should be assigned a 30-day expiration.

If a storage temperature excursion is identified, promptly return AZD2171 (cediranib) to controlled room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Route of Administration: Oral. AZD2171 tablets should be taken either one hour before or two hours after meals.

Potential Drug Interactions: Cediranib (AZD2171) clearance is primarily mediated by flavin-containing monooxygenase enzymes (FMO1 and FMO3) and UGT1A4. It is not a substrate of CYP450 enzymes. In vitro studies suggest that cediranib (AZD2171) is a substrate for P-glycoprotein (Pgp), but not breast cancer resistance protein (BCRP). Since clinically relevant induction or inhibition of FMO enzymes is uncommon**,** use caution in

patients taking concomitant medications that are strong inhibitors (e.g. ketoconazole) or strong inducers (e.g. rifampicin, carbamazepine, phenobarbital, phenytoin and St. John's Wort) of UGT1A4 or Pgp in particular. If chronic concomitant administration of strong inducers or inhibitors is unavoidable, consult the protocol document and/or the principal investigator before making any dose adjustments.

In vitro studies using hepatic cultures show that cediranib (AZD2171) did not inhibit CYP 1A2, 2A6, 2C8, 2C9, 2C19 and 2E1 and showed no induction of CYP 1A2, 2B6 and 3A4/5. It did weakly inhibit CYP 2D6 and 3A4/5, but this inhibition not expected to cause any clinically relevant drug interactions. The possibility that cediranib (AZD2171) may induce gastrointestinal CYP3A and UGT enzymes cannot be excluded; therefore the efficacy of hormonal contraceptives may be reduced. Advise women study participants to use an additional non-hormonal contraceptive method.

In vitro studies show that cediranib (AZD2171) is a weak inhibitor of BCRP, Pgp, OATP1B1, OATP1B3, OCT2 and MATE1. Use caution in patients who are taking concomitant medications that are sensitive substrates of these transporters since there is a low potential for drug-drug interactions. *In vivo* studies show that cediranib (AZD2171) could increase exposure of drugs like metformin by inhibiting renal tubular transporter MATE2-K, but this is thought to be infrequent and mild in severity. Cediranib is not an inhibitor of OAT1 or OAT3.

Cediranib (AZD2171) is approximately 95% bound to human plasma proteins, with human serum albumin and α1-acid glycoprotein accounting for most of this binding. Use caution in patients taking concomitant medications with narrow therapeutic ranges that are also highly protein-bound.

Oral anticoagulants are not absolutely contraindicated during treatment with AZD2171 (cediranib); however, use cediranib (AZD2171) with caution and increase monitoring in patients while on study. Patients who receive VEGF inhibitors are at increased risk of bleeding and hemorrhage.

Patient Care Implications: Agents that inhibit VEGF signaling have the potential to affect wound healing; therefore, it is recommended that AZD2171 is stopped two weeks prior to elective surgery and restarted when the surgical wound has healed. Patients should be excluded from participating in clinical studies with AZD2171 if they have had recent (at least two weeks, or until any wound has completely healed) major thoracic or abdominal surgery prior to study start, or a surgical incision that is not fully healed.

Advise women study participants of reproductive potential to use effective contraception while receiving study treatment and for at least 6 weeks after the last dose of cediranib (AZD2171).

Availability

AZD2171 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

AZD2171 is provided to the NCI under a Clinical Trials Agreement (CTA) between AstraZeneca International (the Pharmaceutical Collaborator) and the DCTD, NCI (see Section 12.3).

8.1.3 Agent Ordering and Agent Accountability

8.1.3.1 NCI-supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://ctepcore.nci.nih.gov/OAOP/). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam/index.jsp) and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

8.1.3.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.3.3 Investigator Brochure Availability – The current versions of the IBs for PMB-supplied agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator at IBCoordinator@mail.nih.gov

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Specimen Requirements

Study	Required Specimen	Collection Time Points	Collection Details
BROCA-HR	7 mL whole blood	Baseline[1]	Collect in yellow top (ACD solution A) tube. Specimen to be shipped at ambient temperature for overnight delivery
	FFPE slides (from primary tumor and/or metastatic sites)	Archival	2 consecutive unstained 10 µm charged slides should be provided
	Biopsy specimen	Pre-treatment (mandatory); On-treatment (mandatory);	FFPE core
CEC/CEP	8mL whole blood	Baseline[1], Day 3 before treatment[2]	Collect in CPT citrate tubes. Samples should be stored and shipped at ambient temperature on the same day sample is drawn for overnight delivery.
Plasma Angiome	Two 4mL tubes of blood	Baseline, Cycle 2 Day 1 before treatment, at time of progression	Collect in purple top tubes. Specimens should be processed on site to obtain plasma in pink capped cryovials and then shipped on dry ice.
Whole exome sequencing (WES) and RNAseq	FFPE slides	Archival	Ten unstained charged slides of 10 micron thickness should be provided.
	Biopsy specimen	Pre-treatment (mandatory); On-treatment (mandatory); Post-progression (optional)	At least 2 fresh cores frozen in OCT. Samples should be shipped by courier on dry ice for overnight delivery.

[1]For patients starting treatment on a Friday, samples must be collected prior to the day of starting treatment to allow for appropriate shipping (see 9.2.1.1 and 9.2.2.1 for additional details).
[2]Day 3 is preferable, but if Day 3 specimen cannot be collected and shipped on a Mon-Thurs (excepting holidays), then sample should be collected on the next possible day (Day 4, 5, or 6, as appropriate).

9.2 Integrated Correlative Studies

9.2.1 BROCA testing (Integrated)

9.2.1.1 Collection of Specimen(s)

Please refer to the Specimen Requirements table in Section 9.1.

Whole blood should be collected in a yellow top (ACD solution A) collection tube as described below:

1. Draw 7mL of blood into the labeled yellow top (ACD solution A) tube (BD vacutainer, catalog number 364606).
2. Immediately after collection, gently invert the tube 6 times to mix the blood and ACD solution A.
3. BROCA-HR whole blood should be stored upright at room temperature until the specimen can be shipped. Ship to the University of Washington the day the specimen is collected (See Section 9.2.1.3 for specific shipping instructions). **Ship for Monday through Friday *delivery* only. Do not ship on Fridays or weekends/holidays.** Patients starting protocol treatment on a Friday should have their specimens collected Monday through Thursday prior to starting on study treatment.
4. Waterproof permanent marker or a printed label should be used to label the specimen with the Protocol Number (NCI#9825), Subject Study #, and Baseline Whole Blood.

2 consecutive 10 μm archival FFPE sections (from primary tumor and/or metastatic sites) should be provided on charged slides. Slides should be shipped in an appropriate slide container and labeled with a waterproof permanent marker or a printed label with the Protocol Number (NCI #9825), Subject Study #, and Archival FFPE.

FFPE specimens from pre- and on-treatment biopsies should be collected as specified in Section 9.2.4.1 (Core #1). Core #1 (FFPE, uncut) should be shipped to the Swisher lab. The FFPE specimen should be labeled with the Protocol Number (NCI #9825), Subject Study #, Date of Collection, and Sample timepoint (Pre-treatment Bx or On-treatment Bx).

9.2.1.2 Handling of Specimens(s)

DNA will be extracted from PBMCs and FFPE archived tumor tissue containing at least 30% tumor nuclei. A targeted capture and massively parallel sequencing approach called BROCA1 will be applied to samples. For the proposed study, a more recent version of BROCA with 55 genes (BROCA-HR) that serve as a single assay to test for inherited risk of ovarian carcinoma and for germline and somatic mutations that influence response to therapy will be utilized. Library preparation has been fully automated to increase sample turnaround and lower cost. Paired-end libraries with 350bp inserts will be prepared from 1ug of constitutional or neoplastic DNA and hybridize to a custom pool of oligonucleotides targeting genomic regions as previously described (27) using the SureSelectXT enrichment system on a Bravo liquid-handling instrument (Agilent). Following capture, samples will be barcoded with 48 different indexed primers. The pooled samples are sequenced on a single lane of a HiSeq flowcell (Illumina) with 2x101bp paired end reads and a 7bp index read to allow for de-multiplexing and binning of individual samples. Single nucleotide variants and insertions and deletions will be detected as previously described with some updates in the bioinformatics pipleline (27). Deletions and duplications of

exons will be detected by a combination of depth of coverage and split read analysis as previously described (39), supplemented with additional alignments generated by SLOPE (40). All germline loss of function mutations in cancer susceptibility genes will be confirmed with PCR amplification and Sanger sequencing. Cases will be identified as HR proficient or deficient based on sequencing data of known Fanconi anemia (FA)-BRCA genes and then correlate HR proficiency with response to platinum or PARPi on the trial. Later, in exploratory analyses, we will add in analyses of NHEJ and other modifying genes, genomic scarring, or other somatic tests by our lab or others to complement the determination of HR deficiency.

9.2.1.3 Shipping of Specimen(s)

Please refer to the Specimen Requirements table in Section 9.1 for specific shipping requirements.

Whole blood must be stored and shipped at ambient temperature for overnight delivery Monday-Thursday on the same day the sample was drawn. Whole blood samples should be shipped only for Monday through Friday delivery (do not ship samples on a Friday or holidays/weekends). FFPE specimens may be batched shipped on a monthly or otherwise basis, as coordinated with the Swisher lab. Samples should be shipped with an accompanying sample shipment form. Sample should be shipped to the following address:

Swisher Lab
ATTN: Kathy Agnew
University of Washington
1959 NE Pacific Street
HSB BB632
Seattle, WA 98195

9.2.1.4 Site(s) Performing Correlative Study

BROCA-HR will be performed by the laboratory of Dr. Elizabeth Swisher at the University of Washington (Seattle, WA).

9.2.2 CEC/CEP (Integrated)

The objectives of the CEC/CEP translational studies in the phase II biomarker study are to determine if there is an association between levels of CEC at baseline, or the change in CEC from baseline to day 3, and PFS in patients receiving cedarinib/olaparib trial, and to determine if there are significant changes from baseline to day 3 in the levels of CEC.

9.2.2.1 Collection of specimens

Please refer to the Specimen Requirements table in Section 9.1 for details regarding specimen collection.

CEC specimens should be collected in CPT (citrate) collection tubes as described below. Note: the CPT (citrate) tube should be at room temperature (i.e., 18-25°C) at the time of sample

collection.

1. Label the CPT (citrate) collection tube (BD vacutainer, catalog number 362761) with a waterproof permanent marker or printed label with Protocol Number (NCI #9825), Subject Study #, Date of collection, Sample timepoint (Baseline or C1D3).
2. Draw 8mL of blood into the labeled CTP (citrate) tube.
3. Immediately after collection, gently invert the tube 6 times to mix the blood and citrate.
4. CEC whole blood should be stored upright at room temperature until the specimen can be shipped. Ship to the Preclinical Development Research Core the day the specimen is collected. If the CEC whole blood absolutely cannot be shipped the day it is collected, the tube should be kept at room temperature until the specimen can be shipped the next day. **Note: The laboratory testing to be done is time sensitive. CEC whole blood specimens must be shipped the day the specimen is collected. If the specimen absolutely cannot be shipped the same day, a note detailing why the specimen needed to be shipped the next day must be included. If the specimen cannot be shipped within 24 hours, it should be discarded.** Due to the time-sensitive shipping requirements, patients starting protocol treatment on a Friday should have their Baseline specimens collected on the Thursday prior to starting on study treatment. Patients whose Cycle 1 Day 3 specimen collection dates fall on a Friday, Saturday or Sunday may have this specimen collected on Cycle 1 Day 4 (if Cycle 1 Day 3 is a Sunday), Cycle 1 Day 5 (if Cycle 1 Day 3 is a Saturday), or Cycle 1 Day 6 (if Cycle 1 Day 3 is a Friday) to allow for appropriate processing and shipping.

9.2.2.2 Handling of specimens

After processing for viable freezing, the samples are frozen at -80oC and then in liquid nitrogen and stored in liquid nitrogen until use, per our SOP. Each patient sample is assigned a unique 2D barcode identifier. Flow cytometric analysis is performed as a batch analysis due to the necessity of running each patient's pre-therapy and post-therapy samples contemporaneously, and to minimize variability due to different runs, reagents, and ambient conditions.

Peripheral blood mononuclear cells (PBMCs) isolated and viably frozen from patients will be analyzed; a minimum of 1 x 10^5 cells is required for each analysis. Identification and analysis of CECs will be performed using a MACSQuant flow cytometer and FlowJo software. Viability is defined by the absence of 7-aminoactinomycin D (7-AAD) staining, and analysis will be restricted to nucleated cells by gating on Hoechst 33342-positive cells. These findings will be correlated with clinical results.

9.2.2.3 Shipping of specimens

Please refer to the Specimen Requirements table in Section 9.1 for specific shipping requirements.

CEC specimens should be shipped at ambient temperature for overnight delivery Monday-

Thursday on the same day the sample was drawn. Whole blood samples should be shipped only for Tuesday through Friday *delivery* (do not ship samples on a Friday). Samples should be shipped with an accompanying sample shipment form. Samples should be shipped to the following address:

Trepel Lab, PDRC, NCI, NIH
Bldg 10, Rm 12N218
10 Center Dr
Bethesda, MD 20892
Phone: 301-496-1547
Emails: trepel@helix.nih.gov, lees@pop.nci.nih.gov, yusuke.tomita@nih.gov

Note: Please notify the PDRC (via the three email addresses provided) when a patient is scheduled for a blood draw and when the specimen will be shipped. The FedEx tracking number should be included in the shipment.

CEC whole blood specimens can be shipped to the PDRC **Monday through Thursday for Tuesday through Friday *delivery***. Do not ship whole blood the day before a government holiday. Ship specimens via **FedEx priority overnight.**

9.2.2.4 Site performing correlative study

CEC/CEP will be performed by the laboratory of Dr. Jane Trepel in the Preclinical Development Research Core (https://ccr.cancer.gov/jane-b-trepel) of the Developmental Therapeutics Branch, CCR, NCI (Bethesda, MD).

9.2.3 Plasma Angiome (Exploratory)

9.2.3.1 Collection of Specimen(s)

Please refer to the Specimen Requirements table in Section 9.1 for details regarding specimen collection.

Samples should be processed on site to obtain plasma and then shipped on dry ice. Biomarker assays are time sensitive, blood should be processed within 2 hours of collection and may remain at room temperature until processed. Instructions for processing and labeling samples are below:

1. Draw two 4ml purple top (K2EDTA) tubes (BD Vacutainer, catalog no. 367861)
2. Invert tubes 10 times to mix blood
3. Centrifuge at 4°C at 2500 x g for 15 minutes (or in accordance with centrifuge manufacturer's instructions)
4. Remove plasma from each tube and transfer equally into two separate clean 15ml polypropylene tubes
5. Repeat centrifuge at 4°C at 2500 x g for 15 minutes (or in accordance with centrifuge manufacturer's instructions)
6. Aliquot approximately 1.0ml of plasma from each tube into each 2.0ml pink-capped cryovial (Wheaton CryoElite Cryogenic Vials, Pink Cap, Mfr No. W985865). A total of 4 pink capped cryovials is needed for EDTA plasma.

7. Label and freeze at -80°C* (see labeling instructions below)

*Please note: If your site does not have a -80°C freezer, samples should be shipped on dry ice on the day of collection. If unable to ship samples on the day of collection, please place the samples on dry ice until they can be shipped. Samples can be stored on dry ice for no more than 48 hours prior to shipping. Please replenish dry ice as needed to ensure samples stay frozen and there is enough to last throughout shipment.

Plasma-containing tubes should be labeled with the following information (using a waterproof marker or label):

- Protocol Number (NCI #9825)
- Subject Study #
- Sample Collection Date and Time
- Sample Type (EDTA plasma)

9.2.3.2 Handling of Specimens(s)

Plasma samples will be analyzed by multiplex ELISA assays for plasma-based biomarkers utilizing the Aushon Cirascan Imaging System. The Aushon Cirascan Imaging System is used specifically for the imaging and analysis of chemiluminescent protein arrays in a 96-well plate. The protein arrays are created by spotting up to 16 different capture antibodies per well in each well of the 96-well plate. The advantage of this system is that multiple target proteins of interest can be analyzed at the same time reducing the amount of sample required for analysis. In brief, a small volume of sample and/or standard is added to each well of the 96-well plate resulting in the capture of the target proteins by the arrayed antibodies. Biotinylated antibodies are then added that specifically bind the captured target proteins. Streptavidin conjugated to HRP (horseradish peroxidase) is then added followed by a chemiluminescent substrate. Imaging of the plate is performed using Aushon Cirascan Imaging System. Protein concentrations in the samples are quantified by comparing the intensity of the spots in the unknown wells to standard curves.

9.2.3.3 Shipping of Specimen(s)

Please refer to the Specimen Requirements table in Section 9.1 for specific shipping requirements. Samples should be stored at -80°C and batch-shipped as coordinated with Dr. Nixon's laboratory. Please provide notification of the sample shipment by e-mail to jchris.brady@duke.edu. All biomarker samples must be shipped on dry ice by overnight delivery Monday through Thursday (no holidays) to the following address:

Attention: Phase I Biomarker Laboratory
ATTN: Chris Brady / Andrew Nixon, PhD
Duke University Medical Center
395 MSRB 1
203 Research Drive
Durham, NC 27710
(919) 681-2239

9.2.3.4 Site(s) Performing Correlative Study

Plasma angiome will be performed by the laboratory of Dr. Andrew Nixon at Duke University Medical Center (Durham, NC).

9.2.4 Whole exome sequencing (WES; Integrated) and RNASeq (Exploratory)

9.2.4.1 Collection of Specimen(s)

Please refer to the Specimen Requirements table in Section 9.1 for details regarding specimen collection.

Archival FFPE consisting of ten unstained sections of 10 µm thickness on charged slides should be obtained and shipped as per Section 9.2.4.3. Each slide should be labeled with Protocol Number (NCI #9825), Subject Study Number, and Date of collection.

Biopsies should be obtained under radiologic or other guidance, as appropriate, per institutional procedures. Biopsies should be frozen on site, ideally with 5-10 minutes of devascularization. Frozen biopsies should be stored at -80°C and shipped on dry ice.

A minimum of 3 and up to 6 core biopsies are requested; however, less than the goal amount of tissue is acceptable, and should be based upon the clinical judgment of the clinician performing the procedure. Based upon prior studies, it is feasible for up to 6 to 8 core biopsies to be obtained depending on the site being sampled, the size of the mass, and the safety of the procedure.

Research cores should be allocated in the following order:
1. Core #1: Placed in neutral buffered formalin and then embedded in FFPE (Formalin Fixed Paraffin Embedded) no more than 16 hours after exposure to neutral buffered formalin.
2. Cores #2 and more: Embed in frozen OCT medium, per instructions below.
    a. Use one 25 mm x 20 mm x 5 mm cryomold (Tissue Tek No. 4557) per core.
    b. Label each cryomold with (i) Protocol Number (NCI #9825), (ii) Subject Study #, (iii) Date of Collection, (iv) Sample timepoint (Pre-treatment, on-treatment, or post-progression)
    c. Fill bottom of each cryomold with OCT medium.
    d. Place the OCT filled cryomold on dry ice for 10 minutes to harden.
    e. Place the fresh tissue sample on top fo the hardened OCT in cryomold
    f. Entirely cover the tissue with OCT and place on dry ice for another 10 minutes.
    g. Once frozen, the blocks can be stored in -80 freezer until shipping.

Core #1 for pre-treatment and on-treatment biopsy should be shipped to Swisher Lab, as detailed in Section 9.2.1. Cores #2 and more for pre-treatment and on-treatment biopsy, and all cores for post-progression biopsy should be shipped to the Broad Institute's CCPM, as detailed in Section 9.2.4.3.

9.2.4.2 Handling of specimen(s)

Sample Management and QC

Sample handling includes an industry-grade high throughput registration, processing, and tracking system for biological samples. The system includes multiple points of quality control (i.e., sample quantitation, tracking, and genetic fingerprinting), allowing receipt and processing of an average of 16,000 samples per month. On arrival, each sample is assigned a unique bar code and entered into a validated database for sample analysis coupled to a bar code tracking system that records sample information (e.g., source, histology, clinical data), nucleic acid quality control information (e.g., genotyping, PCR), location information (e.g., freezer, shelf, rack), and project information. The database is linked directly to the LIMS systems for array and sequencing analysis.

Each DNA sample (optimized fingerprinting and WES processes require 50 to 100ng input DNA) received will be quantified and fingerprinted. Broad will perform triplicate PicoGreen® DNA quantitation. By genotyping a panel of 127 highly polymorphic SNPs (including SNPs on chromosomes X and Y), a unique genetic 'fingerprint' is generated for each sample. These genotypes are stored in the sample-tracking database and compared to genotypes obtained from whole exome sequencing to ensure integrity of sample handling and tracking from sample receipt through library sequencing.

Exome Sequencing – Express Workflow

The Illumina exome specifically targets approximately 37.7Mb of mainly exonic territory made up of all targets from our Agilent exome design (Agilent SureSelect All Exon V2), all coding regions of Gencode V11 genes, and all coding regions of RefSeq gene and KnownGene tracks from the UCSC genome browser (http://genome.ucsc.edu)

The Illumina exome uses Illumina's in-solution DNA probe based hybrid selection method that uses similar principles as the Broad Institute-AgilentTechnologies developed in-solution RNA probe based hybrid selection method (for details please see PMID 19182786 and 21205303) to generate Illumina exome sequencing libraries.

Pooled libraries are normalized to 2nM and denatured using 0.2 N NaOH prior to sequencing. Flowcell cluster amplification and sequencing are performed according to the manufacturer's protocols using either the HiSeq 2000 or HiSeq 2500. Each run is a 76bp paired-end with a dual eight-base index barcode read. Data is analyzed using the Broad Picard Pipeline, which includes de-multiplexing and data aggregation.

Transcriptome Sequencing

Total RNA is quantified using the Quant-iT™ RiboGreen® RNA Assay Kit and normalized to 5ng/ul. An aliquot of 200ng for each sample is transferred into library preparation, which is an automated variant of the Illumina Tru Seq™ RNA Sample Preparation protocol (Revision A, 2010). This method uses oligo dT beads to select mRNA from the total RNA sample followed

by heat fragmentation and cDNA synthesis from the RNA template. The resultant cDNA then goes through library preparation (end repair, base 'A' addition, adapter ligation, and enrichment) using Broad designed indexed adapters substituted in for multiplexing.

Pooled libraries are normalized to 2nM and denatured using 0.1 N NaOH prior to sequencing. Flowcell cluster amplification and sequencing are performed according to the manufacturer's protocols using either the HiSeq 2000 or HiSeq 2500. Each run is a 101bp paired-end with an eight-base index barcode read. Data is analyzed using the Broad Picard Pipeline, which includes de-multiplexing and data aggregation.

9.2.4.3 Shipping of specimens

Please refer to the Specimen Requirements table in Section 9.1 for specific shipping requirements.

FFPE and frozen biopsy specimens should be batch shipped to the Broad CCPM. The CCPM research operations team will coordinate the schedule for shipping with individual sites. Contact information for the CCPM Research Operations Team is as follows:

a. Karla Helvie: karlae_helvie@dfci.harvard.edu; office: 617-582-7924
b. Nelly Oliver: nelly_oliver@dfci.harvard.edu; office: 617-582-8706
c. Lori Marini: lori_marini@dfci.harvard.edu; pager: 617-430-3262

FFPE samples should be shipped in slide holders in a separate package/shipment from frozen specimens. A Specimen Submission Form (SSF) should be included for each sample included in the shipment. Additionally, please complete the DFCI Shipping Manifest; include a printed copy of the Shipping Manifest with the package and email a separate copy to CCPM_ResearchOps@dfci.harvard.edu at the time of shipment. The shipping site should receive email confirmation of delivery receipt from the CCPM research operations team.

Frozen samples should be shipped on dry ice in a separate package/shipment from FFPE specimens. A Specimen Submission Form (SSF) should be included for each sample included in the shipment. Additionally, please complete the DFCI Shipping Manifest; include a printed copy of the Shipping Manifest with the package and email a separate copy to CCPM_ResearchOps@dfci.harvard.edu at the time of shipment. The shipping site should receive email confirmation of delivery receipt from the CCPM research operations team. Frozen samples should be shipped via FedEx Overnight priority according to the schedule discussed with the CCPM research operations team. In additionl to the Specimen Submission Form, the shipping container for frozen tissue should include (i) Priority Overnight Frozen Material labeling, (ii) Dry Ice UN number, (iii) Class 9 label). **Frozen samples should only be sent for Monday through Friday delivery. Please do not ship on Fridays or on weekends/holidays.**

All samples should be shipped to the following address:

Lori Marini, PA
Dana-Farber Cancer Institute, Dana 820
450 Brookline Avenue
Boston, MA 02215

9.2.4.4 Site(s) performing the correlative study

WES and RNASeq will be performed by the Center for Cancer Precision Medicine at the Broad Institute (Cambridge, MA).

9.2.5 Pharmacokinetics (Integrated)

9.2.5.1 Collection of specimens

The steady-state plasma pharmacokinetics of cediranib and olaparib will be tested at the recommended phase II doses of the combination, cediranib 30 mg QD and olaparib 200 mg BID. Pharmacokinetic sampling will be performed during a single 24 h dosing interval after steady-state pharmacokinetic conditions for the repeated oral dosing schedules have been achieved fpr the two drug combination. Pharmacokinetic samples will be collected before and for 8 hr after dosing on days 15-16 after the patients have received 14 days of combined therapy, as per the timepoints outlined below.

The sampling schedule has been devised to accommodate treatment on an outpatient basis. Patients will be instructed to take the doses of the two drugs as per outlined in the protocol at the same time every day during the pharmacokinetic study. Cediranib will be taken first thing in the morning on an empty stomach. One hour later, the patient may have a light meal, followed by the morning dose of olaparib. Dosing should be scheduled for times that will allow the patient to arrive at the clinic to obtain pharmacokinetic samples before dosing and to remain for an additional 8 hours after the morning dose of olaparib. The second daily dose of olaparib should be taken 12.0 ± 0.25 h after the morning dose. It is very important that the patient is aware that the morning doses of the two drugs on day 16 must not be taken before arriving at the clinic and the 24.0 h pharmacokinetic sample has been collected. Of note, on days that PKs are being obtained, olaparib will be taken 2 hours (instead of 1 hour) after cediranib (following a light meal) due to the timing required for PKs. This will allow for cediranib and olaparib samples to be taken at the same timepoint and reduces the number of blood draws patients would be subjected to by approximately half.

Blood samples (6 mL) will be obtained during cycle 1 starting on day 15 with the following schedule, to accommodate the sequential dosing schedule of the two drugs:

PK specimen	Day	Timing
#1	Cycle 1 Day 15	Just prior to cediranib dose
#2	Cycle 1 Day 15	0.5 hrs after cediranib dose
#3	Cycle 1 Day 15	1.0 hrs after cediranib dose
#4	Cycle 1 Day 15	2.0 hrs after cediranib dose, just prior to olaparib dose
#5	Cycle 1 Day 15	2.5 hrs after cediranib dose (= 0.5 hrs after olaparib dose)
#6	Cycle 1 Day 15	3.0 hrs after cediranib dose (= 1.0 hrs after olaparib dose)
#7	Cycle 1 Day 15	4.0 hrs after cediranib dose (= 2.0 hrs after olaparib dose)
#8	Cycle 1 Day 15	5.0 hrs after cediranib dose (= 3.0 hrs after olaparib dose)

#9	Cycle 1 Day 15	6.0 hrs after cediranib dose (= 4.0 hrs after olaparib dose)
#10	Cycle 1 Day 15	8.0 hrs after cediranib dose (= 6.0 hrs after olaparib dose)
#11	Cycle 1 Day 16	24.0 hrs after C1D15 cediranib dose, just prior to C1D16 cediranib dose
#12	Cycle 1 Day 16	24.0 hrs after C1D15 morning olaparib dose, just prior to C1D16 morning olaparib dose

PK samples #1 through #5 should be drawn within +/- 5 minutes of the appropriate timepoint. PK samples #6 through #9 should be drawn within +/- 10 minutes of the appropriate timepoint. PK sample #10 should be drawn within +/- 15 minutes of the appropriate timepoint. PK samples #11 and #12 should be drawn within +/- 30 minutes of the appropriate timepoints. Samples will be collected in plastic green stoppered Vacutainer 6.0 mL plasma collection tubes with spray-coated sodium heparin (BD Vacutainer, catalog number 367878), gently inverted 5-times to thoroughly mix the blood with the anticoagulant, and placed on wet ice until centrifuged (1,300 x g, 10 min, 4°C) within 15 min after collection. Separate the plasma from the blood cells using a disposable pipette and transfer the plasma into a 4.5 mL self-standing polypropylene cryogenic storage vial with external threads (Fisher Scientific, catalog number 12-565-291). Plasma from each timepoint should be aliquoted into 2 cryovials (Aliquot A and B). Affix a pre-printed label, with the protocol number, patient accession number, and sample number onto the cryovial, oriented crosswise toward the upper part of the tube, without overlapping the vial cap. Completely cover the label with polyester protective label tape (Fisher Scientific, catalog number 03-411-631) to prevent the label from detaching from the vial when stored frozen. Store the plasma samples in a freezer at < -70°C until packaged for shipment to the analytical laboratory.

If PK samples cannot be obtained on Cycle 1 Day 15 and Day 16, these samples may be obtained on a separate date after the patient has received 14 continuous days of study drug dosing at the same dose, in consultation with the overall PI.

9.2.5.2 Handling of specimens

The concentration of cediranib and olaparib in the plasma samples will be determined by the DF/HCC Cancer Pharmacology Core laboratory located on the main campus of the Massachusetts General Hospital (Boston, MA). An analytical method facilitating the concurrent determination of the two drugs based upon for both compounds based upon high performance liquid chromatography with tandem mass spectrometric detection has been developed. The analytical methods will be validated and applied to the analysis of study samples as recommended by the FDA Guidance for Industry: Bioanalytical Method Validation, May 2001 (http://www.fda.gov/-downloads/Drugs/Guidances/ucm070107.pdf).

Individual patient plasma concentration-time curves will be analyzed by noncompartmental methods using routines supplied in the WinNonlin Professional Version 5.0.1 software package (Pharsight Corp., Cary, NC). Pharmacokinetic parameters and variables will be calculated according to standard equations. Mean values of pharmacokinetic parameters will be statistically compared using the paired two-tailed t-test of the log-transformed data.

9.2.5.3 Shipping of specimens

Send complete sets of primary samples (labelled Aliquot A) from one or more patients by next day delivery to the address listed below. Place the sample tubes in a zip lock plastic bag. Package samples in a seamless styrofoam container. Place the sample bag over at least 3-4 inches of dry ice on the bottom of the container and completely cover with an additional 3-4 inches or more of dry-ice. Seal the styrofoam container within a tight-fitting cardboard shipping box. Insert copies of the redacted Cycle 1 drug diaries and Pharmacokinetic Data Form for each set of samples into a separate zip-lock plastic bag placed on top of the styrofoam container before the external shipping box is sealed. Send the samples from Monday to Wednesday by overnight courier for delivery by 10 a.m. on the following day. Samples should not be shipped on a Thursday or Friday. Please provide notification of the sample shipment by e-mail to jsupko@partners.org, Jmayo1@partners.org and Amartella1@partners.org. The shipping address is:

Dr. Jeffrey G. Supko
Massachusetts General Hospital
55 Fruit St., GRJ 1025
Boston, MA 02114
Tel: 617-724-1970

Back-up samples (labelled Aliquot B) should be shipped at a later date when/ if requested by Dr. Supko's lab.

9.2.5.4 Site performing correlative study

Pharmacokinetic studies will be performed by the DF/HCC Cancer Pharmacology Core laboratory located on the main campus of the Massachusetts General Hospital (Boston, MA).

9.2.6 RAD51 assay (Exploratory)

9.2.6.1 Collection of Specimen(s)

RAD51 assay testing will be performed on available archival and biopsy tumor samples after samples have been distributed for BROCA-HR and WES/RNASeq testing. Two slides will be provided to the D'Andrea Lab for RAD51 and geminin control IHC.

9.2.6.2 Handling of Specimens(s)

Staining will be performed on two serial 4-5um sections of tumor tissue for RAD51 and Geminin. Samples will be analyzed per the following criteria:

1. There must be more than 3 (>3) sub-nuclear RAD51 foci to call a cell RAD51-foci positive
2. There must be 4 or more 40X fields of tumor cells with at least one RAD51-foci positive cell to call HR proficient
3. If the percentage of Geminin positive cells is greater than 3 (i.e. >3%) and there are no RAD51-foci positive cells, the sample is HR deficient
4. If the percentage of Geminin positive cells is less than 3 (i.e. <3%) and there are no RAD51

foci positive cells, the assay is not informative.

9.2.6.3 Shipping of Specimen(s)

No additional samples will be shipped by sites. Samples will be provided centrally by the study team to D'Andrea Lab from previously shipped archival and biopsy specimens.

9.2.6.4 Site(s) Performing Correlative Study

RAD51 assay will be performed by the laboratory of Dr. Alan D'Andrea at Dana Farber Cancer Institute (Boston, MA).

9.3 eCO Mobile Application Study Plan

9.3.1 Study Visit 1 (Cycle 1, Day 1)

At this study visit, the following procedures will be completed:

- Answer baseline questions regarding current use of technology (smartphone, tablet, computers, and eReaders). (See Appendix)
- Install the eCO app on the subject's personal iPhone or provide pre-loaded iPhone 6 (limited to study use only).
- Instruct subject on the use of the eCO app and the User's Guide.
- Instruct subject on the use of the A&D Bluetooth enabled Blood Pressure Monitor and verify pairing with the iPhone.
- Verify that the patient's app works properly and that data entered are recorded properly before patient leaves site (i.e., test out the app for each patient and confirm that they can use it as intended)
- Obtain baseline diastolic blood pressure. The study team member will enter the value into the patient profile on the eCO HCP web portal.
- Obtain baseline stools per day. The study team member will enter the number into the patient profile on the eCO HCP web portal.
- Provide paper BP diary used in the 9825 study as back-up should technical issues with the eCO app occur.
- Provide the eCO User Support number to contact as needed.

9.3.2 One Week Follow-up Phone Call

Upon enrollment, patients will be asked to participate in a 1-week follow-up call conducted by User Centered Design. Structured questions to obtain initial feedback on the eCO app will be asked and the responses will be documented (See Appendix). This call will last approximately 10 minutes. Patients will have the option to decline participation in this call.

9.3.3 Study Visit 2 (Cycle 2, Day 1)

At this study visit the following procedures will be completed:

- Complete perceived usability and satisfaction questionnaires regarding the eCO app. (See Appendix)
- Subjects will be offered to continue use of the eCO app during their participation in the 9825 trial. At the end of the study, the iPhone 6 provided as part of the trial will be returned.

9.3.4 Health care provider (HCP)/Study Team Survey

HCP/Study Team feedback will be obtained several times during the study:

- 1 week after the first patient has been initiated at the site to gain their experience with the eCO app and web portal, they will be offered the option of discussing their experience learning and using the app and web portal. This discussion will occur by phone.
- 4 months after the first patient enrolled a survey will be completed by study team members who have worked with a patient using the app.
- Upon completion of the patient's use of the eCO app during the 1st Cycle of therapy for all patients enrolled at the sites, the study personnel who were involved in patient care (oncologists, NP/PAs, clinical research coordinators, clinical research assistants) will complete the survey regarding their perceived usability and satisfaction with the eCO app and web portal. (Note: the 4 months and end of study survey is the same).
- Monitor eCO User Support calls/questions.

Surveys completed as part of the pilot study will be administered electronically using a pre-loaded iPad (limited to study use only).

10. STUDY CALENDAR

Scans, x-rays must, and ECHOs be done ≤4 weeks prior to the start of therapy. All other baseline assessments, including labs, must be done ≤14 days from the start of treatment. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.

	Pre-Study[a]	**Each Cycle Day 1[a]**	**Cycles 1&2 Weekly[b]**	**Additional studies Cycle 1**					**Additional studies Cycle 2**		**Every 2 Cycles**	**Every 4 Cycles**	**Off Treatment[o]**
				Day				Wk	Day				
				1	3	15	16	4	1	15			
Informed Consent[a]	X[a]												
Medical History	X												
Concomitant Medications[c]	X[c]	X[c]	X[c]										X[c]
Adverse Event Assessment		X	X[b]										X
Vital Signs[d]	X[d]	X[d]											X[d]
BP Measurement at Home		As directed (see Section 5.4)											
Physical Exam	X	X											X
Height	X												X
Weight	X	X											
Performance Status (ECOG)[e]	X[e]	X[e]											X[e]
CBC with Differential	X	X				X				X			X
Serum Chemistry[f]	X[f]	X[f]				X[f]				X[f]			X[f]
INR and PTT	X												
TSH and Free T4[g]	X[g]	X[g]											X
Urine protein: creatinine ratio	X	X[h]											X[h]
EKG	X												
MUGA or Echocardiogram[i]	X											X	
Pregnancy Test[j]	X[j]												
CA-125	X	X											X
Tumor Measurements[k]	X[k]										X[k]		
Tumor Biopsy	X[l]							X[l]					X[l]
Translational bloodwork[m]				X	X				X				X
Pharmacokinetic studies[n]						X	X						
Optional eCO sub-		Optional eCO substudy assessments, as per Section 9.3											

study			

a: Informed consent will be obtained prior to any study-related screening tests and within 4 weeks of starting study drug. For Cycle 1 Day 1, physical examination, and laboratory evaluations do not have to be repeated if they have been performed at screening within 7 days of Cycle 1 Day 1.
b: Participants should be contacted at least once weekly over the phone or be assessed in person for the first two cycles on study to assess for adverse events and concomitant medications. Pre-cycle and off-study AE assessments must be done at a scheduled clinic visit.
c: Because of a potential for interaction of cediranib and olaparib with other drugs through the cytochrome P450 system, special attention should be paid to other medications known to affect P450 isoenzymes, in particular CYP3A4.
d: Temperature, pulse, blood pressure
e: See Appendix A for ECOG performance status
f: Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, albumin, calcium, phosphorus, AST (SGOT), ALT (SGPT), alkaline phosphatase, total bilirubin.
g: Pre-study, prior to the first 2 cycles, and at off-study visit for all participants. Otherwise, should be checked prior to each cycle if clinically indicated.
h: Urinalysis may be used instead. See Section 6.5 for Management of Proteinuria.
i: MUGA or echocardiogram should be done at baseline and every 4 cycles for those patients at increased risk for compromised LVEF. Increased risk patients have had one or more of the following: (1) prior treatment with anthracyclines, (2) prior treatment with trastuzumab, (3) NY Heart Association classification of II, (4) prior central thoracic RT, (5) history of myocardial infarction within the 12 months prior.
j: beta-HCG for women of childbearing potential.
k: Tumor measurements by CT scans or MRI (of the chest, abdomen, and pelvis) will be performed within the 4 weeks prior to starting cediranib/olaparib and will be performed after every 8 weeks (+/- 1 week) of treatment. The frequency of restaging studies will decrease to once every 12 weeks (+/- 1 week) after the 20th cycle of treatment. If a partial or complete response is noted, a confirmatory CT scan or MRI should be performed. The next planned restaging CT scan or MRI may be used as the confirmatory scan.
l: Presence of biopsiable disease is required for eligibility. Willingness to undergo pre-treatment and on-treatment biopsies is mandatory for the study. Pre-treatment biopsy should be performed within 14 days of starting study treatment. On-treatment biopsy should be performed during the 4th week of cycle 1 of treatment. If, at the time of biopsy, the previously biopsiable disease is no longer deemed to be biopsiable, the biopsy may be waived. The PI should be informed about mandatory biopsies that cannot be performed. Inability to be biopsied for safety reasons will not preclude patients from receiving study treatment. Post-progression biopsy is optional, but encouraged.
m: Bloodwork will be drawn for translational studies of CEC on Cycle 1 Day 1 (pre-treatment) and Cycle 1 Day 3 (pre-treatment), BROCA-HR on Cycle 1 Day 1 (pre-treatment), and of plasma angiome on Cycle 1 Day 1 (pre-treatment), Cycle 2 Day 1(pre-treatment), and at Off-treatment/time of progression. Participation in these translational studies is required for study participation. Details on the required specimens are found in Section 9. Patients may choose to opt out of translational bloodwork at the time of progression.
n: Details on required specimens and timepoints for pharmacokinetic studies is found in Section 9.
o: Off-treatment assessments should be performed within 30 days of stopping study treatment.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 8 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area are not considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and 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. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being

followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm in diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed. Please note: decisions regarding RECIST must be made on the diagnostic CT scan *only*. New lesions may not be determined on the basis of the FDG PET.

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment

for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

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

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or

unequivocal progression of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.1.4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	

Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** The next planned imaging scan may be used as the confirmatory scan.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

11.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.6 Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

11.1.7 Response Review

For patients enrolled at DF/HCC sites, tumor metrics central imaging will serve as the reading for all radiographic imaging for this study.

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

Regular and ongoing communication with Participating Institutions, will be accomplished by holding regular teleconferences with all sites. The Lead Institution will keep in close touch with the Participating Institutions via email and phone.

12.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

12.2 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the

trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and the appropriate Rave role (Rave CRA, Read-Only, CRA Lab Admin, SLA or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave. If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

12.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

12.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI, and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials) the recommended phase 2 dose (RP2D), and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

12.3 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring with 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request. The DSMC will provide the Overall PI an outcome of the review, which will be forwarded to all sites, and discussed on regular teleconferences if needed.

12.4 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a study participant or participant's family member, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party

Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

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

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

13. STATISTICAL CONSIDERATIONS

The purpose of this phase II study is to test the clinical activity and safety of the combination of olaparib and cediranib in patients with platinum-resistant as well as platinum-sensitive ovarian cancer, and to evaluate integrated biomarkers as predictors of response to this regimen.

13.1 Study Design/Endpoints

The clinical activity of cediranib/olaparib will be separately evaluated in cohorts of patients with and platinum-sensitive (single-stage design) and platinum-resistant (Simon two-stage design) ovarian cancer

For the primary objective to evaluate BROCA_HR as a predictor of response in women with platinum-sensitive ovarian cancer, the primary endpoint will be progression-free survival (PFS), defined as the interval from start of treatment to documented disease progression per RECIST 1.1 or death from any cause, whichever occurs first. Patients who remained event-free at the time of final analysis will be censored at their last date of follow-up.

For the platinum-resistant cohort, the endpoint for the primary objective to determine clinical activity will be objective response rate (confirmed CR or PR under RECIST 1.1).

Secondary objectives to evaluate CECs and WES, and for biomarker signature development will use PFS as the endpoint for clinical activity of cediranib/olaparib in both platinum-sensitive and –resistant ovarian cancer.

Overall survival and adverse events (using CTCAE v4.0 until March 31, 2018, and CTCAE version 5.0 beginning April 1, 2018) will be secondary endpoints for each cohort.

13.2 Sample Size, Accrual Rate and Study Duration

Total sample size for the study will be 70 patients (35 with platinum-sensitive and 35 with platinum-resistant disease). With a monthly accrual of 7 patients across the ETCTN sites, a total of 10 months of patient accession is anticipated. A minimum of 12 months of additional follow-up will occur before analysis, in order to have sufficient clinical follow-up for the identification of biomarker signatures.

Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	5	0	0	0	**5**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
Black or African American	4	0	1	0	**5**
White	55	0	4	0	**59**
More Than One Race	1	0	0	0	**1**
Total	**65**	**0**	**5**	**0**	**70**

13.3 Stratification Factors

Stratification will be stratified and enrolled into separate cohorts at registration through eligibility criteria to define platinum resistant versus platinum sensitive recurrence.

13.4 Interim Monitoring Plan

Clinical activity in the platinum-resistant cohort will be evaluated using a two-stage Simon Optimal design. In the first stage, 18 patients will be enrolled. If there are at least 3 responses, accrual will continue to the second stage where an additional 17 patients will be enrolled. If there are 7 or more responses among the 35 patients, the regimen will be considered worthy of further study in platinum-resistant disease. If fewer than three responses are observed with the 18th platinum-resistant patient is enrolled, accrual to the study will be suspended, and amended to enroll only platinum-sensitive patients once sufficient information is obtained to stop for futility basedon a lack of response in the first stage.

13.5 Analysis of Secondary Endpoints

13.5.1 BROCA-HR:

Descriptive statistics will be used to summarize the genetic alterations detected by the BROCA-HR assay and Bioinformatics Pipeline. In studies of two previous phase III GOG trials (GOG218, and GOG262), we identified 15% of women to have a germline *BRCA1* or *BRCA2* mutation and an additional 5% to have a mutation in another DNA repair gene that would be expected to cause homologous recombination deficiency (HRD). Additionally, in primary ovarian cancers, we identified an additional 8% of cases to have somatic mutations in HR genes

including 6% in *BRCA1* and *BRCA2* (Pennington *et al.*, 2014). We will pool cases with *BRCA1* and *BRCA2* mutations, somatic or germline, into a single group, the BRCA-mutant cases. A second exploratory group will be the pooled group of other germline or somatic mutations that would be predicted to cause HRD including *PALB2, BRIP1, RAD51C, RAD51D, BARD1, ATM, NBN, BLM, CHEK2,* and *FAM175A*. The minimal expected germline mutation rate for *BRCA1* and *BRCA2* is 15%, but studies with PARP inhibitors over-enroll *BRCA1* and *BRCA2* mutation carriers unless that enrollment is capped or limited. Therefore, the germline BRCA mutation rate could range between 15% and 60%, with a likely estimate of 35%. The somatic BRCA mutation rate may be slightly higher in a population selected for platinum sensitivity, but should be in the range of 6-10%. Therefore, we estimate the total BRCA germline and somatic mutated rate will be 40-45%. We estimate the mutation rate of other HRD genes to be consistent with our previous studies at about 8%. Approximately 50% of cases will have no HR mutation.

With a total of 70 patients enrolled, there will 0.50 and 0.76 probabilities of observing at least one alternation if the true frequency is as low as 1% and 2%, respectively, in the general population of ovarian cancers represented by this cohort. The prevalence of each genetic alteration will be reported overall, and within stratum defined by platinum-sensitive and platinum-resistant disease using binomial exact 95% confidence intervals.

The primary analysis will associate BRCA mutations (germline or somatic) and other HR gene mutations, as a pooled group, against progression-free survival as a time-to-event endpoint, using Kaplan-Meier product-limit estimates and stratified logrank test using a two-sided alpha of 0.05. With 24 months of patient accession, 12 months of additional follow-up, and a median PFS of 16.7 months for platinum-sensitive disease (as observed in NCT01116648) and 5 months for platinum-resistant disease (Mutch *et al*. 2007; Gordon *et al*, 2001), a total of 26 and 33 events are anticipated at analysis for platinum-sensitive and platinum-resistant disease, respectively. Under the assumption that 40% of patients will have genomic mutations, there will be 80% power to detect a HR of 3.1 in the platinum-sensitive cohort.

As secondary analyses, the association of pooled genetic mutations will be evaluated in the platinum-resistant cohort, and with more events anticipated with poorer prognosis, there will be 80% power to detect a HR of 2.7. Finally, exploratory analyses will evaluate genetic mutations across the two cohorts using multivariable Cox regression modes, and the table below gives a power analysis for analyses in the combined cohort with varying prevalences of genetic alterations, using nominal two-sided alpha = 0.05.

Table: Power analysis of effect-sizes (HR) under varying prevalence rates of mutation

Prevalence	**80% power**
40%	HR = 2.1
30%	HR = 2.2
20%	HR = 2.5
15%	HR = 2.8
10%	HR = 3.4

For the exploratory analyses to develop biomarker signatures with the BROCA-HR assay, there will be inadequate power to control for family-wise error and false-discovery rates, and to detect associations for individual genetic alterations with lower prevalence in the individual cohorts.

13.5.2 Clinical activity of cediranib/olaparib in platinum-resistant ovarian cancer

Clinical activity in the platinum-resistant cohort will be established using a target 30% objective response rate as worthy of further study, while a rate of 10% would not be of clinical interest. The following two-stage Simon Optimal design gives high power (>90%) with a Type I error no more than 0.05: In the first stage, 18 patients will be enrolled. If there are at least 3 responses, accrual will continue to the second stage where an additional 17 patients will be enrolled. If there are 7 or more responses among the 35 patients, the regimen will be considered worthy of further study in platinum-resistant disease. Objective response rates will be reported using the maximum-likelihood estimator, with 95% confidence interval adjusted for the two-stage design (Atkinson and Brown, 1985)

13.6 Analysis of Secondary Objectives

13.6.1 Secondary clinical endpoints

Secondary clinical endpoints will be evaluated separately in the platinum-sensitive and platinum-resistant cohorts. Time-to-event endpoints, including OS and PFS, will be summarized using the Kaplan-Meier product-limit estimator with 95% confidence bands derived using Greenwood's formula. Binary endpoints, including maximum grade AE during treatment, will be reported using 95% binomial confidence intervals.

13.6.2 CEC/CEP

The objectives of the CEC/CEP translational studies in the phase II biomarker study are to determine if there is an association between levels of CEC at baseline, or the change in CEC from baseline to day 3, and PFS in patients receiving cedarinib/olaparib trial, and to determine if there are significant changes from baseline to day 3 in the levels of CEC.

Patients with platinum-sensitive disease may have a median PFS of approximately 12 months. Assuming there are 35 samples at baseline and at 3 days, and therefore also 35 changes from baseline, there would be approximately 17 patients below the median baseline CEC or change in CEC, and approximately 17 at or above the median baseline CEC or change in CEC. Using a log-rank test, there would be 75% power in each case to detect a difference between two groups having median PFS of 5 and 20 months divided on the basis of their CEC level or changes, using a two-sided 0.05 significance level test.

Similarly, patients with platinum resistant disease may have a median PFS of approximately 5 months. Again, assuming 35 samples at baseline and at 3 days, and therefore 35 changes from baseline, approximately 17 patients would be below the median baseline CEC or change in CEC,

and approximately 17 at or above the median baseline CEC or change in CEC. Using a log-rank test, there would be 88% power in each case to detect a difference between two groups having median PFS of 2 and 8 months divided on the basis of their CEC level or changes, using a two-sided 0.05 significance level test. Power would be reduced to 81% if we required a 0.025 test for each to very conservatively account for two comparisons being performed; however, this adjustment and reduction in power may not be considered necessary if a Hochberg correction is applied instead of the overly conservative Bonferroni adjustment.

Finally, separately within platinum sensitive and platinum resistant patients, we will form the change in CEC from baseline to 3 days and test whether this change differs from zero using a paired t-test. With 35 patients in either category there is 81% power to detect a difference equal to approximately 0.5 SD (0.5 effect size) with a two-sided 0.05 significance level test. If we require sample sizes to support a strict Bonferroni correction of 0.025 as the p-value for each group separately, this would have 80% power to detect a 0.54 SD effect size. In practice, the adjustment comparing the two results may be performed using a less overly stringent Hochberg correction. If we were to combine all 70 patients, there would be 90% power to detect an effect size of 0.40 SD using a two-tailed 0.05 significance level paired t-test. In addition, if the paired differences in values are not normally distributed ($p<0.05$ by a Shapiro-Wilk test), then a Wilcoxon signed rank test will be used instead of a paired t-test.

13.6.3 Whole exome sequencing

With a total of 70 patients enrolled, there will 0.50 and 0.76 probability of observing at least one alternation if the true frequency is as low as 1% and 2%, respectively, in the general population of ovarian cancers represented by this cohort. The prevalence of each genetic alteration will be reported overall, and within platinum-sensitive and platinum-resistant cohorts using binomial exact 95% confidence intervals. Exploratory analyses will associate alterations of a single-gene against progression-free survival as a time-to-event endpoint, using Kaplan-Meier product-limit estimates and logrank test using a nominal two-sided alpha of 0.05. There will be inadequate power to control for family wise error and false-discovery rates and to detect associations for genetic alterations with low prevalence

13.6.4 Biomarker signatures

For biomarker signature development, we will first evaluate the assay failure rates and data completeness of candidate markers from each platform. Imputation procedures (eg. K-nearest neighbors) will be considered if individual features are thought to be missing-at-random in 20% of the study population or less; otherwise features will be filtered before signature development. Genomic profiles will be explored using unsupervised hierarchical clustering of all analytes and patients. The association of each candidate marker to PFS will be evaluated by Cox proportional hazard models using a two-sided alpha = 0.05, while estimating the false discovery rate for any sets of identified markers by the Benjamini-Hochberg step-up procedure. Assuming that 85% of subjects will provide evaluable tissue/blood and a landmark-time in the survival function of each cohort will give complete information and approximate 70%/30% split (e.g. 12-month PFS in platinum-sensitive disease, as seen in Figure 3), nominal Type I error control will have 85%

power to detect a 1.25 s.d. change in candidate marker levels between responders and non-responders.

Next, we will attempt to build classifiers from the identified sets of biomarkers using multivariate Cox proportional hazard models with L1 (lasso) constraints on coefficients to prevent overfitting in the high-dimensional biomarker space. Operating characteristics will be characterized under leave-one-out cross-validation, using Harrell's C-index as a summary measure of the performance of predictive models. Sample size constraints are considered using the method from Dobbin and Simon (2007), whereby a classier developed from 100 candidate markers that has a standardized fold-change of 1.25 will have a tolerance of 10% (i.e. the expected accuracy of the predictor derived from 30 samples would be within 10% of the best accuracy possible for the general population).

13.7 Analysis of eCO Objectives

Since participants will be volunteers, the total number of participants cannot be predicted. Participants will be obtained from several sites participating in the trial. Given an anticipated medium to large effect size, the goal is to obtain 20 participants depending on enrollment. A small sample is likely to provide statistical significant for the research questions using the intended nonparametric analysis.

Demographic data: Demographic data on the participants will be summarized using descriptive statistics. The demographics collected will be age, race, and experience with smart phones.

Perceived Usability/Satisfaction

Patients

Significance testing of perceived usability and satisfaction data will be done using a one tailed Wilcoxon Signed Rank Test ($\alpha = 0.05$).

Health Care Professionals

Significance testing of perceived usability and satisfaction data will be done using a one tailed Wilcoxon Signed Rank Test ($\alpha = 0.05$).

eCO App/Web Portal Metrics

Web portal metrics will be summarized using descriptive statistics. The metrics will include:

- Number of patients who accessed the app
- Number of diarrhea events reported
- % BP values entered compared to the % expected
- Number of follow-up BP measures entered compared to the number recommended
- Number and type of BP events reported
- Average duration of BP event and diarrhea event in days
- Number of other symptoms reported (headache, change in vision, shortness of breath, chest pain, uncontrolled diarrhea, cramping, blood in stool)
- Number and type of email alerts generated to the study team

User Support Call Summary
User support calls will be summarized including:

- Number of calls
- The reason for contacting eCO User Support (patients and study team)

13.8 Reporting and Exclusions

13.8.1 Evaluation of Toxicity

All participants who receive at least one dose of cediranib or olaparib will be evaluable for toxicity from the time of their first treatment. Toxicities will be graded via CTCAE version 4.0 until March 31, 2018. CTCAE version 5.0 will be utilized beginning April 1, 2018.

13.8.2 Evaluation of the Primary Efficacy Endpoint

The study populations for analyses of clinical activity will be as follows for stratum of platinum-sensitive and platinum-resistant ovarian cancer that are defined at enrollment. Analysis of clinical activity by progression free survival in platinum-sensitive and platinum-resistant will include all participants who receive at least one dose of cediranib or olaparib, even if there are major protocol therapy deviations. For platinum resistant disease, clinical activity assessed by objective response will include all evaluable patients who have received at least on cycle of therapy. Participants who exhibit objective disease progression or discontinue treatment for toxicity prior to the end of cycle 1 will also be considered evaluable, but patients who go off study before the end of cycle 1 for other reasons will not be evaluable for objective response.

13.8.3 Evaluation of the Integrated Biomarkers

Analyses of integrated biomarkers will be based on all eligible and treated participants that are evaluable for each assay.

14. PUBLICATION PLAN

The results should be made public within 12 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

REFERENCES

Agboola S, Flanagan C, Searl M, et al. (2014). Improving outcomes in cancer patients on oral anti-cancer medications using a novel mobile phone-based intervention: Study design of a RCT. *JMIR Res Protoc.* 3(4):e79.

Aghajanian C, Blank SV, Goff BA, Judson PL, Teneriello MG et al. (2012) OCEANS: A randomized, double-blind, placebo-controlled phase III study of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. Journal of Clinical Oncology 30:2039-2045.

Alberts, S.R., T.R. Fitch, G.P. Kim, *et al.* (2012). Cediranib (AZD2171) in patients with advanced hepatocellular carcinoma: A phase II North Central Cancer Treatment Group clinical trial. *Am J Clin Oncol.* 35:329-333.

Audeh, M.W., J. Carmichael, R.T. Penson, *et al.* (2010). Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with *BRCA1* or *BRCA2* mutations and recurrent ovarian cancer: A proof-of-concept trial. *Lancet* 376 (9737): 245-251.

Bardelli, A., D.W. Parsons, N. Silliman, *et al.* (2003) Mutational analysis of the tyrosine kinome in colorectal cancers. *Science* 300:949.

Bashshur Rl, Shannon GW, Smith BR, et al. (2014). The empirical foundations of telemedicine interventions for chronic disease management. *Telemed J E Health*. 20(9):769-800.

Batchelor, T.T., A.G. Sorensen, E. di Tomaso, *et al.* (2007). AZD2171, a pan-VEGF tyrosine kinase inhibitor, normalizes tumor vasculature and alleviates edema in glioblastoma patients. *Cancer Cell.* 11:83-95.

Batchelor, T.T., D.G. Duda, E. di Tomaso, *et al.* (2010). Phase II study of cediranib, an oral pan-vascular endothelial growth factor receptor tyrosine kinase inhibitor, in patients with recurrent glioblastoma. *J Clin Oncol.* 28:2817-2823.

Bertolini F, shaked Y, Mancuso P, *et al.* (2006). The multifaceted circulating endothelial cell in cancer: towards marker and target identification. *Nat Rev Cancer* 6:835-45.

Bindra, R.S., S.L. Gibson, A. Meng, *et al.* (2004). Hypoxia-induced down-regulation of *BRCA1* expression by E2Fs. *Cancer Res.* 65:11597-11604.

Bindra, R.S., P.J. Shaffer, A. Meng, *et al.* (2005). Down-regulation of Rad51 and decreased homologous recombination in hypoxic cancer cells. *Mol Cell Biol.* 24:8504-8518.

Bookman MA, Brady MF, McGuire WP, Harper PG, Alberts DS, et al. (2009) Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: a Phase III Trial of the Gynecologic Cancer Intergroup. *J Clin Oncol.* 27:1419-25.

Bouwman P, Aly A, Escandell JM, *et al.* (2010). 53BP1 loss rescues BRCA1 deficiency and is associated with triple-negative and BRCA-mutated breast cancers. Nat Struct Mol Biol 17:688-95.

Bryant HE, Schultz N, Thomas HD, *et al* (2005). Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. *Nature* 434:913-7.

Bunting SF, Callen E, Wong N, *et al.* (2010). 53BP1 inhibits homologous recombination in Brca1-deficient cells by blocking resection of DNA breaks. *Cell* 141:243-54.

Cediranib (AZD2171, RECENTIN™) Investigator's Brochure, Edition 13 (August 2009). AstraZeneca, Wilmington, DE.

Charpentier G, Benhamou PY, Dardari D, et al. (2011) The Diabeo Software Enabling Individualized Insulin Dose Adjustments Combined With Telemedicine Support Improves HbA1c in Poorly Controlled Type 1 Diabetic Patients: A 6-month, randomized, open-label, parallel-group, multicenter trial (TeleDiab 1 Study). *Diabetes Care*. 34(3):533-9.

Dahut, W.L., R.A. Madan, J.J. Karakunnel, *et al.* (2013). Phase II clinical trial of cediranib in patients with metastatic castration-resistant prostate cancer. *BJU Int.* 111:1269-1280.

Denduluri, N., A.W. Berman, U. Vatas, *et al.* (2007). Cardiotoxicity after doxorubicin and AZD2171, an oral vascular endothelial growth factor receptor (VEGFR) inhibitor, in patients (pts) with breast cancer. *Proc Am Soc Clin Oncol*. 25:A554.

Drevs, J., J. Esser, S.R. Wedge, *et al.* (2004) Effect of AZD2171, a highly potent VEGF receptor tyrosine kinase inhibitor, on primary tumor growth, metastasis and vessel density in murine renal cell carcinoma. *Proc Am Assoc Cancer Res*: A4554.

Economopoulou, M., H.F. Langer, A. Celeste, *et al.* (2009). Histone H2AX is integral to hypoxia-driven neovascularization. *Nat Med*. 15:553-558.

Farmer, H., N. McCabe, C.J. Lord, *et al.* (2005). Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. *Nature* 434(7035):917-921.

Ferrara, N, H.-P. Gerber, and J. LeCouter. (2003). The biology of VEGF and its receptors. *Nature Med*. 9:669-676.

Fong, P.C., T.A. Yap, D.S. Boss, *et al.* (2010). Poly(ADP)-ribose polymerase inhibition: Frequent durable responses in *BRCA* carrier ovarian cancer correlating with platinum-free interval. *J Clin Oncol*. 28(15):2512-2519.

Gadgeel, S.M., A. Wozniak, M.J. Edelman, *et al.* (2009). Cediranib, a VEGF receptor 1, 2, and 3 inhibitor, and pemetrexed in patients (pts) with recurrent non-small cell lung cancer (NSCLC). *J Clin Oncol*. 27(suppl):Ae19007.

Garland, L.L., K. Chansky, A.J. Wozniak, *et al.* (2011). Phase II study of cediranib in patients with malignant pleural mesothelioma. *J Thoracic Oncol*. 6:1938-1945.

Gelmon, K.A., M. Tischkowitz, H. Mackay, *et al.* (2011). Olaparib in patients with recurrent high-grade serous or poorly differentiated ovarian carcinoma or triple-negative breast cancer: A phase 2, multicentre, open-label, non-randomised study. *Lancet Oncol*. 12(9):852-861.

Gerstner, E.R., K.E. Emblem, A.S. Chi, *et al.* (2012). Effects of cediranib, a VEGF signaling inhibitor, in combination with chemoradiation on tumor blood flow and survival in newly diagnosed glioblastoma. *J Clin Oncol.* 30(Suppl):A2009.

Goon Pk, Lip GY, Boos CJ. (2006). Circulating endothelial cells, endothelial progenitor cells, and endothelial microparticles in cancer. *Neoplasia* 8:79-88.

Graeber, T.G., C. Osmanian, T. Jacks, *et al.* (1996). Hypoxia-mediated selection of cells with diminished apoptotic potential in solid tumours. *Nature* 379(6560):88-91.

Hammond, E.M., N.C. Denko, M.J. Dorie, *et al.* (2002). Hypoxia links ATR and p53 through replication arrest. *Mol Cell Biol*. 22(6):1834-1843.

Hammond, E.M., M.J. Dorie, and A.J. Giaccia. (2004). Inhibition of ATR leads to increased sensitivity to hypoxia/reoxygenation. *Cancer Res*. 64(18):6556-6562.

Hegan, D.C., Y. Lu, G.C. Stachelek, M.E. Crosby, *et al.* (2010). Inhibition of poly(ADP-ribose) polymerase downregulates BRCA1 and RAD51 in a pathway mediated by E2F4 and p130. *Proc Nat Acad Sci USA*. 107:2201-2206.

Hennequin, L.F., A.P. Thomas, C. Johnstone, *et al.* (1999). Design and structure-activity relationship of a new class of potent VEGF receptor tyrosine kinase inhibitors. *J Med Chem*. 42:5369-5389.

Herbst, R.S. (2006). Toxicities of antiangiogenic therapy in non-small cell lung cancer. *Clin Lung Cancer*. 8(suppl 1): S23-S30.

Hicklin, D.J., and L.M. Ellis. (2005). Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J Clin Oncol*. 23:1011-1027.

Hirte, H.W., L.Vidal, G.F. Fleming, *et al.* (2008). A phase II study of cediranib (AZD2171) in recurrent or persistent ovarian, peritoneal or fallopian tube cancer: Final results of a PMH, Chicago and California consortia trial. *Proc Am Soc Clin Oncol*. 26:A5521.

Izzedine, H., O. Rixe, B. Billemont, *et al.* (2007). Angiogenesis inhibitor therapies: Focus on kidney toxicity and hypertension. *Am J Kidney Dis*. 50:203-218.

Johnson N, Johnson SF, Yao W, *et al.* (2013). Stabilization of mutant BRCA1 protein confers

PARP inhibitor and platinum resistance. *Proc Natl Acad Sci U S A* 110:17041-6.

Jurgensmeier, J.M., S.R. Brave, N.H. James, *et al.* (2005). AZD2171, a highly potent inhibitor of VEGF receptor signaling, has additional activity *versus* the c-Kit receptor tyrosine kinase. *Proc Am Assoc Cancer Res*. 46:A5834.

Kamba, T.,and D.M. McDonald, (2007). Mechanisms of adverse effects of anti-VEGF therapy for cancer. *Br J Cancer*. 96:1788-1795.

Kappers,M.H.W., J.H.M. van Esch, S. Sleijfer, *et al.* (2009). Cardiovascular and renal toxicity during angiogenesis inhibition: Clinical and mechanistic aspects. *J Hypertens*. 27:2297-2309.

Kaye SB, Lubinski J, Matulonis U, *et al.* (2012). Phase II, open-label, randomized, multicenter study comparing the efficacy and safety of olaparib, a poly (ADP-ribose) polymerase inhibitor, and pegylated liposomal doxorubicin in patients with BRCA1 or BRCA2 mutations and recurrent ovarian cancer. *J Clin Oncol*, 30(4): 372-9.

Kearney N, McCann L, Norrie J, et al. (2009). Evaluation of a mobile phone-based advanced symptom management system (ASySM) in the management of chemotherapy-related toxicity. *Support Care Cancer*. 17(4):437-44.

Klinowska, T.C., J.A. Jackson, P.M. Farrington, *et al.* (2004) AZD2171, a highly potent inhibitor of VEGF receptor tyrosine kinase activity, inhibits the growth of spontaneous mammary tumors in the MMTV-neu transgenic mouse. *Proc Am Assoc Cancer Res:* A4540.

Kroenke K, Theobald D, Wu J, et al. (2010). Effect of telecare management on pain and depression in patients with cancer: a randomized trial. *JAMA*. 304(2): 163-71.

Kummar S, Gutierrez ME, Chen A, *et al.* (2011). Phase I trial of vandetanib and bevacizumab evaluating the VEGF and EGF signal transduction pathways in adults with solid tumours and lymphomas. Eur J Cancer 47:997-1005.

Langenberg, M.H.G., C.M.L. van Herpen, J. de Bono, *et al.* (2009). Effective strategies for management of hypertension after vascular endothelial growth factor signaling inhibition therapy: Results from a phase II randomized, factorial, double-blind study of cediranib in patients with advanced solid tumors. *J Clin Oncol*. 36:6152-6159.

Launay-Vacher, V., and G. Deray. (2009). Hypertension and proteinuria: A class-effect of antiangiogenic therapies. *Anticancer Drugs*. 20:81-82.

Ledermann, J.A., P. Harter, C. Gourley, *et al.* (2012). Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med*. 366 (15):1382-1392.

Lee, J.M., J. Squires, J.L. Hays, *et al.* (2011). A pharmacokinetics/pharmacodynamics study of sequence specificity of the PARP inhibitor olaparib with carboplatin in refractory/recurrent women's cancers: NCT01237067. *J Clin Oncol. (ASCO Annual Meeting Proceedings)* 29s:

Abstract TPS158.

Lindsay, C.R., I.R.J. MacPherson, and J. Cassidy. (2009). Current status of cediranib: The rapid development of a novel anti-angiogenic therapy. *Future Oncol*. 5:421-432.

Liu, J.F., S. M. Tolaney, M. Birrer, *et al*. (2013). A Phase 1 trial of the poly(ADP-ribose) polymerase inhibitor olaparib (AZD2281) in combination with the anti-angiogenic cediranib (AZD2171) in recurrent epithelial ovarian or triple-negative breast cancer. *Eur J Cancer*. 49:2972-2978.

Liu JF, Barry WT, Birrer M, et al. (2014) Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study. Lancet Oncol. Oct;15(11):1207-14.

Liu J and Matulonis UA. New strategies in ovarian cancer: Translating the Molecular Complexity of Ovarian Cancer into Treatment Advances. (2014) Clin Cancer Res. 20:5150-6.

Maguire R, McCann L, Miller M, et al. (2008). Nurse's perceptions and experiences of using a mobile-phone based Advanced Symptom Management System (ASySM©) to monitor and manage chemotherapy related toxicity. *Eur J Oncol Nurs*. 12(4):380-6.

Matulonis, U.A., S. Berlin, P. Ivy, *et al*. (2009). Cediranib, an oral inhibitor of vascular endothelial growth factor receptor kinases, is an active drug in recurrent epithelial ovarian, fallopian tube, and peritoneal cancer. *J Clin Oncol*. 27:5601-5606.

McCann L, Maguire R, Miller M, et al. (2009). Patients' perceptions and experiences of using a mobile-phone based Advanced Symptom Management System (ASySM©) to monitor and manage chemotherapy related toxicity. *Eur J Cancer Care (Engl)*. 18(2):156-64.

McGuire WP, Hoskins WJ, Brady MF et al. (1996) Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. New Engl Journal of Medicine 334:1-6.

Menear, K.A., C. Adcock, R. Boulter, *et al*. (2008). 4-[3-(4-cyclopropanecarbonylpiperazine-1-carbonyl)-4-fluorobenzyl]-2H-phthalazin-1-one: a novel bioavailable inhibitor of poly(ADP-ribose) polymerase-1. *J Med Chem*. 51(20):6581-6591.

Mengden T, Hernandez Medina RM, Beltran B, et al. (1998) Reliability of reporting self-measured blood pressure values by hypertensive patients. *Am J Hypertens*. 11(12):1413-7.

Mooney KH, Beck Sl, Friedman RH, et al. (2014). Automated monitoring of symptoms during ambulatory chemotherapy and oncology providers' use of the information: a randomized clinical trial. *Support Care Cancer*. 22(9):2343-50.

Ning YM, Gulley JL, Arlen PM, *et al.*. (2010). Phase II trial of bevacizumab, thalidomide, docetaxel, and prednisone in patients with metastatic castration-resistant prostate cancer. *J Clin*

Oncol 28:2070-6.

Nord AS, Lee M, King MC, *et al*. (2011). Accurate and exact CNV identification from targeted high-throughput sequence data. *BMC Genomics* 12:184.

Olaparib (AZD2281, KU-0059436) Investigator's Brochure, Edition 10 (November 2013). AstraZeneca, Wilmington, DE.

Park SR, Speranza G, Piekarz R, *et al*. (2013). A multi-histology trial of fostamatinib in patients with advanced colorectal, non-small cell lung, head and neck, thyroid, and renal cell carcinomas, and pheochromocytomas. *Cancer Chemother Pharmacol* 71:981-90.

Pennington KP, Swisher EM. (2012). Hereditary ovarian cancer: beyond the usual suspects. *Gynecol Oncol*, 124(2): 347-53.

Pennington KP, Walsh T, Harrell MI, *et al*. (2014). Germline and somatic mutations in homologous recombination genes predict platinum response and survival in ovarian, fallopian tube, and peritoneal carcinomas. *Clin Cancer Res*, 20(3):764-75.

Pfisterer J, Plante M, Vergote I et al. (2006) Gemcitabine/carboplatin compared with carboplatin in patients with platinum-senstive recurrent ovarian cancer: An Intergroup Trial of the AGO OVAR, NCIC CTG and EORTC GCG. Journal of Clinical Oncology 24:4699-4706.

Pritchard CC, *et al*. (2012) ColoSeq Provides Comprehensive Lynch and Polyposis Syndrome Mutational Analysis Using Massively Parallel Sequencing. *J Mol Diagn* 14:357-366.

Pujade-Lauraine E, Wagner U, Aavall-Lundqvist E, Gebski V, Heywood M, et al. (2010)Pegylated liposomal Doxorubicin and Carboplatin compared with Paclitaxel and Carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. J Clin Oncol. 28:3323-9.

Raja, FA, Griffin Cl, Qian W, et al. (2011). Initial toxicity assessment of ICON6: a randomized trial of cediranib plus chemotherapy in platinum-sensitive relapsed ovarian cancer. *Br J Cancer*. 105(7):884-9.

Ramalingam, S.S., P.C. Mack, E.E. Vokes, *et al*. (2008). Cediranib (AZD2171) for the treatment of recurrent small cell lung cancer (SCLC): A California Consortium phase II study (NCI #7097A). *Proc Am Soc Clin Oncol*. 26:A8078.

Robinson, E.S., U.A. Matulonis, P. Ivy, et al. (2010). Rapid development of hypertension and proteinuria with cediranib, an oral vascular endothelial growth factor receptor inhibitor. *Clin J Am Soc Nephrol* 5:477-483.

Siegel R, Ma J, Zou Z, Jemal A. (2104) Cancer Statistics 2014 CA Cancer J Clin 64:9-29.

Sorensen, A.G., T.T. Batchelor, W.-T. Zhang, *et al*. (2009). A "vascular normalization index"

as potential mechanistic biomarker to predict survival after a single dose of cediranib in recurrent glioblastoma patients. *Cancer Res*. 69:5296-5300.

Sridhar, S.S., M.J. Mackenzie, S.J. Hotte, *et al*. (2008). Activity of cediranib (AZD2171) in patients (pts) with previously untreated metastatic renal cell cancer (RCC). A phase II trial of the PMH Consortium. *Proc Am Soc Clin Oncol*. 26:A5047.

Tentori, L., P.M. Lacal, A. Muzi. (2007). Poly(ADP-ribose) polymerase (PARP) inhibition or PARP-1 gene deletion reduces angiogenesis. *Eur J Cancer*. 43:2124-2133.

Walsh T, Casadei S, Lee MK, *et al*. (2011). Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. *Proc Natl Acad Sci U S A* 108:18032-7.

Walsh T, Lee MK, Casadei S, *et al*. (2010) Detection of inherited mutations for breast and ovarian cancer using genomic capture and massively parallel sequencing. *Proc Natl Acad Sci U S A* 107:12629-33.

Weaver A, Young Am, Rowntree J, et al. (2007). Application of mobile phone technology for managing chemotherapy-associated side effect. *Ann Oncol*. 18(11):1887-92.

Wedge, S.R., J. Kendrew, L.F. Hennequin, *et al*. (2005). AZD2171: A highly potent, orally bioavailable, vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor for the treatment of cancer. *Cancer Res*. 65:4389-4400.

Wickramanayake A, Bernier G, Pennil C, *et al*. (2012). Loss of function germline mutations in RAD51D in women with ovarian carcinoma. *Gynecol Oncol*, 127(3):552-5.

Zhu, A.X., M. Ancukiewicz, J.G. Supko, *et al*. (2012). Clinical, pharmacodynamic (PD), and pharmacokinetic (PK) evaluation of cediranib in advanced hepatocellular carcinoma (HCC): A phase II study (CTEP 7147). *J Clin Oncol*. 30(Suppl):A4112.

APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. 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.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, 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.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B PATIENT DRUG DIARY

Today's Date _____ Cycle # _____
Patient Name _____ Patient Study ID _____

1. Complete one form for each cycle (28 days).
2. Record the date, the number of tablets you took, and when you took them.
3. Bring your pill bottles (including empty bottles) and this form to every appointment.
4. Do not chew, dissolve, or crush medications. DO NOT make up vomited doses.
5. If you miss a dose, you have up to 2 hours to make this dose up. Otherwise, write "missed" where you would normally write the time of your dose.
6. The first row in the table below is an EXAMPLE ROW for how to complete this diary.

CEDIRANIB
Take ____(number)_____mg tablets once a day. Take on an empty stomach 1 hour before taking the morning dose of olaparib.

OLAPARIB
Take _____(number)_____mg and _____(number)_____mg tablets twice a day 12 hours apart after a light meal.

Day	Date	15mg	20mg	AM	Day	Date	100mg	150mg	AM	PM
1	*1/1/15*	*2*	*0*	*7:00*	*1*	*1/1/15*	*2*	*0*	*8:00*	*8:00*
1					1					
2					2					
3					3					
4					4					
5					5					
6					6					
7					7					
8					8					
9					9					
10					10					
11					11					
12					12					
13					13					
14					14					
15					15					
16					16					
17					17					
18					18					
19					19					
20					20					
21					21					
22					22					
23					23					
24					24					
25					25					
26					26					
27					27					
28					28					

Patient's Signature: _____ Date: _____

Physician/Nurse/Data Manager's Signature _____ Date_____

APPENDIX C: PATIENT'S BLOOD PRESSURE DIARY

Today's Date _____ Cycle # _____

Patient Name _____ Patient Study ID _____

Instructions to the Patient:

1. Your blood pressure readings have two numbers. The first number is the pressure in your blood vessels during a heart beat (systolic), and the second number is the pressure in the vessels when the heart rests in between beats (diastolic). These numbers are usually written with a slash in between them (for example, normal blood pressure is 120/80).
2. Record the date, then record your blood pressure twice each day using a home blood pressure monitor.
   - Each morning while you are resting (not while you are active: dressing, making breakfast, etc.)
   - Each evening at bedtime or while you are relaxing during the evening
3. If you take your blood pressure at other times, record the numbers and time under "Other Readings."
4. If your systolic pressure is greater than 140 **OR** your diastolic blood pressure is greater than 90, please contact your local doctor's office at _____ for instructions.
5. Please bring this form to every clinic visit or appointment.

Day	Date	AM Readings	PM Readings	Other Readings (include time)	Day	Date	AM Readings	PM Readings	Other Readings (include time)
1		/	/		15		/	/	
2		/	/		16		/	/	
3		/	/		17		/	/	
4		/	/		18		/	/	
5		/	/		19		/	/	
6		/	/		20		/	/	
7		/	/		21		/	/	
8		/	/		22		/	/	
9		/	/		23		/	/	
10		/	/		24		/	/	
11		/	/		25		/	/	
12		/	/		26		/	/	
13		/	/		27		/	/	
14		/	/		28		/	/	

Patient's Signature: _____ Date: _____

Physician's office will complete this section:

Date of this clinic visit _____

Physician/Nurse/Data Manager's Signature _____ Date _____

APPENDIX D: PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, **olaparib (AZD2281).** This clinical trial is sponsored by the National Cancer Institute (NCI). This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a prescriber need to know:

Olaparib interacts with certain specific enzymes in the liver and certain transport proteins that help move drugs in and out of cells.

- The enzymes in question are CYP 3A4/5, 1A2, 2B6, 2C9, 2C19 and UGT1A1. Olaparib is cleared by CYP3A4/5 and is affected by strong and moderate inhibitors and inducers of CYP3A4/5. Olaparib inhibits CYP3A4 and UGT1A1 enzymes and may increase levels of other drugs that are cleared by these enzymes. Olaparib induces CYP 1A2, 2B6 and 3A4 enzymes and has the possibility of inducing CYP 2C9, 2C19 enzymes that may result in decreased levels of other drugs that are cleared by these enzymes.
- The transport proteins in question are P-glycoprotein (P-gp), organic anion-transporting polypeptides (OATP1B1 and OAT3), organic cation transporters (OCT1 and OCT2), multi-drug and toxin extrusion proteins (MATE1 and MATE2K) and breast cancer resistance protein (BCRP). Olaparib requires P-gp to move in and out of cells and concomitant administration of strong P-gp inhibitors and inducers should be avoided. Olaparib inhibits P-gp, BCRP, OATP1B1, OCT1, OCT2, OAT3, MATE1 and MATE2K transporters and has the possibility of inducing P-gp and that may affect the transport of other drugs that depend on these proteins to move in and out of cells. Use caution when taking substrates of these transporters, such as statins.

November 2015

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Olaparib may interact with many drugs which can cause side effects. Because of this, it is very important to tell your study doctors about all of your medicines before you enroll on this clinical trial. It is also very important to tell them if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care prescribers can write prescriptions. You must also tell your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Olaparib must be used very carefully with other medicines that need certain liver enzymes and transport proteins to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of CYP3A4/5 and P-gp." Olaparib inhibits enzymes "CYP3A4, UGT1A1, P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1, MATE2K and BCRP." Olaparib possibly induces "CYP 1A2, 2B6, 3A4, 2C9, 2C19 and P-gp." These characteristics may change how other medicine works in your body.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctor or pharmacist to determine if there could be any side effects.
- Avoid ingesting grapefruit, grapefruit juice and Seville oranges while taking olaparib.
- You may need to be monitored more frequently if you are taking any drugs that have narrow therapeutic ranges.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____.

November 2015

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental drug **olaparib (AZD2281).** This clinical trial is sponsored by the NCI. Olaparib interacts with drugs that are processed by your liver, or use certain transport proteins in your body. Because of this, it is very important to:

- Tell your doctors if you stop taking regular medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Olaparib interacts with liver enzymes, CYP3A4/5, 1A2, 2B6, 2C9, 2C19, UGT1A1, and transport proteins, P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1, MATE2K and BCRP.

- Olaparib must be used very carefully with other medicines that interact with these enzymes and proteins.
- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines that are considered ""strong or moderate inducers/inhibitors of CYP3A4/5 and P-gp." Olaparib inhibits "CYP 3A4, UGT1A1 and transport proteins P-gp, OATP1B1, OCT1, OCT2, OAT3, MATE1, MATE2K and BCRP and induces CYP 1A2, 2B6, 3A4, 2C9, 2C19 and transport protein P-gp." It may change how other medicine works in your body.
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____ and can be contacted at _____.

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient _____ is enrolled on a clinical trial using the experimental study drug, **cediranib (AZD2171).** This clinical trial is sponsored by the National Cancer Institute (NCI). This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a prescriber need to know:

Cediranib (AZD2171) interacts with certain specific enzymes in the liver and certain transport proteins that help move drugs in and out of cells.

- The enzymes in question are CYP 3A4, 2D6, flavin-containing monooxygenase (FMO) and UGT1A4. Cediranib (AZD2171) is metabolized by FMO1, FMO3 and UGT1A4 and may be affected by other drugs that strongly inhibit or induce these enzymes. Cediranib (AZD2171) weakly inhibits CYP 2D6 and 3A4 and may increase levels of affected substrates.
- Cediranib (AZD2171) may induce gastrointestinal CYP3A and UGT enzymes, therefore potentially reducing the effectiveness of hormonal contraceptives.
- The transport proteins in question are P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). Cediranib (AZD2171) requires P-gp to move in and out of cells. Cediranib (AZD2171) inhibits BCRP, P-gp, OATP1B1, OATP1B3, OCT2, MATE1 and MATE2-K and this may affect the clearance of other drugs that are dependent on these transport proteins.
- Cediranib (AZD2171) is 95% protein bound (human serum albumin and alpha-1-acid glycoprotein) and may displace other highly protein-bound drugs. Use caution in patients taking concomitant medications with narrow therapeutic ranges.
- Patients receiving Cediranib (AZD2171) are at increased risk of bleeding and hemorrhage. Increase monitoring in patients who also receive anticoagulation therapy.

June 2016

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Cediranib (AZD2171) interacts with many drugs which can cause side effects. Because of this, it is very important to tell your study doctors about all of your medicines before you enroll on this clinical trial. It is also very important to tell them if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care prescribers can write prescriptions. You must also tell your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a

clinical trial.

These are the things that you and they need to know:

Cediranib (AZD2171) must be used very carefully with other medicines that need certain liver enzymes and transport proteins to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inducers/inhibitors of FMO1, FMO3, UGT1A4 and P-gp." Cediranib (AZD2171) inhibits enzymes "CYP 2D6 and 3A4, transport proteins BCRP, P-gp, OATP1B1, OATP1B3, OCT2, MATE1 and MATE2-K and is highly protein-bound." These characteristics may change how other medicine works in your body.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctor or pharmacist to determine if there could be any side effects.
- Cediranib (AZD2171) can increase the risk of bleeding and interferes with wound healing. Let your doctor know if you recently had or are planning to have any surgery.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____ and he or she can be contacted at _____.

June 2016

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental drug **AZD2171 (cediranib).** This clinical trial is sponsored by the NCI. Cediranib (AZD2171) interacts with drugs that are processed by your liver, or use certain transport proteins in your body. Because of this, it is very important to:

- Tell your doctors if you stop taking regular medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistant, nurse practitioners, pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Cediranib (AZD2171) interacts with CYP3A4, 2D6, FMO1, FMO3, UGT1A4 and transport proteins, P-gp and BCRP and must be used very carefully with other medicines that interact with these enzymes and proteins.
- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines that are considered ""strong inducers/inhibitors of FMO1, FMO3, UGT1A4 and P-gp." Cediranib (AZD2171) inhibits "CYP 2D6 and 3A4 and transport proteins BCRP, P-gp, OATP1B1, OATP1B3, OCT2, MATE1 and MATE2-K and is highly protein-bound." It may change how other medicine works in your body.
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____ and can be contacted at _____.

THE FOLLOWING TABLES LIST KNOWN CYP3A4 INDUCERS AND INHIBITORS. INVESTIGATORS SHOULD ALSO REFERENCE THE FOLLOWING WEBSITES FOR UPDATED INFORMATION REGARDING CYP3A4 INTERACTIONS:

CYP3A4 Inducers (prohibited)

Armodafenil[1]	Modafinil[2]	Primidone[1]
Barbiturates[2]	Nafcillin[1]	Rifabutin
Bosentan[1]	Nevirapine	Rifampin
Carbamazepine	Oxcarbazepine	Rifapentine[1]
Dexamethasone[1]	Pentobarbital[1]	St. John's wort[2]
Efavirenz	Phenobarbital	Troglitazone[3]
Fosphenytoin[1]	Phenytoin	
Glucocorticoids[2] (see note)	Pioglitazone[2]	

Note: Topical steroids are permitted. Systemic steroids may be allowed if clinically indicated while on trial after discussion with the overall PI.

[1] Cited in Cytochrome P450 Enzymes: Substrates, Inhibitors, and Inducers. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL, eds. Drug Information Handbook 20th ed. Hudson, OH; LexiComp Inc. 2011-2012: 1810-1818

[2] Cited in Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). http://medicine.iupui.edu/clinpharm/ddis/table.asp. Accessed Nov 2011.

[3] Weak inhibitor per Lacy et al. May be used with caution.

Note: Drugs without a superscript are cited in both the Lacy and Flockhart references.

CYP3A4 Inhibitors

Strong Inhibitors (prohibited)	**Moderate Inhibitors** (avoid if possible; reduce olaparib dose per 5.4 if use unavoidable)	**Weak Inhibitors** (use with caution, avoid if possible)
Amprenavir[1]	Amiodarone[1]	Chloramphenicol[2]
Atazanavir[1]	Aprepitant	Ciprofloxacin[2]
Clarithromycin	Cimetidine[1]	Diethyldithiocarbamate[2]
Conivaptan[1]	Clotrimazole[1]	Fluvoxamine[2]
Delavirdine[1]	Cyclosporine[1]	Gestodene[2]
Fosamprenavir[1]	Desipramine[1]	Mibefradil[2]
Fospropofol[1]	Doxycycline[1]	Mifepristone
Imatinib[1]	Efavirenz[1]	Norfluoxetine[2]
Indinavir	Erythromycin	Star fruit[2]
Isoniazid[1]	Fluconazole	Troleandomycin[2]
Itraconazole	Fosaprepitant[1]	
Ketoconazole	Grapefruit juice	
Miconazole[1]	Haloperidol[1]	
Nefazodone	Lidocaine[1]	
Nelfinavir	Metronidazole[1]	
Nicardipine[1]	Norfloxacin[1]	
Posaconazole[1]	Sertraline[1]	
Propofol[1]	Tetracycline[1]	
Quinidine[1]	Verapamil	
Ritonavir	Voriconazole[1]	
Saquinavir[2]		
Telithromycin		

[1] Cited in Cytochrome P450 Enzymes: Substrates, Inhibitors, and Inducers. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL, eds. Drug Information Handbook 20th ed. Hudson, OH; LexiComp Inc. 2011-2012: 1810-1818

[2] Cited in Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). http://medicine.iupui.edu/clinpharm/ddis/table.asp. Accessed Nov 2011.

Note: Drugs without a superscript are cited in both the Lacy and Flockhart references.

APPENDIX E: New York Heart Association Classifications

Clinical Evaluation of Functional Capacity of Patients With Heart Disease in Relation to Ordinary Physical Activity

Class	Cardiac Symptoms	Limitations	Need for Additional Rest*	Physical Ability to Work**
I	None	None	None	Full Time
II	Only moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, and any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician

** At accustomed occupation or usual tasks

APPENDIX F: GENOMIC DATA SHARING PLAN

NCI GENOMIC DATA SHARING PLAN FOR THE EXPERIMENTAL THERAPEUTICS CLINICAL TRIALS NETWORK

Data produced through this award will be shared in a manner consistent with the NIH Genomic Data Sharing Policy (NOT-OD-14-124).

Grants: Awarded through FOA RFA-CA-13-006.
Project Title: NCI Experimental Therapeutics Clinical Trials Network
Principal Investigators: Joyce Liu, Dana-Farber Cancer Institute
NCI Project Scientists: S.P. Ivy, Investigational Drug Branch/CTEP/DCTD
J. Moscow, Investigational Drug Branch/CTEP/DCTD

1. Data to be Shared

Genomic data:
The genomic data to be shared will be human (and may include the human microbiome).

It will be acquired from analysis of either tumor or normal tissues or body fluids.

It will include sequencing data from either RNA or DNA, from either genome-wide sequencing or more targeted panels or arrays. It may also include DNA methylation data, chromatin immunoprecipitation (ChIP-seq) data or other data types that fall under the NIH Genomic Data Sharing Policy.

It may include either somatic or germline sequences.

Phenotypic data:
The phenotypic data to be shared will include at a minimum the information needed to reproduce the primary analysis of the clinical trial. Relevant metadata (e.g. protocols and methods) will be shared.

2. Data Repository

Each study will be registered in dbGAP and the data will be submitted for controlled-access release to an NCI-approved data repository (e.g., dpGAP or, Cancer Genomics Hub, NCI Genome Data Commons.)

3. Data Submission and Release Timeline

Data should generally be submitted once it has been cleaned (e.g., the analytical dataset is finalized)." "Data will be released six months after initiation of submission process or at the time of first publication (whichever comes first); the **exception** to data submission and release timelines is for data subject to a binding collaborative agreement and is bound by the terms of

the agreement.

In no case will this precede the publication of the primary analysis of the clinical trial. Once released, data will be available for secondary research access without restrictions on publication.

4. IRB Assurance of the Genomic Data Sharing Plan

This data sharing plan will be approved by the Central Institutional Review Board (IRB) of the ETCTN, which will assure, prior to protocol activation, that

A. The protocol for collection of genomic and phenotypic data is consistent with 45 CFR Part 46;

B. Data submission and subsequent data sharing for research purposes are consistent with the informed consent of study participants from whom the data were obtained;

C. Consideration was given to risks to individuals participants and their families associated with data submitted to NIH-designated repositories and subsequent sharing;

D. To the extent relevant and possible, consideration was given to risks to groups or populations associated with submitting data to NIH-designated data repositories and subsequent sharing, and

E. The plan for de-identifying datasets is consistent with the standards outlined in the GDS policy.

An institutional certification signed by the Signing Official of each ETCTN awardee institution has been submitted and approved by the Central IRB of the ETCTN.

5. Appropriate Uses of the Data

The NCI model consent form provides consent for the data to be used for future research and to be shared through controlled-access databases subject to the following limitations:

A. The requestor must agree to make results of studies using the data available to the larger scientific community.

APPENDIX G: ORAL ANTIHYPERTENSIVE MEDICATIONS

Agents in bold characters are suggested as optimal choices to avoid or minimize potential drug-interactions with cediranib through CYP450. Agent classes are listed in order of preference in the absence of any other compelling indication, such as impaired renal function, proteinuria, etc. Note that each agent's dosing should be maximized before being replaced or adding another agent class.

Agent class	Agent	Initial dose	Intermediate dose	Maximum dose	Hepatic metabolism
Angiotensin Converting Enzyme Inhibitors (ACEIs)	captopril	12.5 mg 3x daily	25 mg 3x daily	50 mg 3x daily	CYP 2D6 substrate
	enalapril	5 mg daily	10-20 mg daily	40 mg daily	Yes (CYP450 unknown)
	ramipril	2.5 mg daily	5 mg daily	10 mg daily	Yes (CYP450 unknown)
	lisinopril	**5 mg daily**	**10-20 mg daily**	**40 mg daily**	**No**
	fosinopril	10 mg daily	20 mg daily	40 mg daily	**Yes, but not CYP450**
	Rarely used: **perindopril**	**4 mg daily**	**none**	**8 mg daily**	**Yes, but not CYP450**
	Rarely used: **quinapril**	**10 mg daily**	**20 mg daily**	**40 mg daily**	**No**
Angiotensin II Receptor Blockers (ARBs)	losartan	25 mg daily	50 mg daily	100 mg daily	CYP 3A4 and 2C9 substrate
	candesartan	4 mg daily	8-16 mg daily	32 mg daily	CYP 2C9 substrate
	irbesartan	75 mg daily	150 mg daily	300 mg daily	CYP 2C9 substrate
	telmisartan	**40 mg daily**	**none**	**80 mg daily**	**Yes, but not CYP450**
	valsartan	**80 mg daily**	**none**	**160 mg daily**	**Yes, but not CYP450**

Selective β Blockers (BB)	metoprolol	25 mg twice daily	50 mg twice daily	100 mg twice daily	CYP 2D6 substrate
	atenolol	**25 mg daily**	**50 mg daily**	**100 mg daily**	**No**
	acebutolol	100 mg twice daily	200-300 mg twice daily	400 mg twice daily	Yes (CYP450 unknown)
	bisoprolol	2.5 mg daily	5-10 mg daily	20 mg daily	CYP 3A4 substrate
α and β Blocker	labetalol	100 mg twice daily	200 mg twice daily	400 mg twice daily	Yes, but not CYP450
Diuretics	Hydralazine	10 mg four times daily	25 mg four times daily	50 mg four times daily	no
	Hydrochlorothiazide	12.5 mg AM daily	25 mg AM daily	50 mg AM daily	no
	Furosemide	20 mg daily	20 mg twice daily	40 mg twice daily	no
Nitrates	Isosorbide dinitrate ER	40 mg daily	40 mg twice daily	80 mg twice daily	CYP 3A4 substrate
	Isosorbide mononitrate ER	30 mg AM daily	60 mg AM daily	90 mg AM daily	CYP 3A4 substrate
Dihydro-pyridine Calcium-Channel Blockers (DHP CCB)	nifedipine XL	30 mg daily	60 mg daily	90 mg daily	CYP 3A4 substrate
	amlodipine	2.5 mg daily	5 mg daily	10 mg daily	CYP 3A4 substrate
	felodipine	2.5 mg daily	5 mg daily	10 mg daily	CYP 3A4 substrate

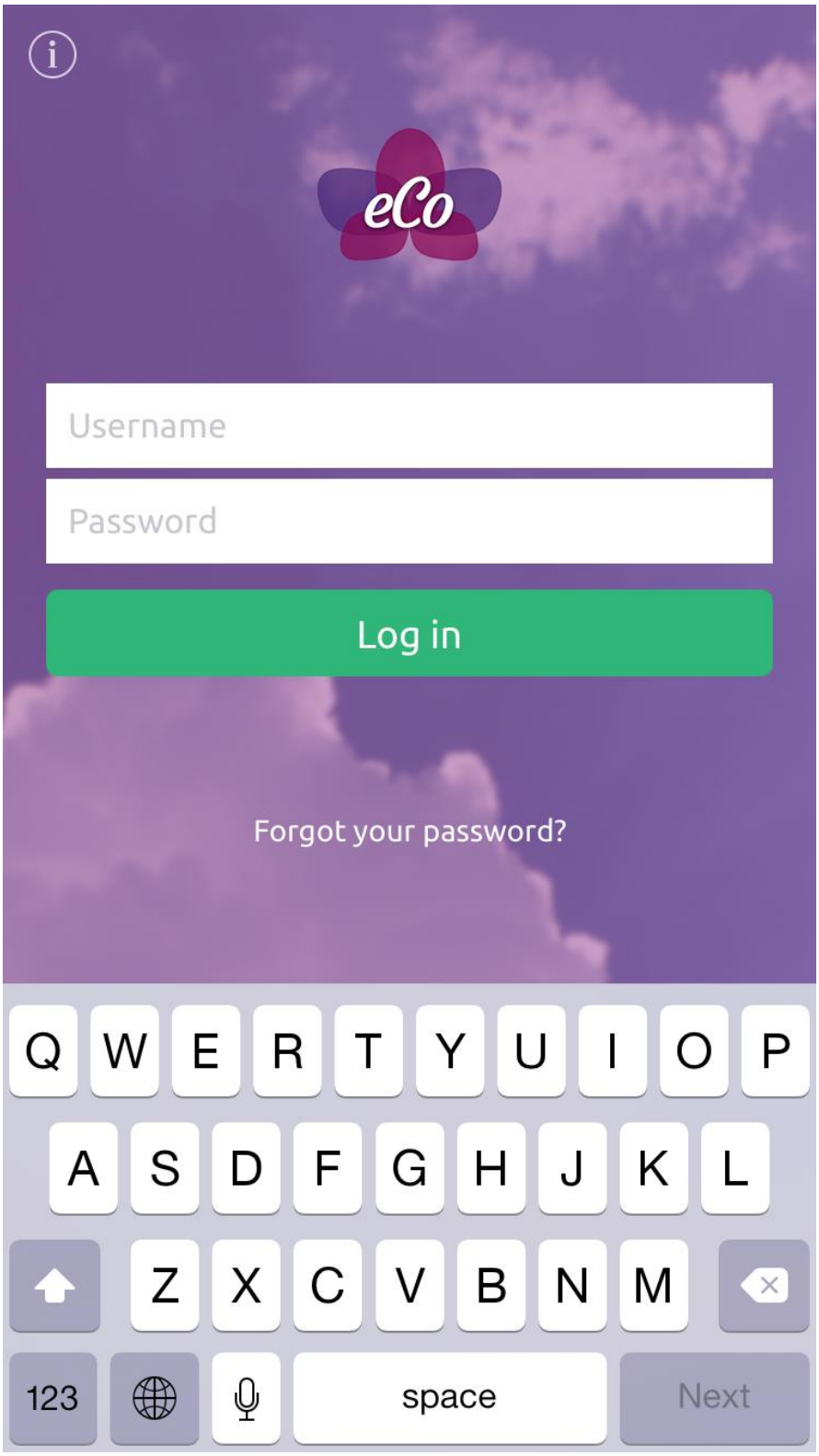
APPENDIX H: eCO MOBILE

eCo Mobile App Screenshots

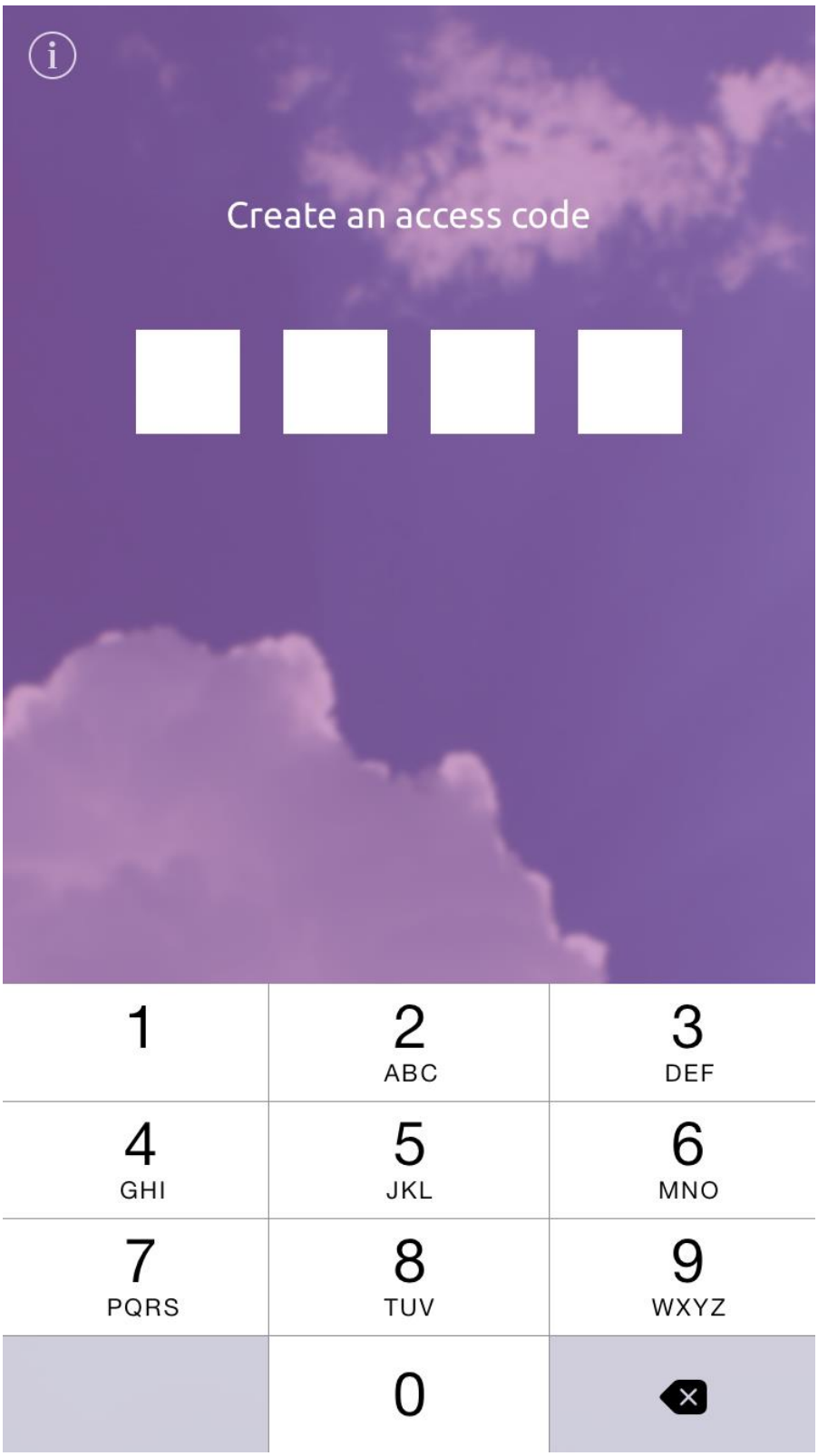
Patients

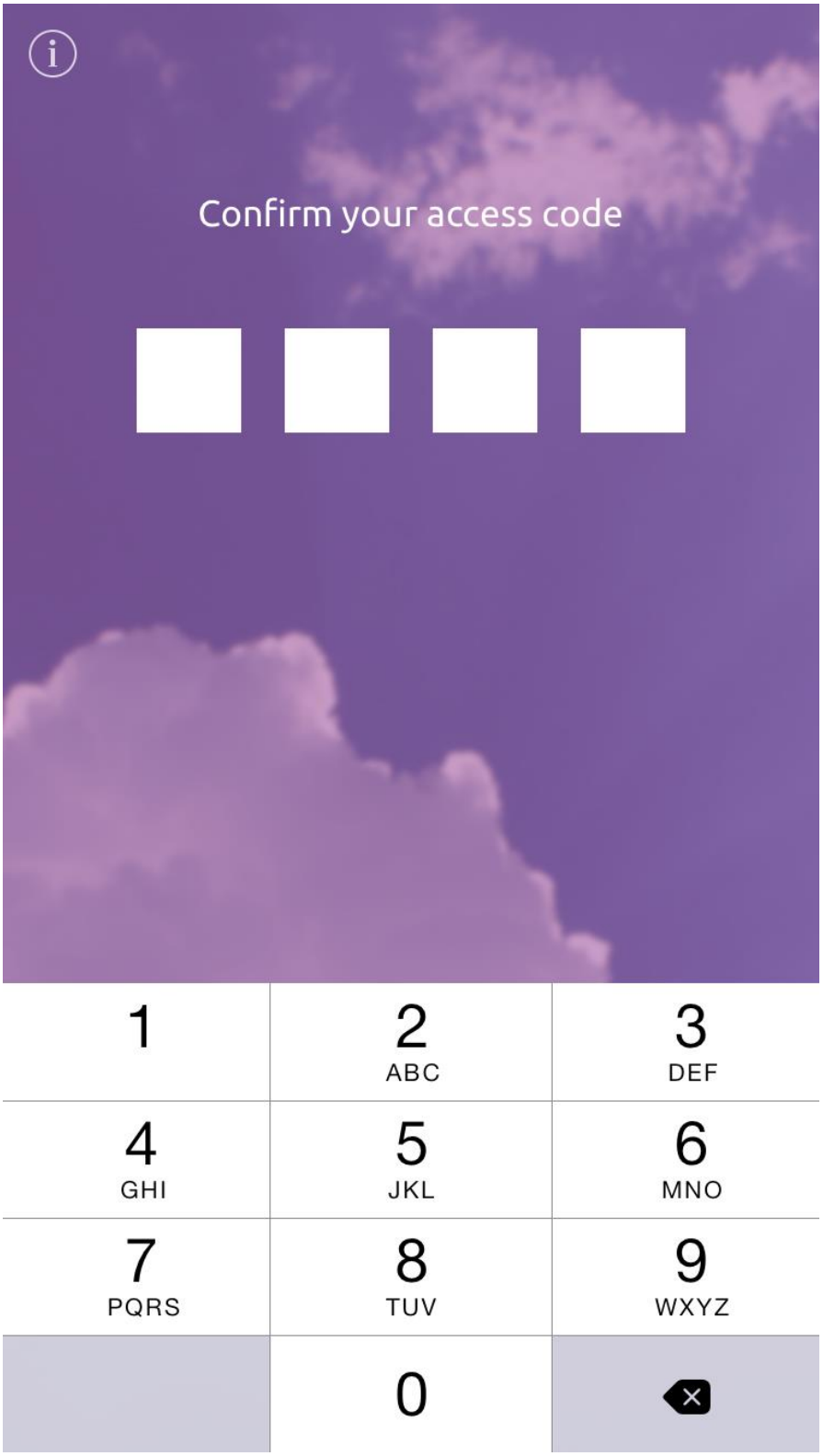
Set-Up

First Login Screen

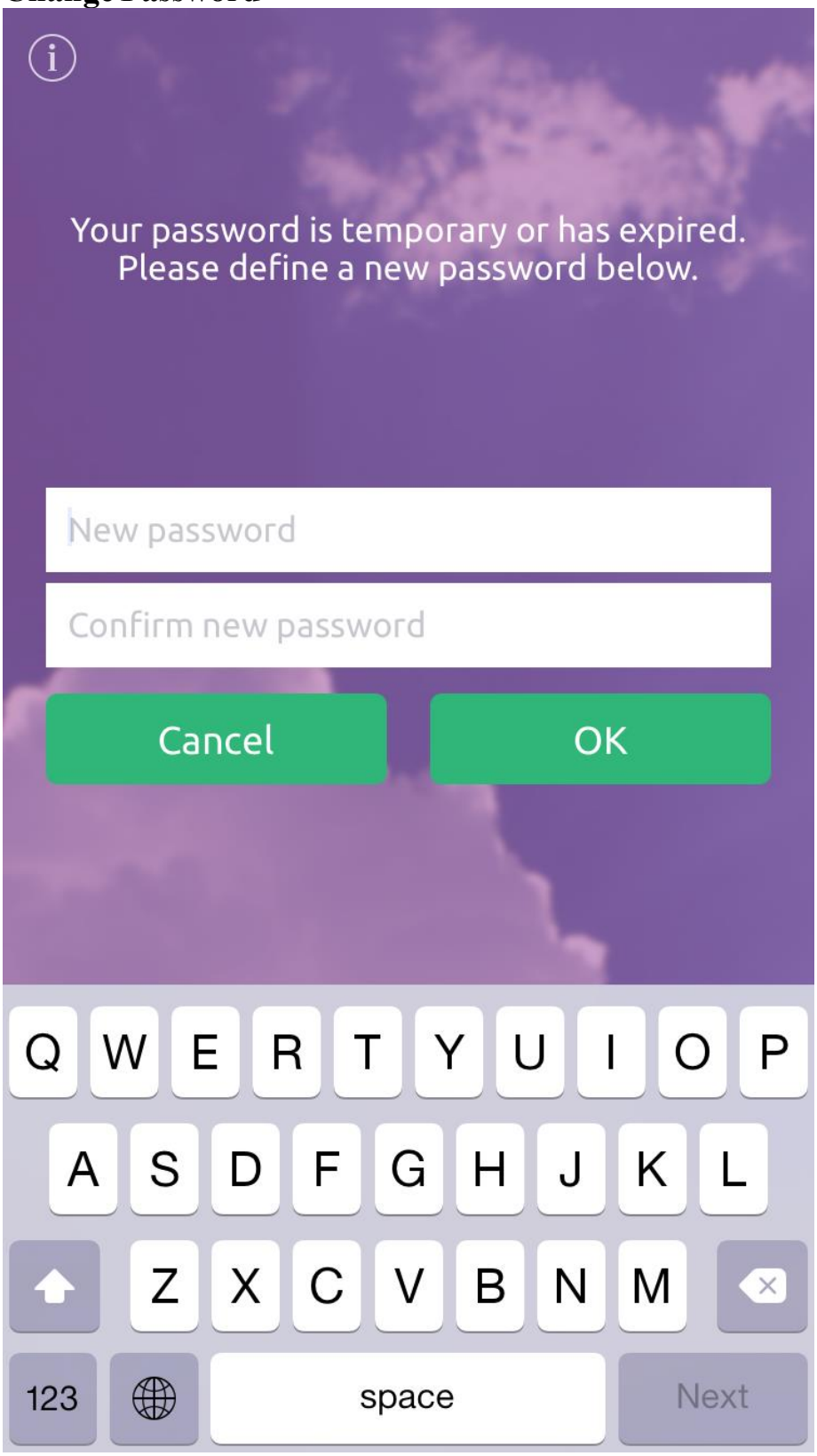


Create Access Code



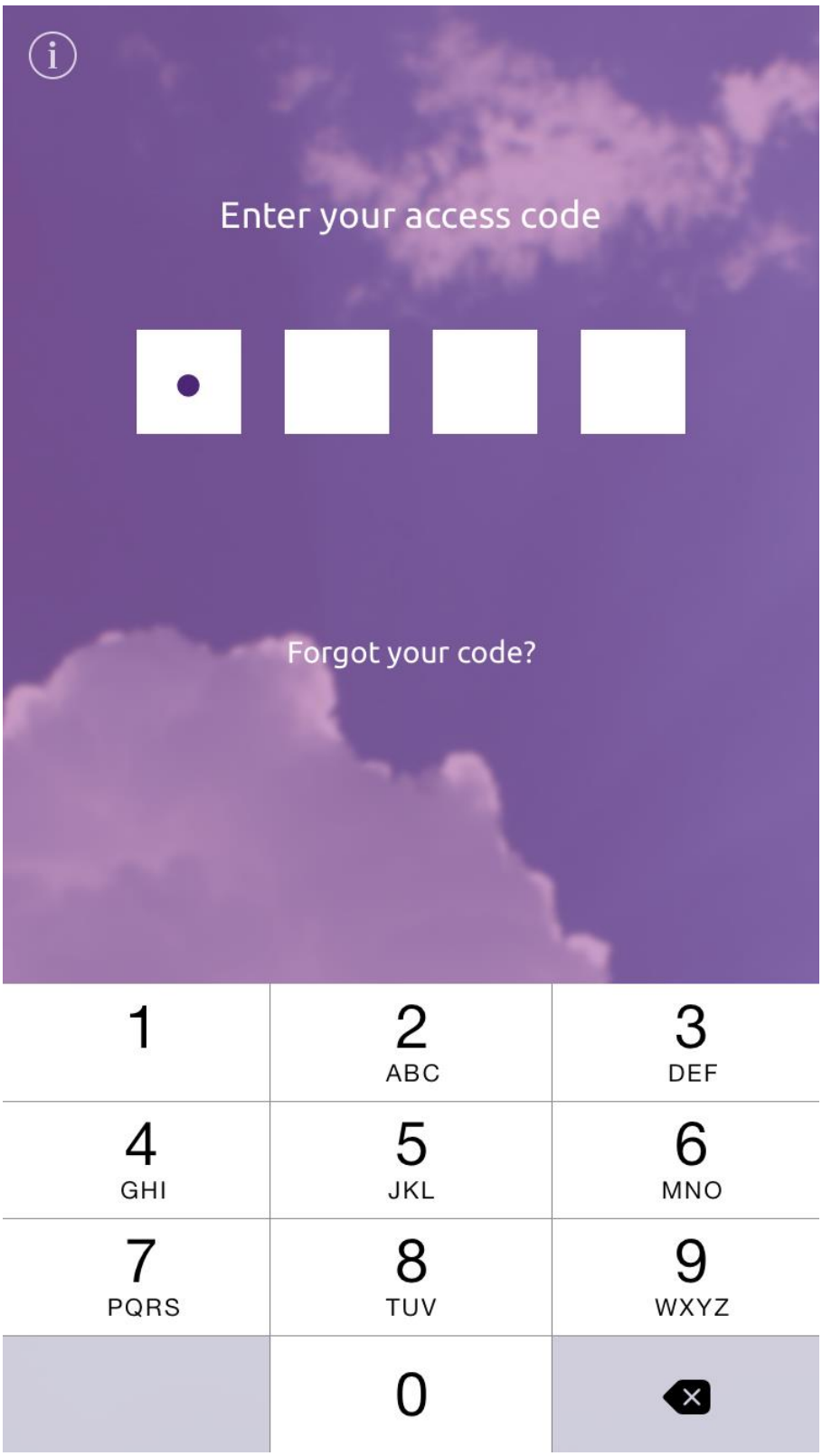

Confirm your access code
1
2 ABC
3 DEF
4 GHI
5 JKL
6 MNO
7 PQRS
8 TUV
9 WXYZ
0

Change Password

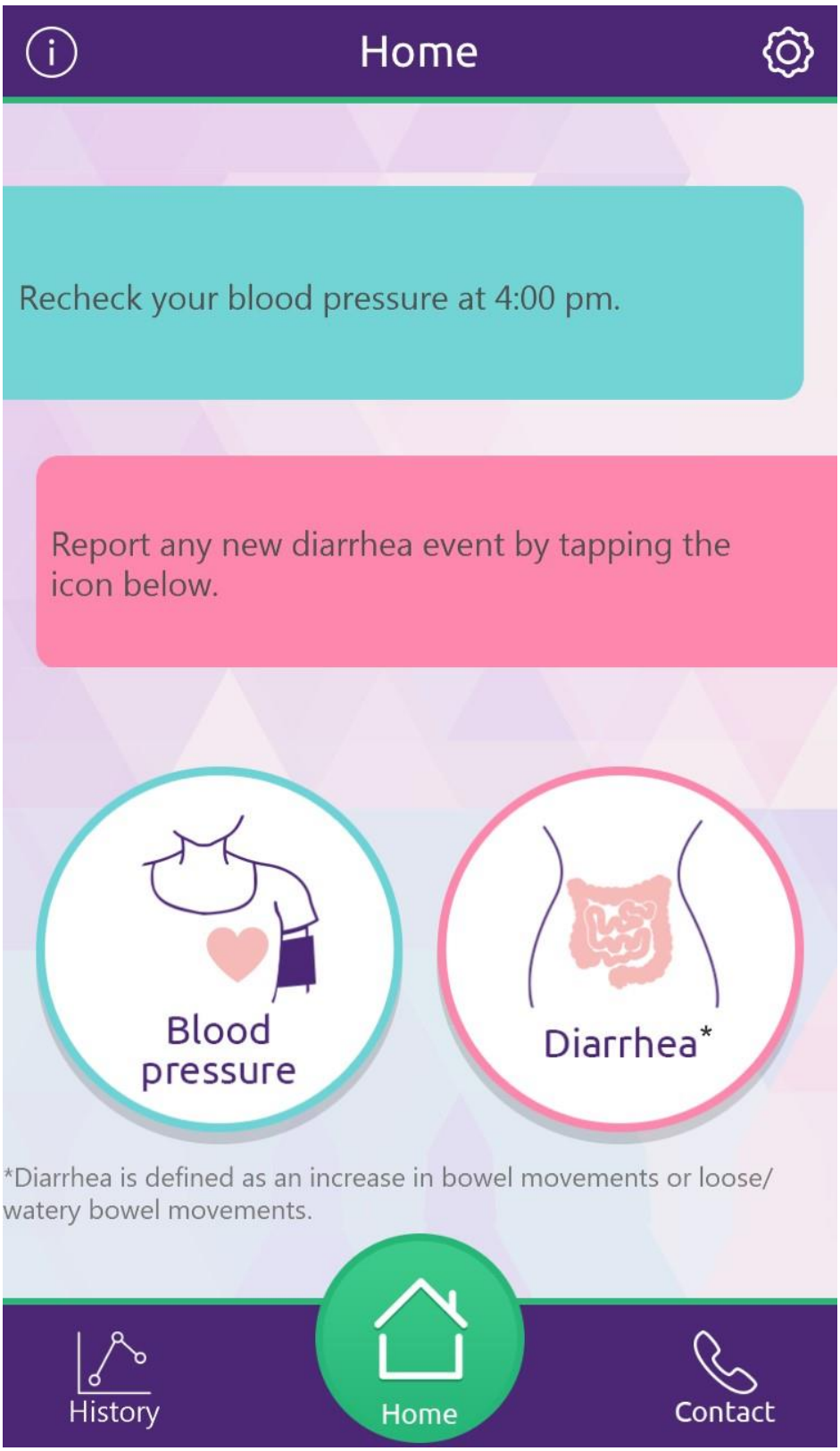


Ongoing Use

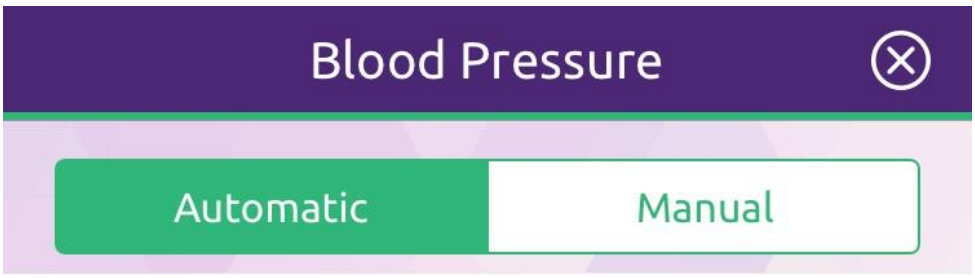
Enter Access Code



Home Screen


Home
Recheck your blood pressure at 4:00 pm.
Report any new diarrhea event by tapping the icon below.
Blood pressure
Diarrhea*
*Diarrhea is defined as an increase in bowel movements or loose/ watery bowel movements.
History
Home
Contact

Enter Blood Pressure (using Bluetooth enabled BP monitor)

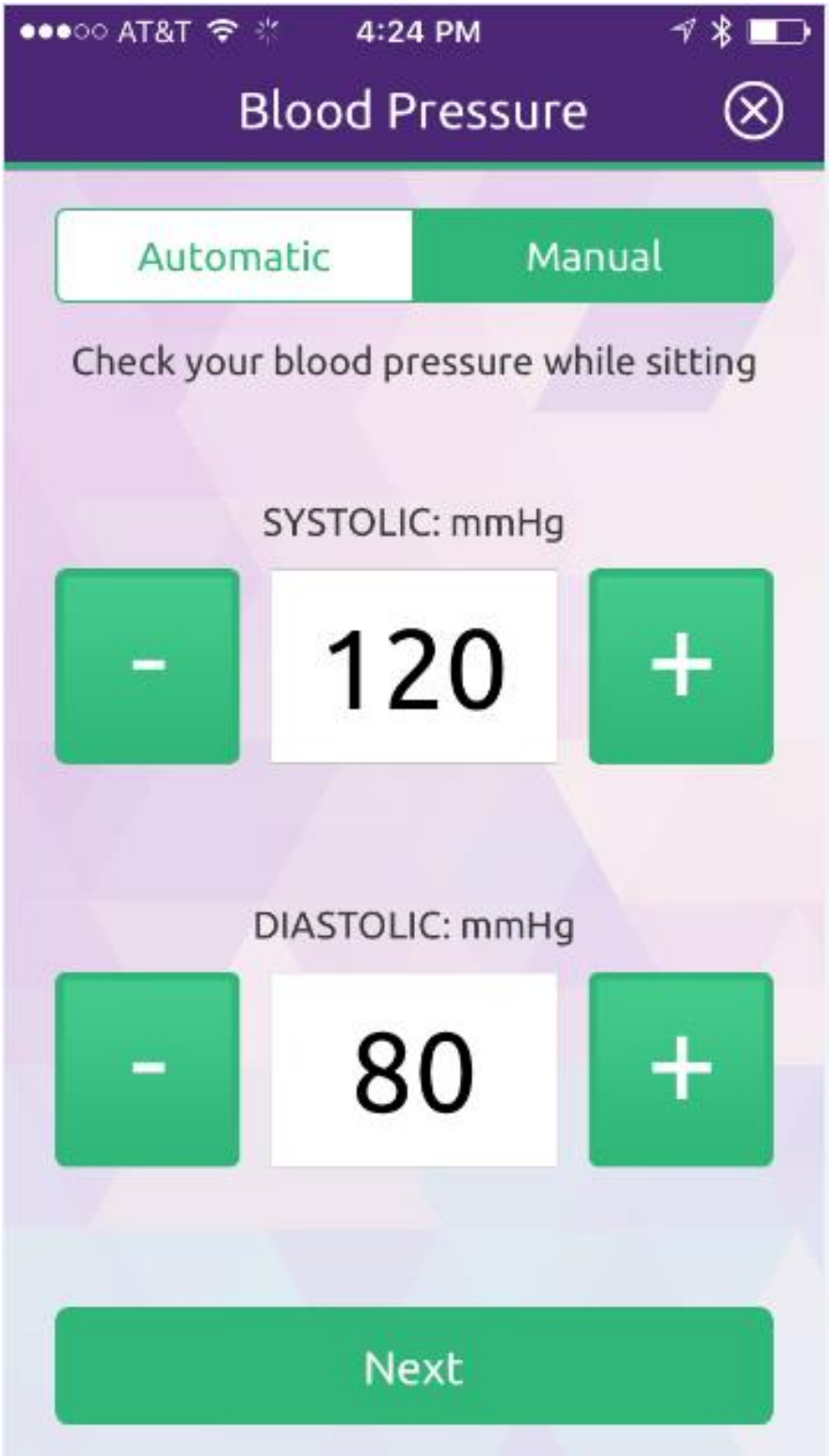


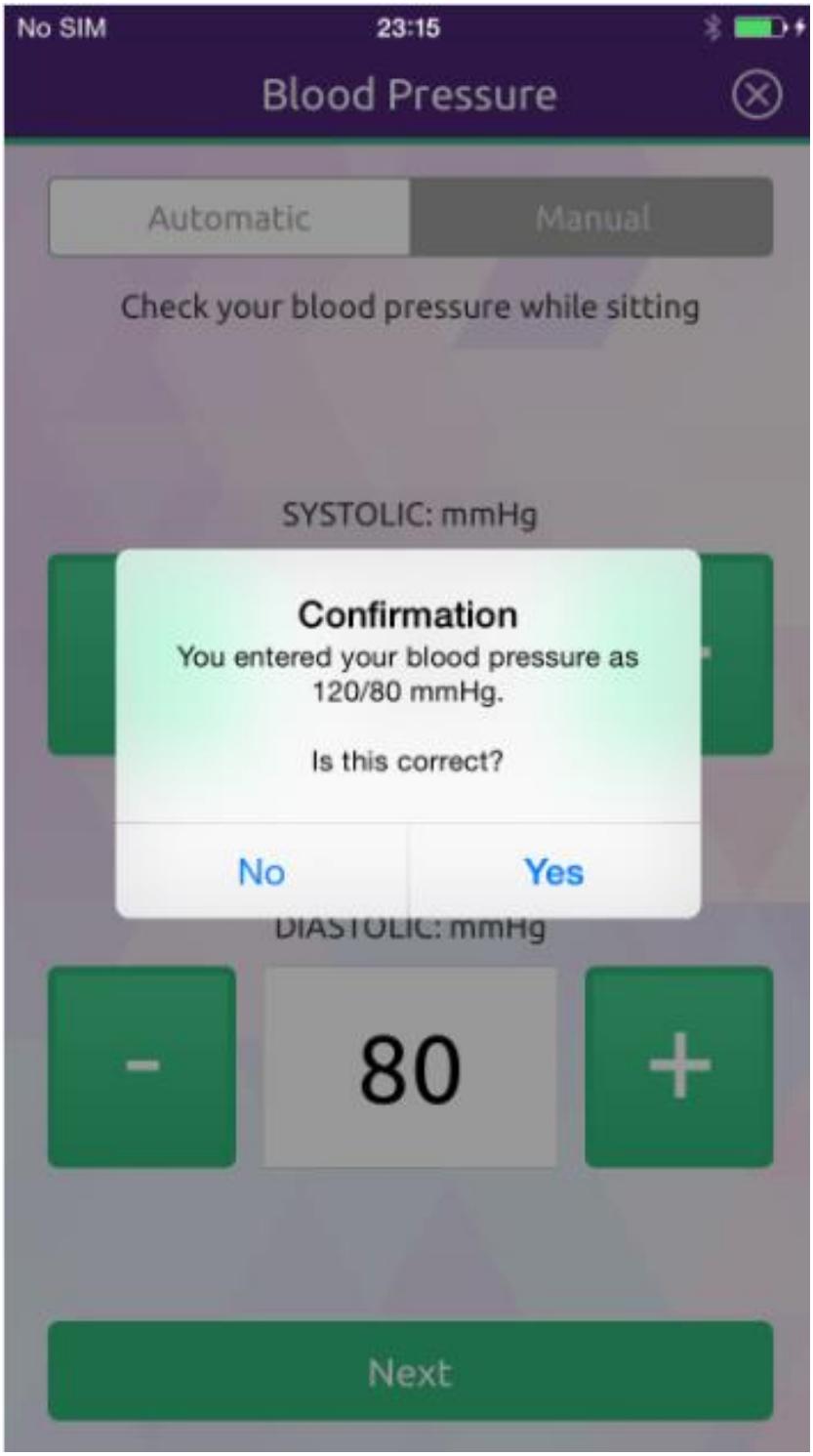
- Check your blood pressure while sitting.
- Put on the blood pressure cuff
- Press the "Start" button on the device.
- Wait for the measure to be taken.


No SIM
18:31
Blood Pressure
Automatic
Manual
Wait while data is transferring to your phone...
A&D Medical
SYS.
DIA.
PUL.
START
Bluetooth

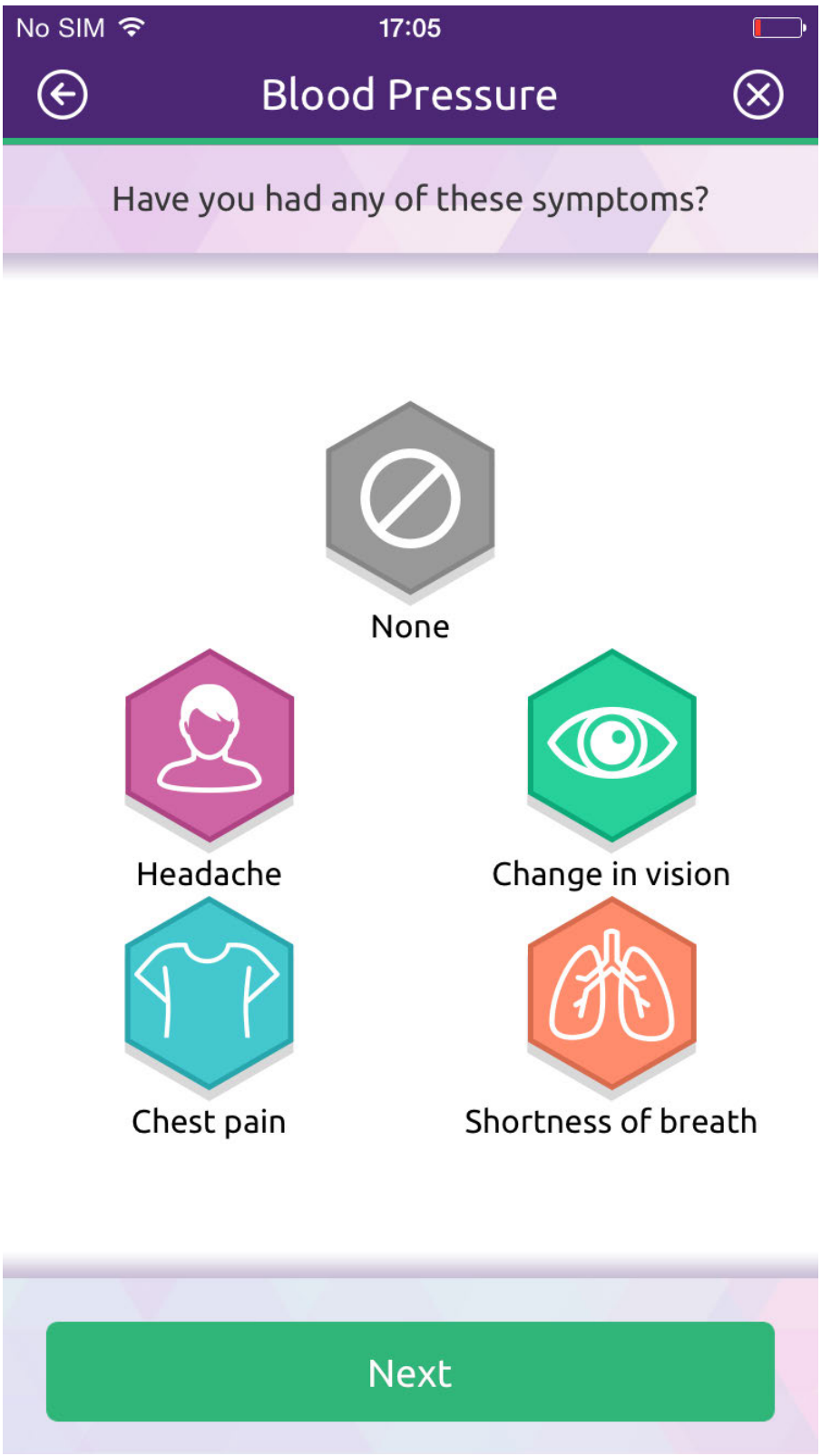

Blood Pressure
SYSTOLIC: mmHg
110
DIASTOLIC: mmHg
78
Next

Enter Blood Pressure (Manual)

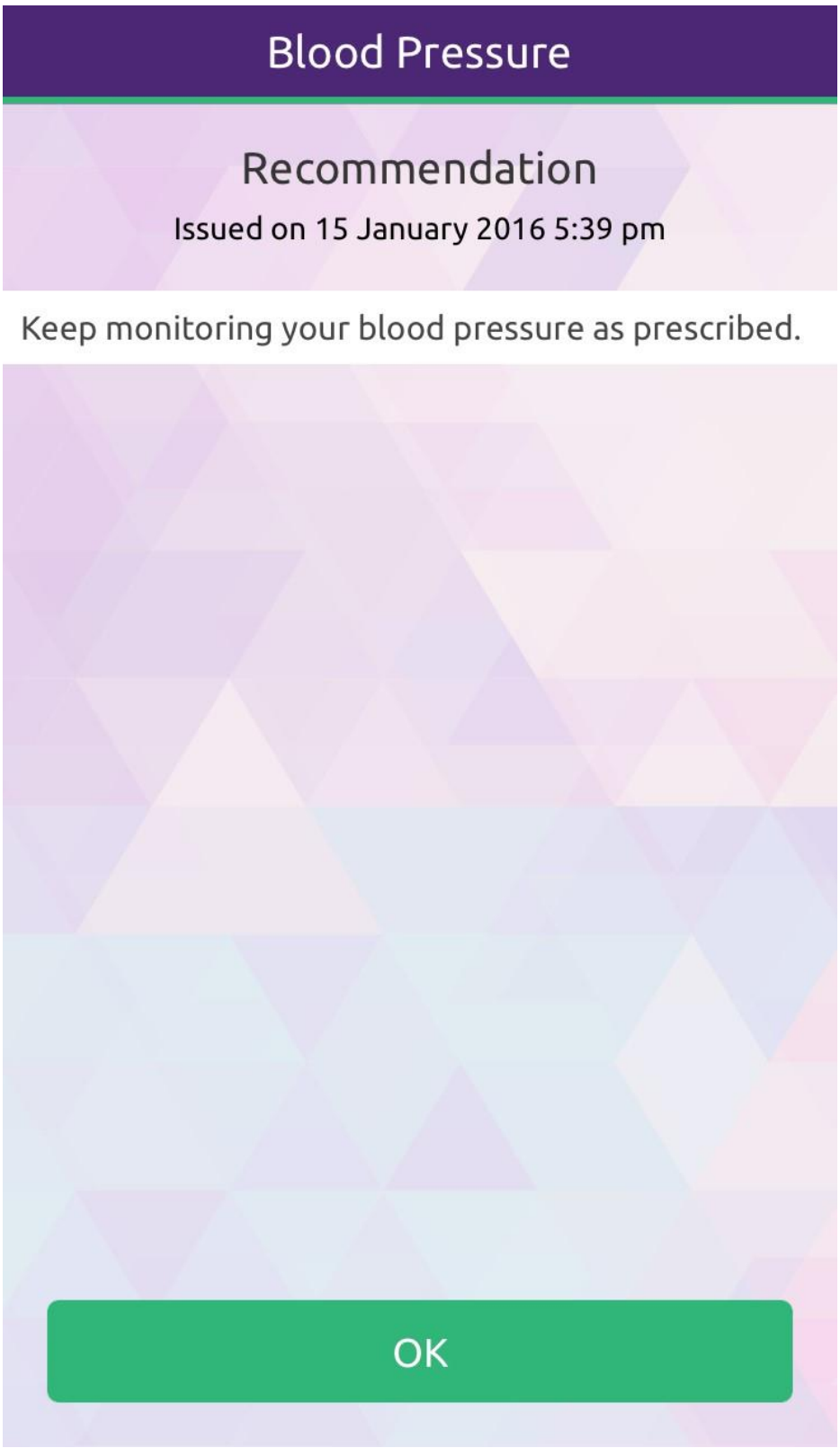


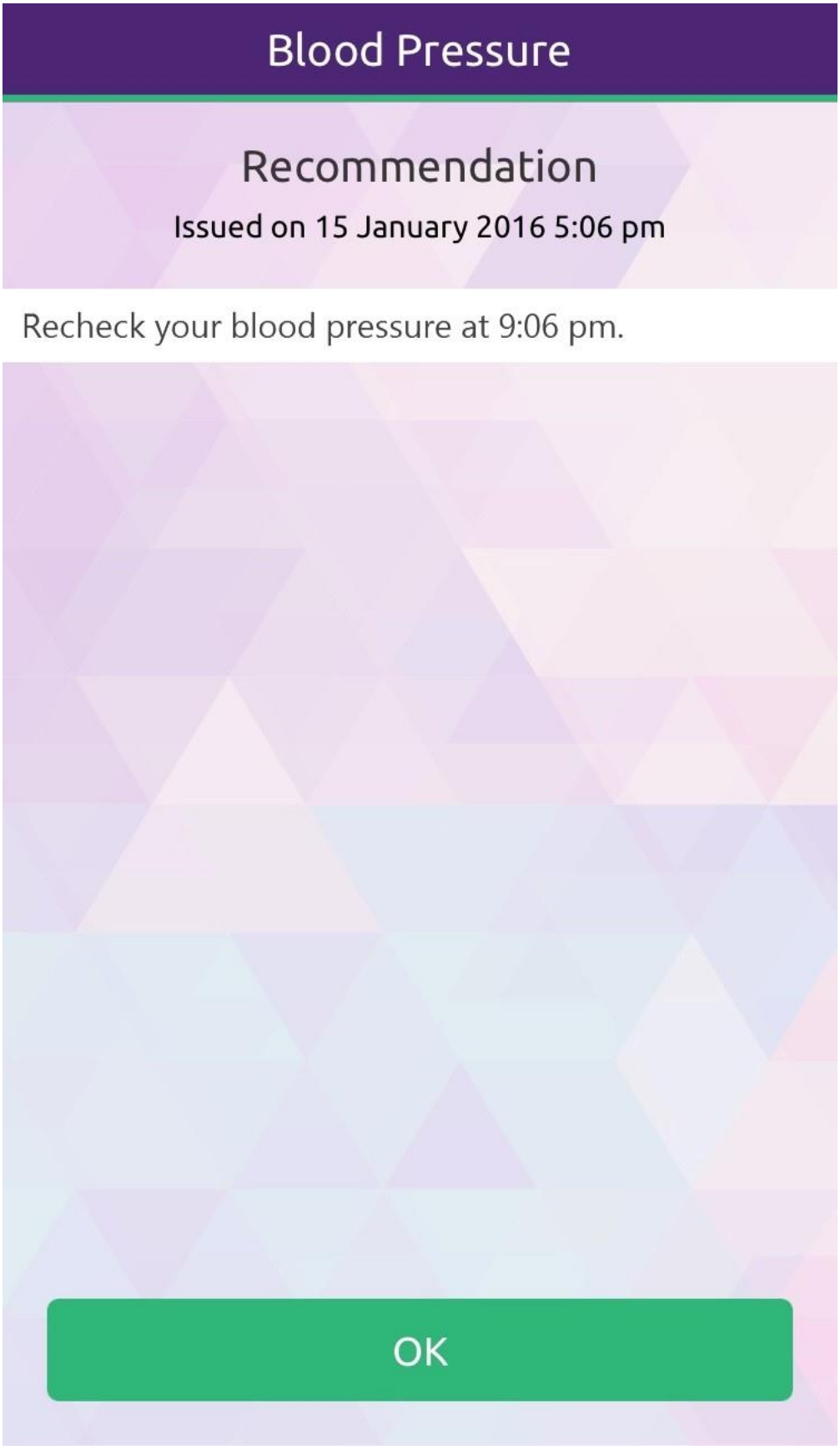

No SIM
23:15
Blood Pressure
Automatic
Manual
Check your blood pressure while sitting
SYSTOLIC: mmHg
Confirmation
You entered your blood pressure as 120/80 mmHg.
Is this correct?
No
Yes
DIASTOLIC: mmHg
-
80
+
Next

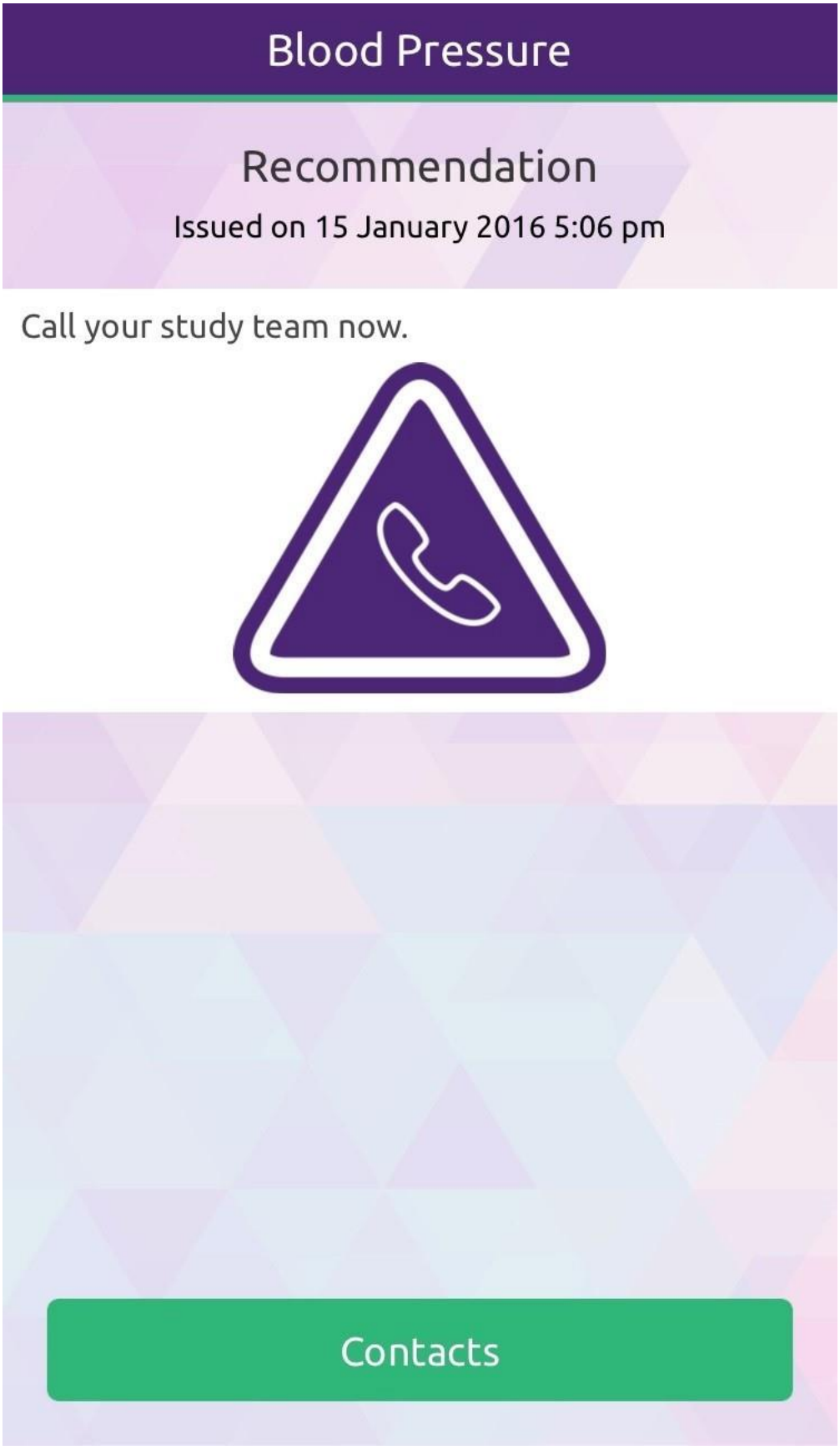
Add Blood Pressure Related Symptoms



Examples of BP Recommendations

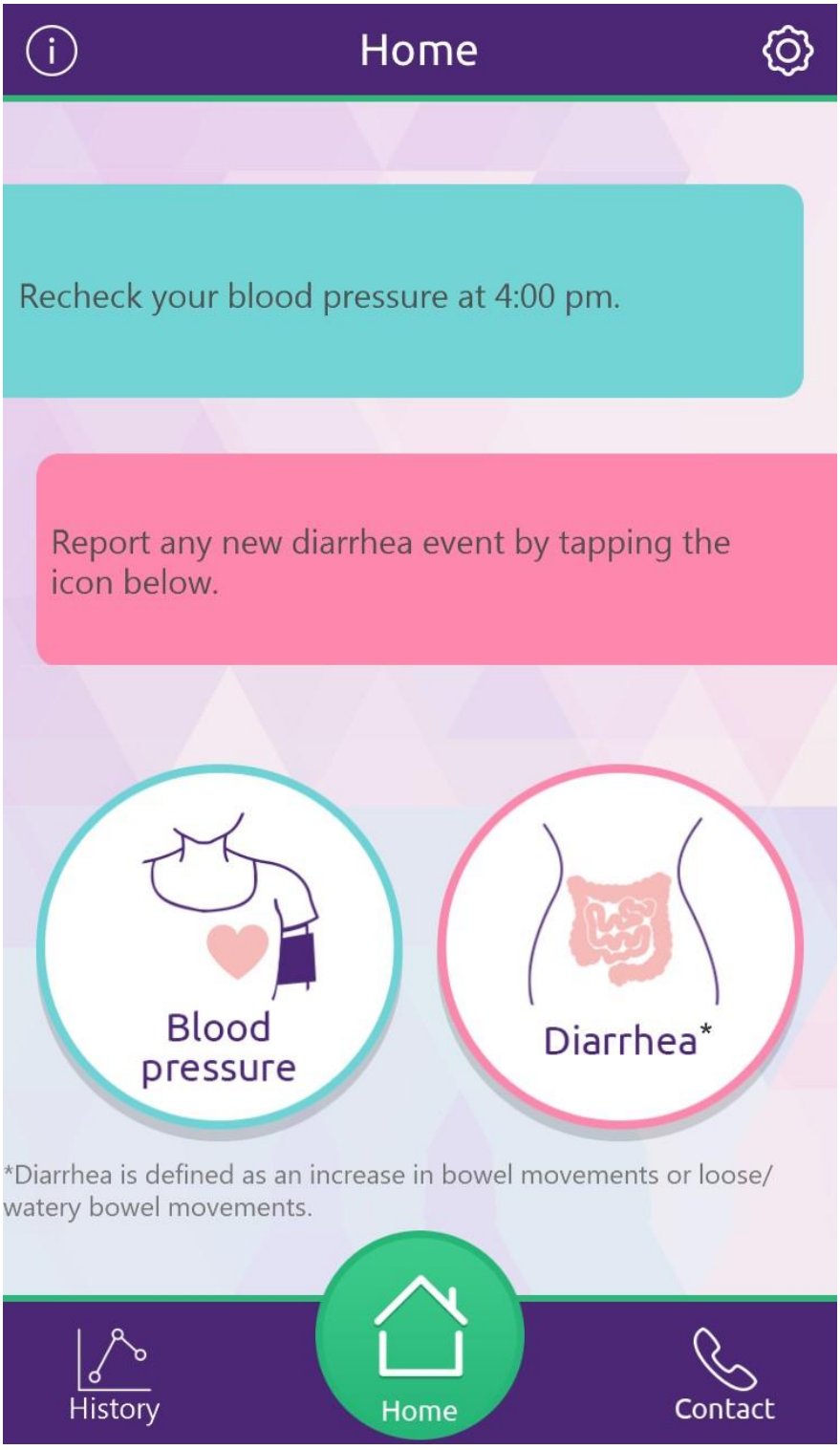



Blood Pressure
Recommendation
Issued on 15 January 2016 5:06 pm
Recheck your blood pressure at 9:06 pm.
OK

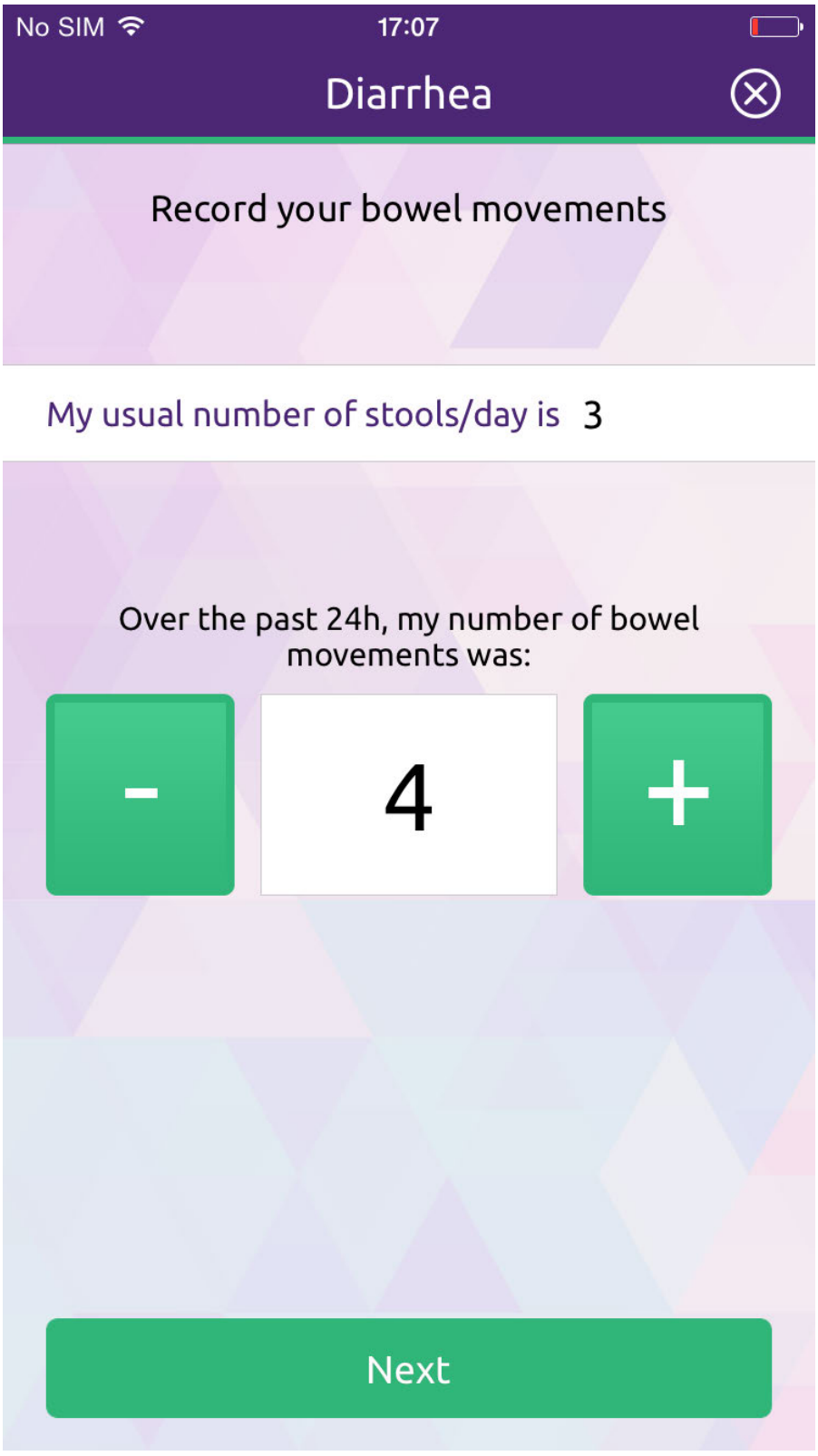

Blood Pressure
Recommendation
Issued on 15 January 2016 5:06 pm
Call your study team now.
Contacts

Record a Diarrhea Event:

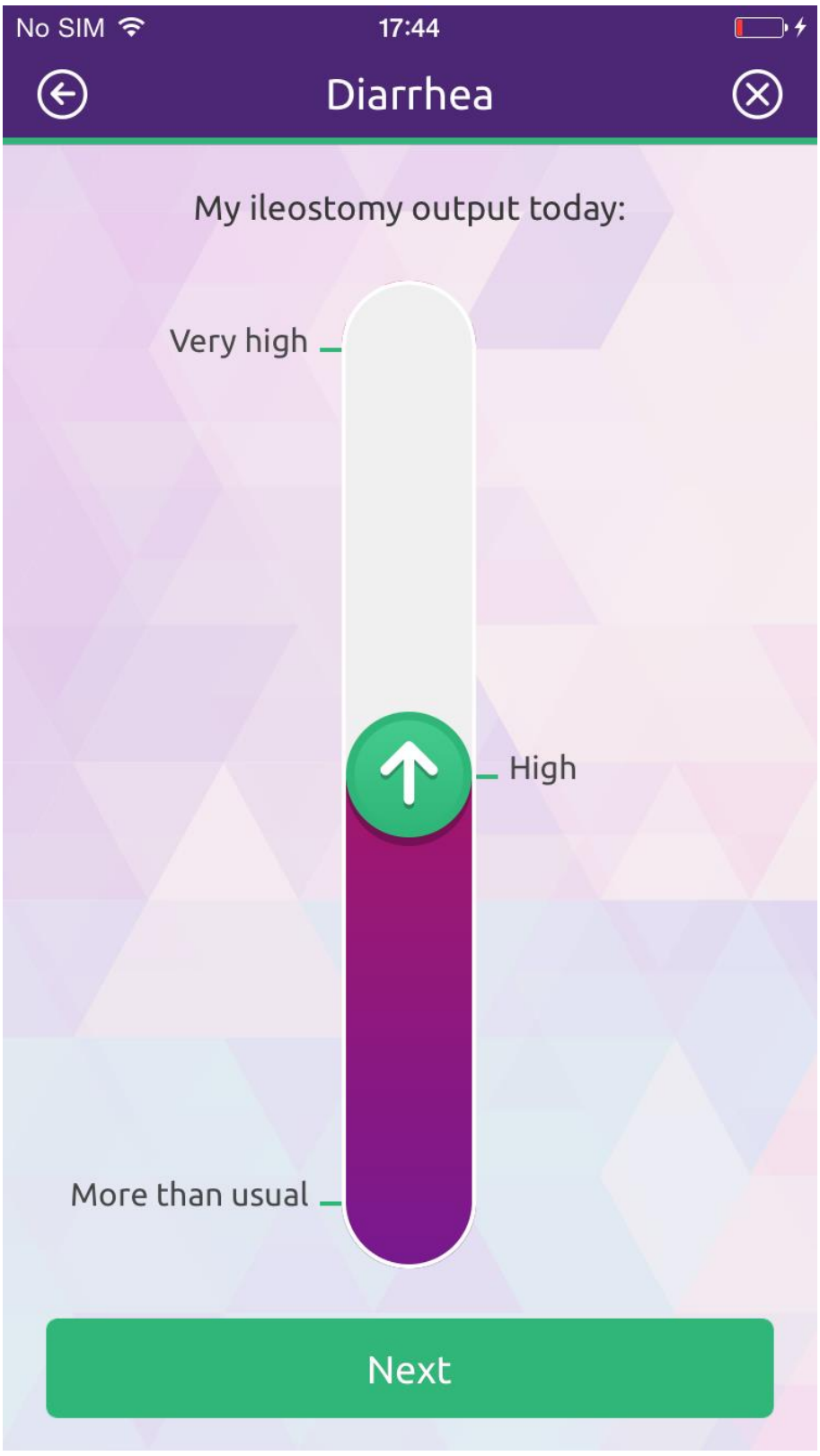
Tap on "Diarrhea" icon



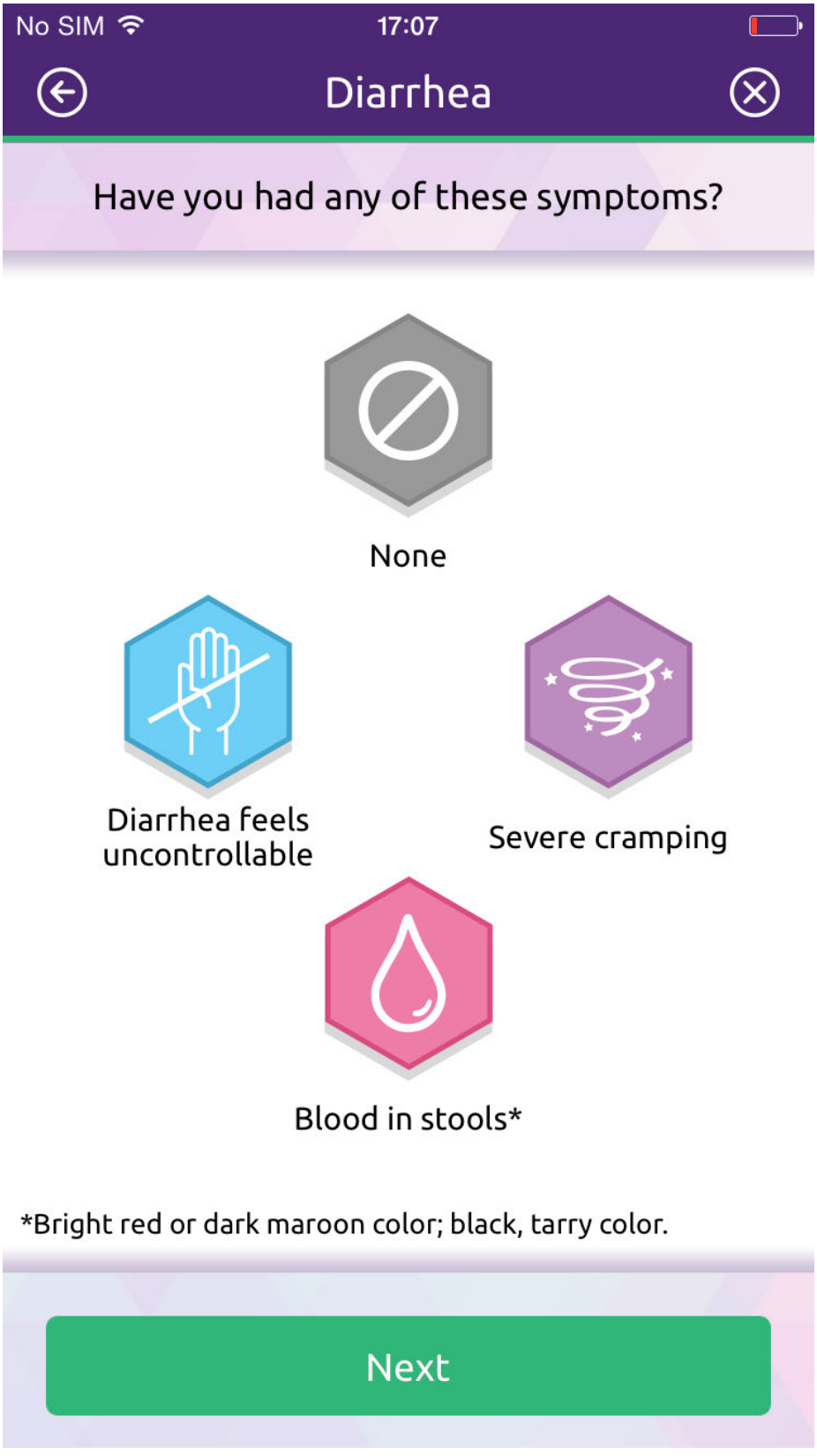
Recording diarrhea using number of bowel movements



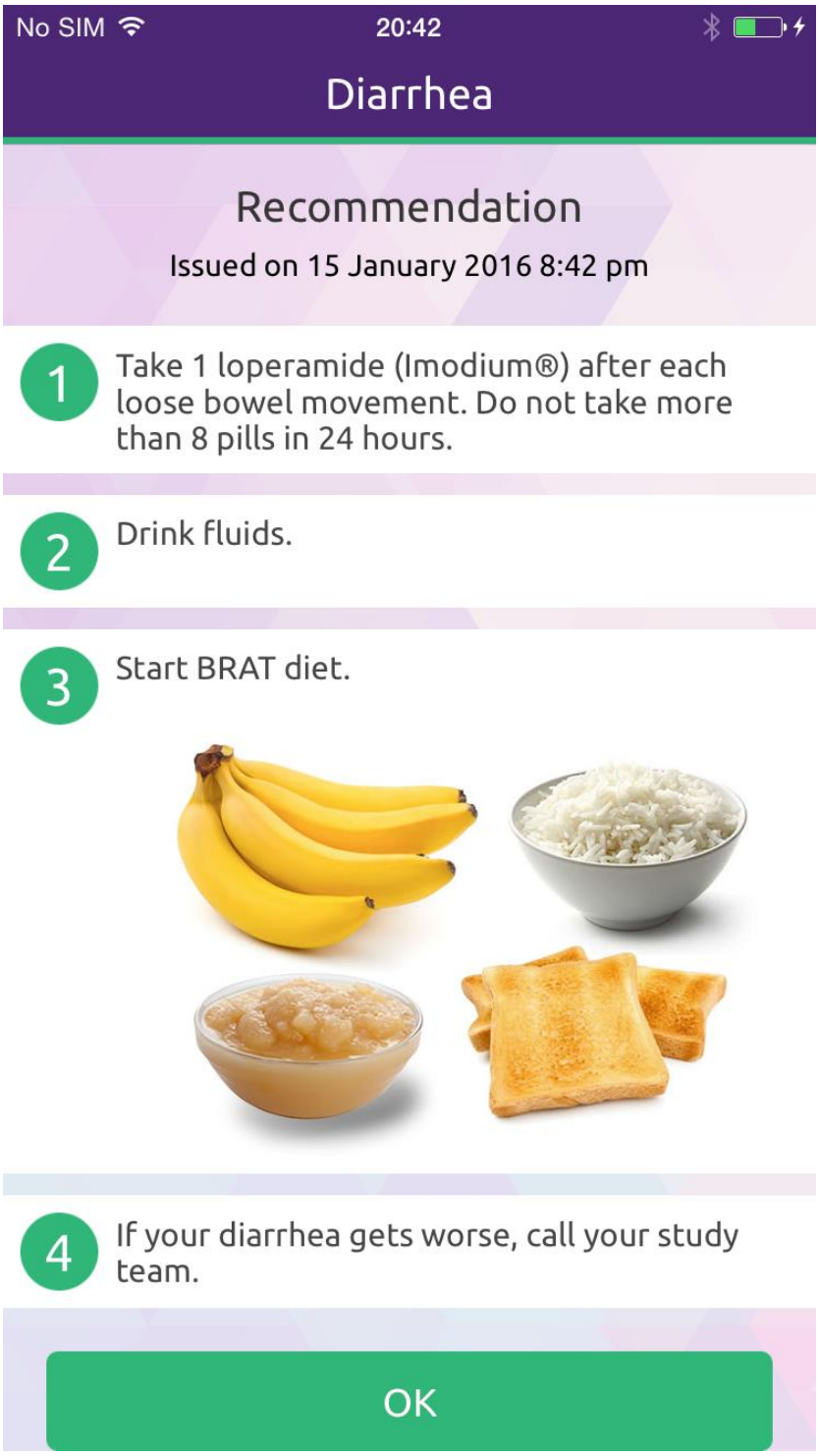
Recording diarrhea using ileostomy output

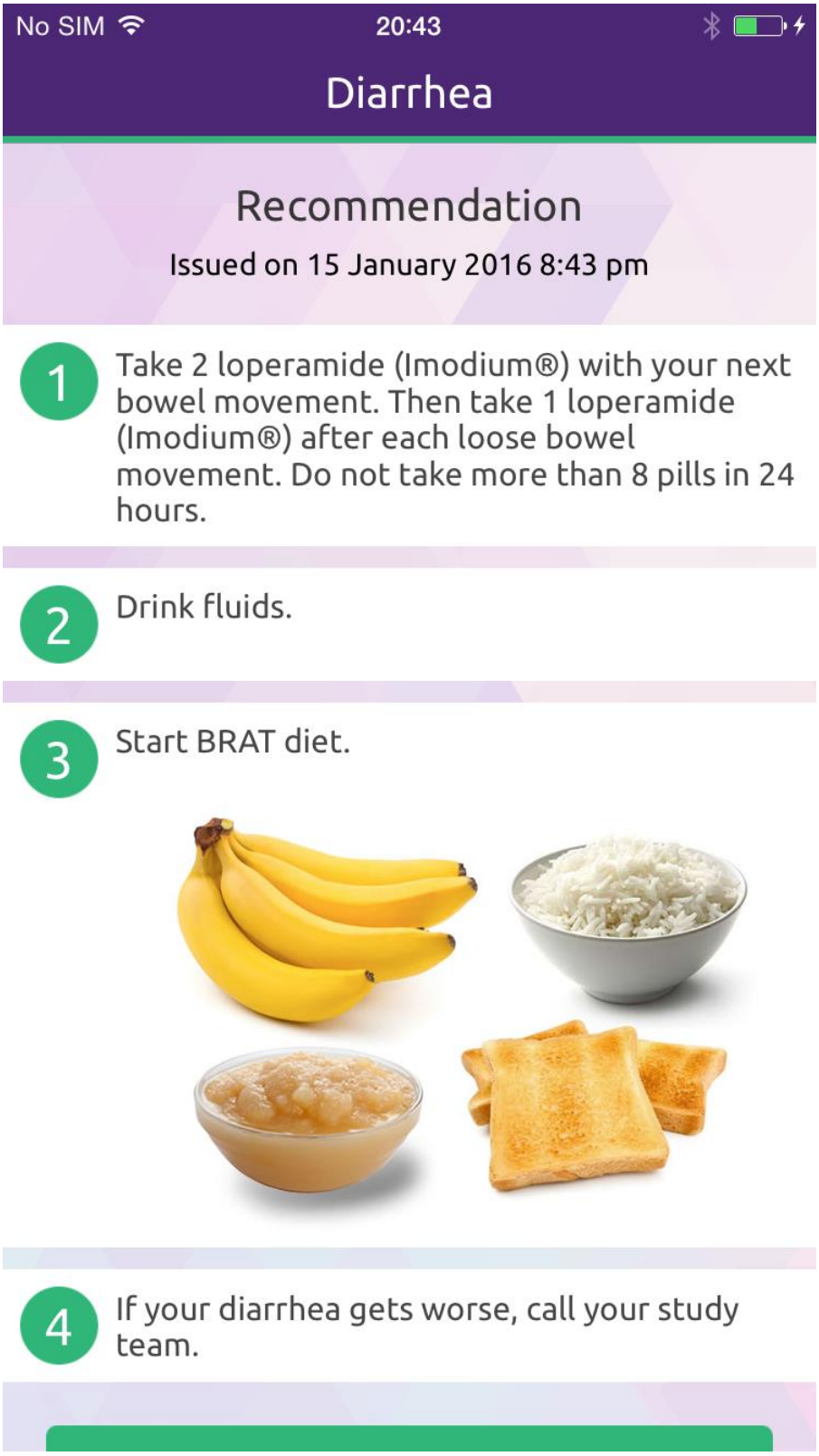


Adding diarrhea related symptoms

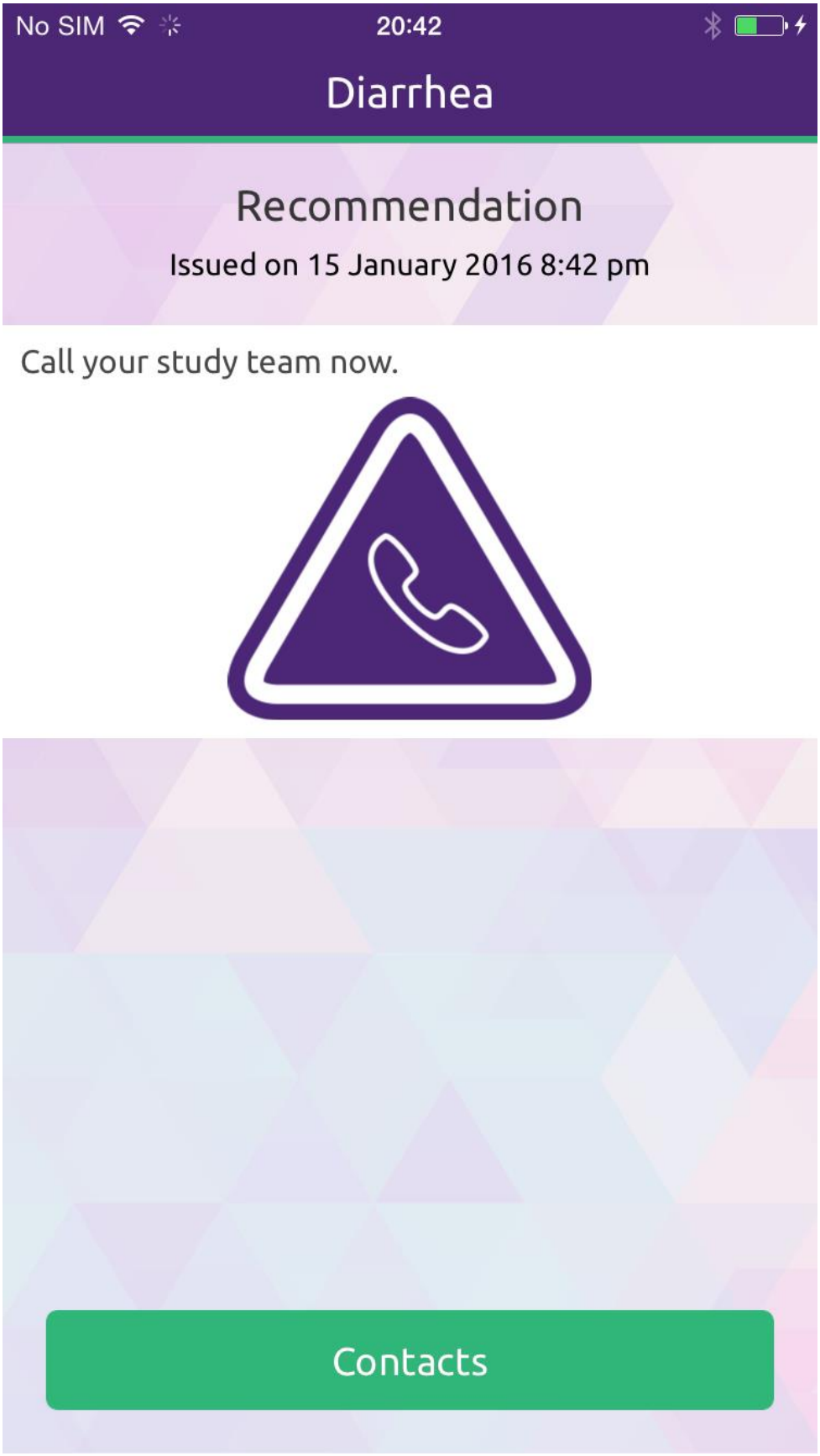


Diarrhea recommendations based on patient entry

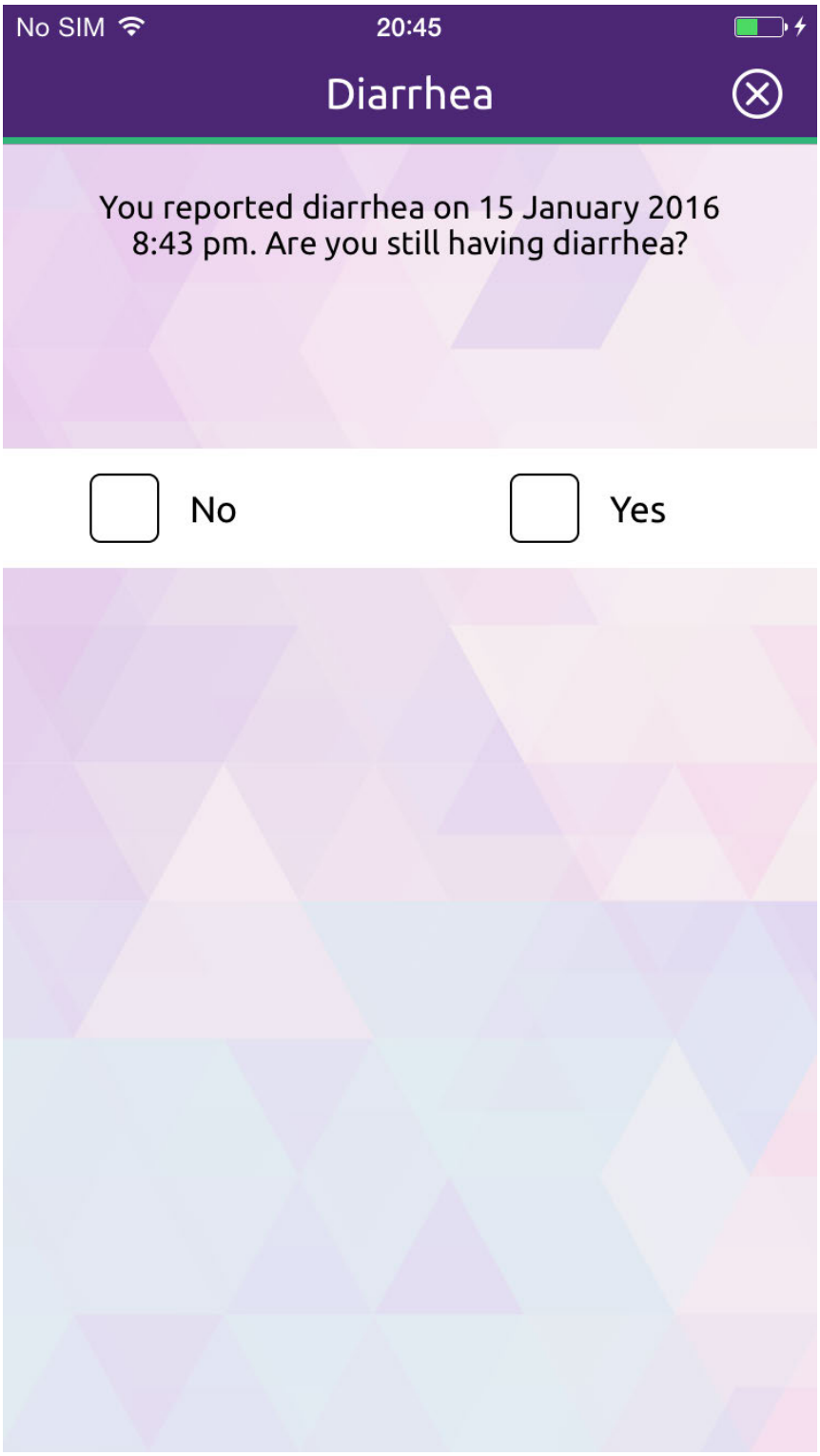

No SIM
20:42
Diarrhea
Recommendation
Issued on 15 January 2016 8:42 pm
1
Take 1 loperamide (Imodium®) after each loose bowel movement. Do not take more than 8 pills in 24 hours.
2
Drink fluids.
3
Start BRAT diet.
4
If your diarrhea gets worse, call your study team.
OK


No SIM
20:43
Diarrhea
Recommendation
Issued on 15 January 2016 8:43 pm
1
Take 2 loperamide (Imodium®) with your next bowel movement. Then take 1 loperamide (Imodium®) after each loose bowel movement. Do not take more than 8 pills in 24 hours.
2
Drink fluids.
3
Start BRAT diet.
4
If your diarrhea gets worse, call your study team.

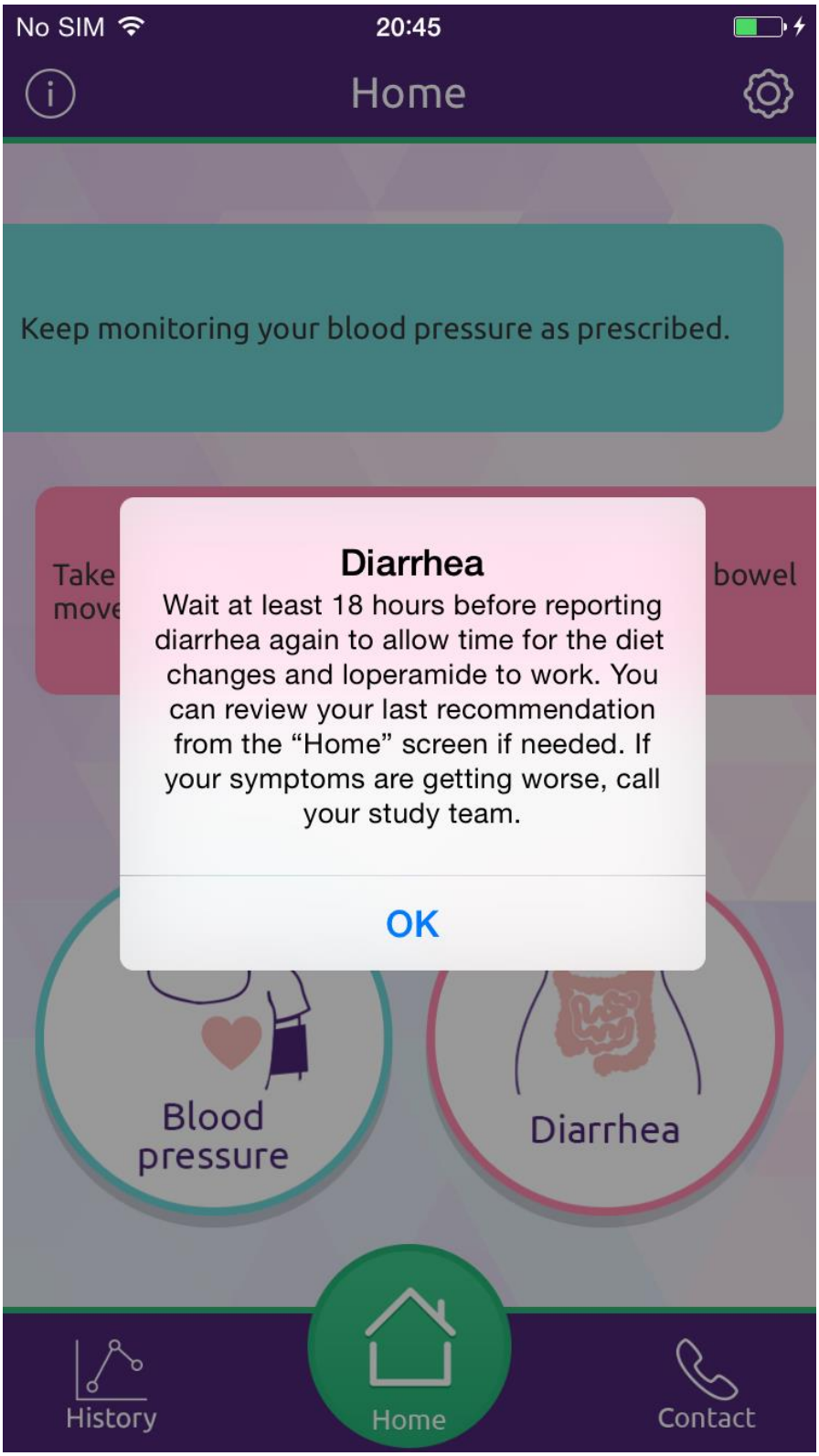
-


No SIM
20:42
Diarrhea
Recommendation
Issued on 15 January 2016 8:42 pm
Call your study team now.
Contacts

Diarrhea reminders (sent every 24 hours until "No" is entered)

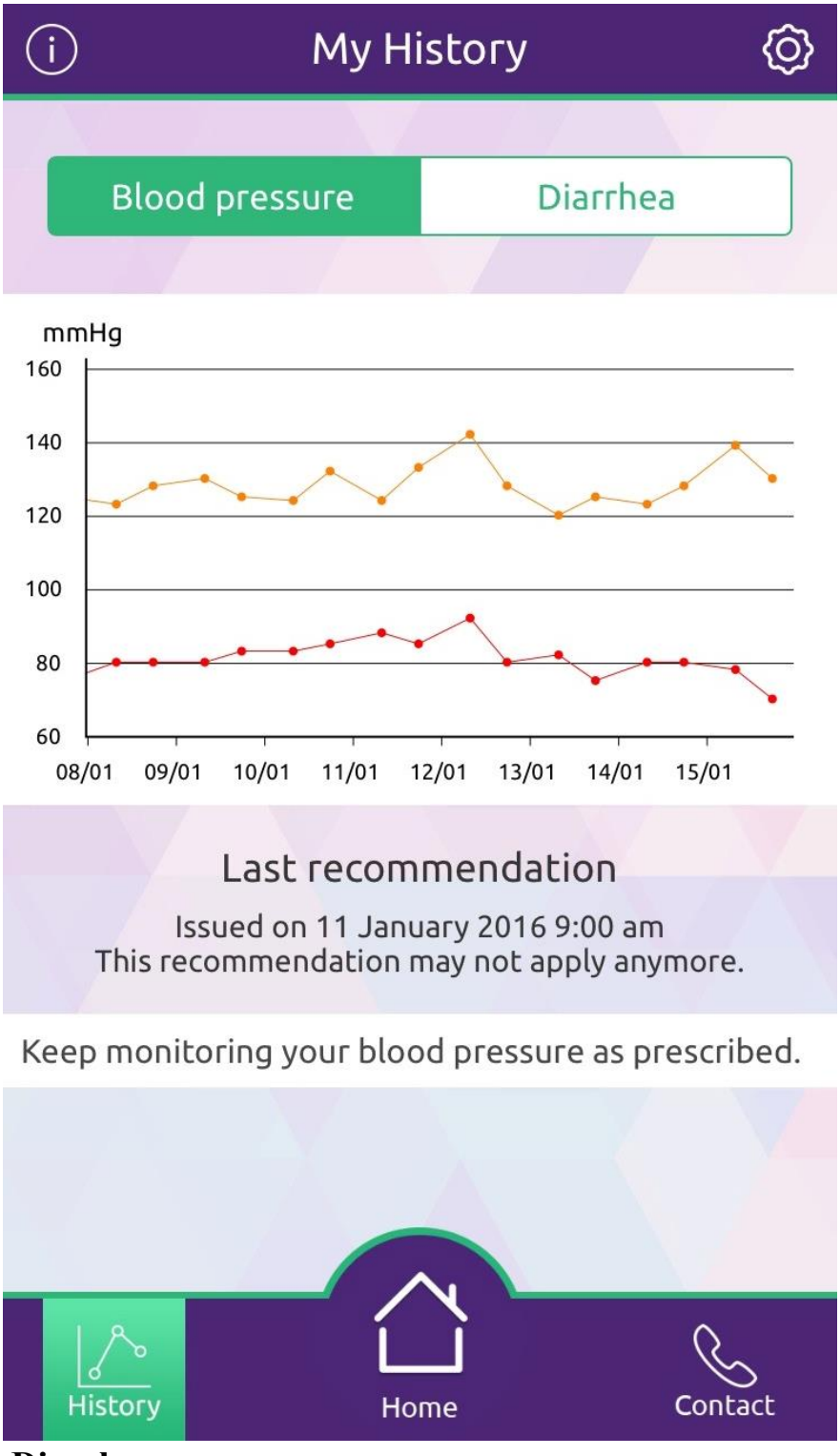


If a new diarrhea event is entered before time allowed, this message is sent:

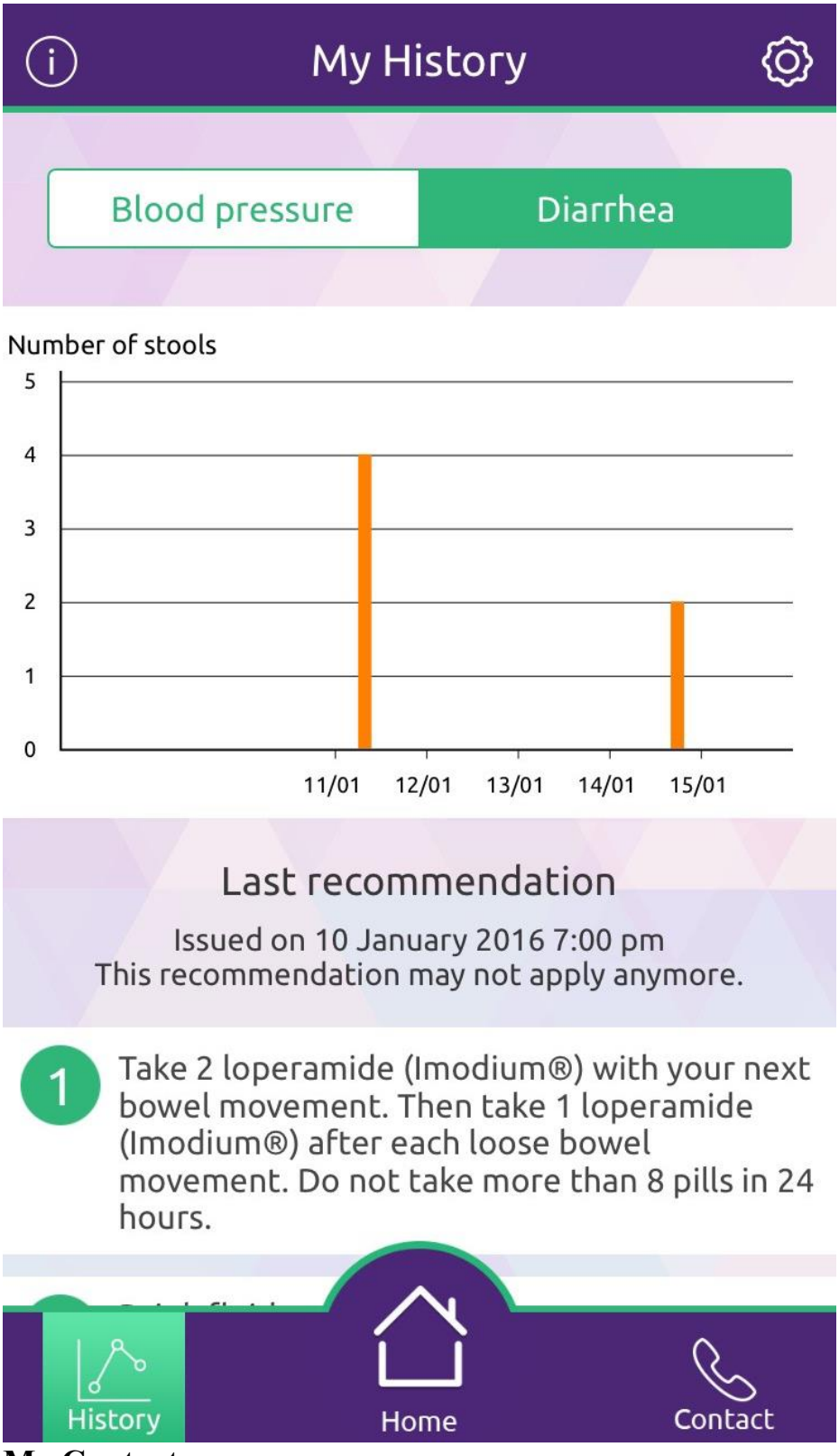


History:

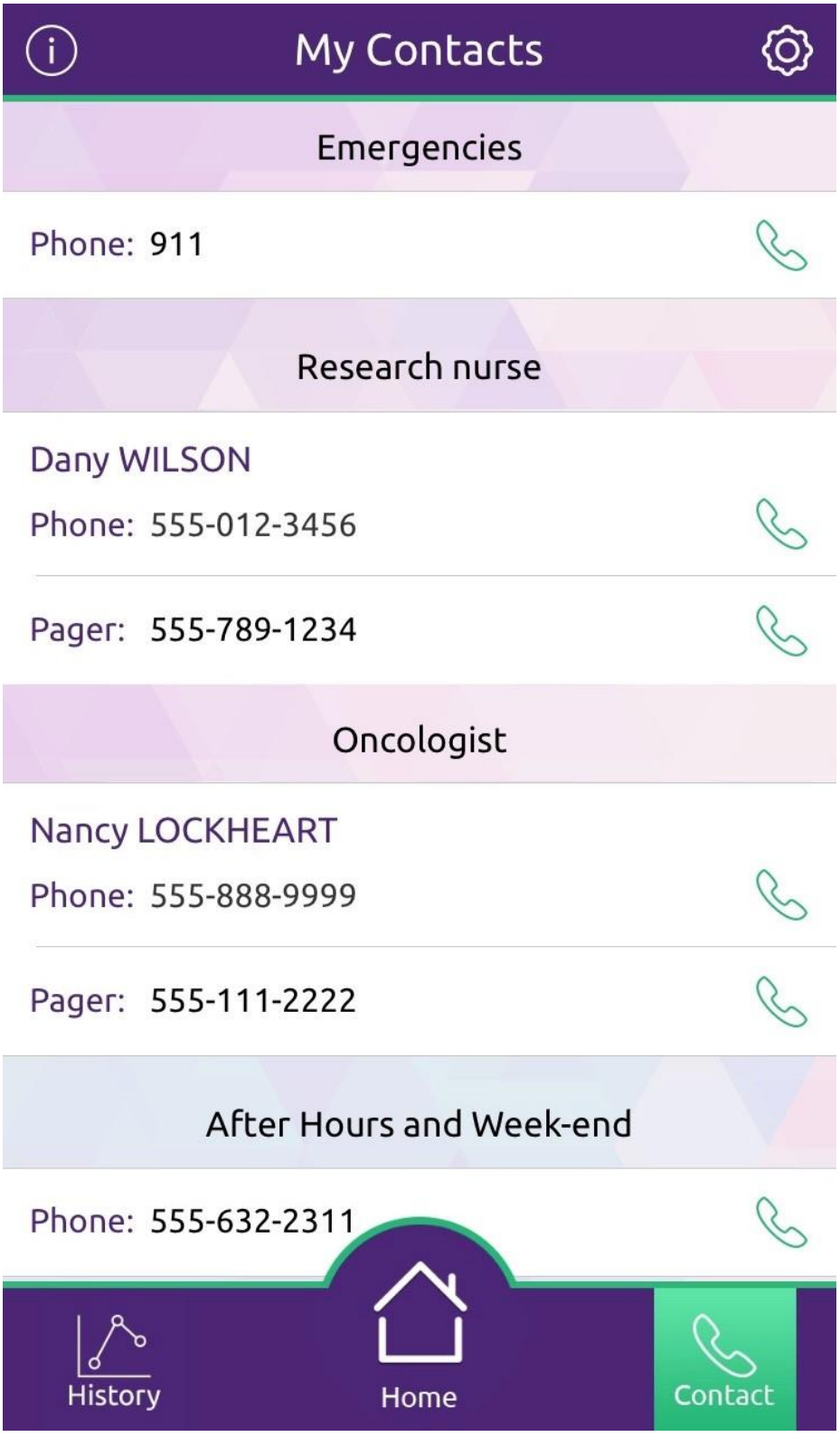
Blood pressure


My History
Blood pressure
Diarrhea
mmHg
160
140
120
100
80
60
08/01
09/01
10/01
11/01
12/01
13/01
14/01
15/01
Last recommendation
Issued on 11 January 2016 9:00 am
This recommendation may not apply anymore.
Keep monitoring your blood pressure as prescribed.
History
Home
Contact

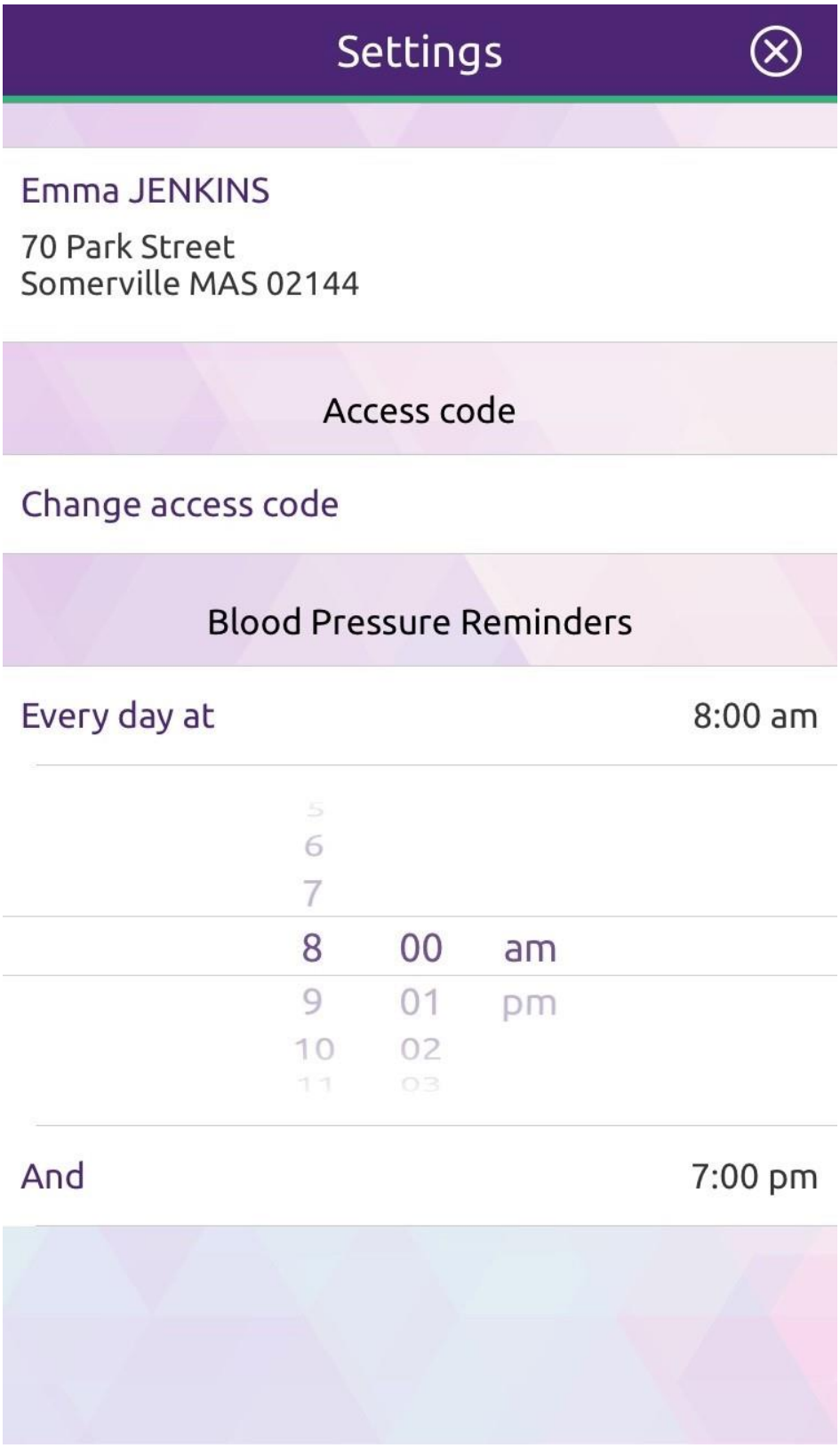
Diarrhea


My History
Blood pressure
Diarrhea
Number of stools
5
4
3
2
1
0
11/01
12/01
13/01
14/01
15/01
Last recommendation
Issued on 10 January 2016 7:00 pm
This recommendation may not apply anymore.
1
Take 2 loperamide (Imodium®) with your next bowel movement. Then take 1 loperamide (Imodium®) after each loose bowel movement. Do not take more than 8 pills in 24 hours.
History
Home
Contact

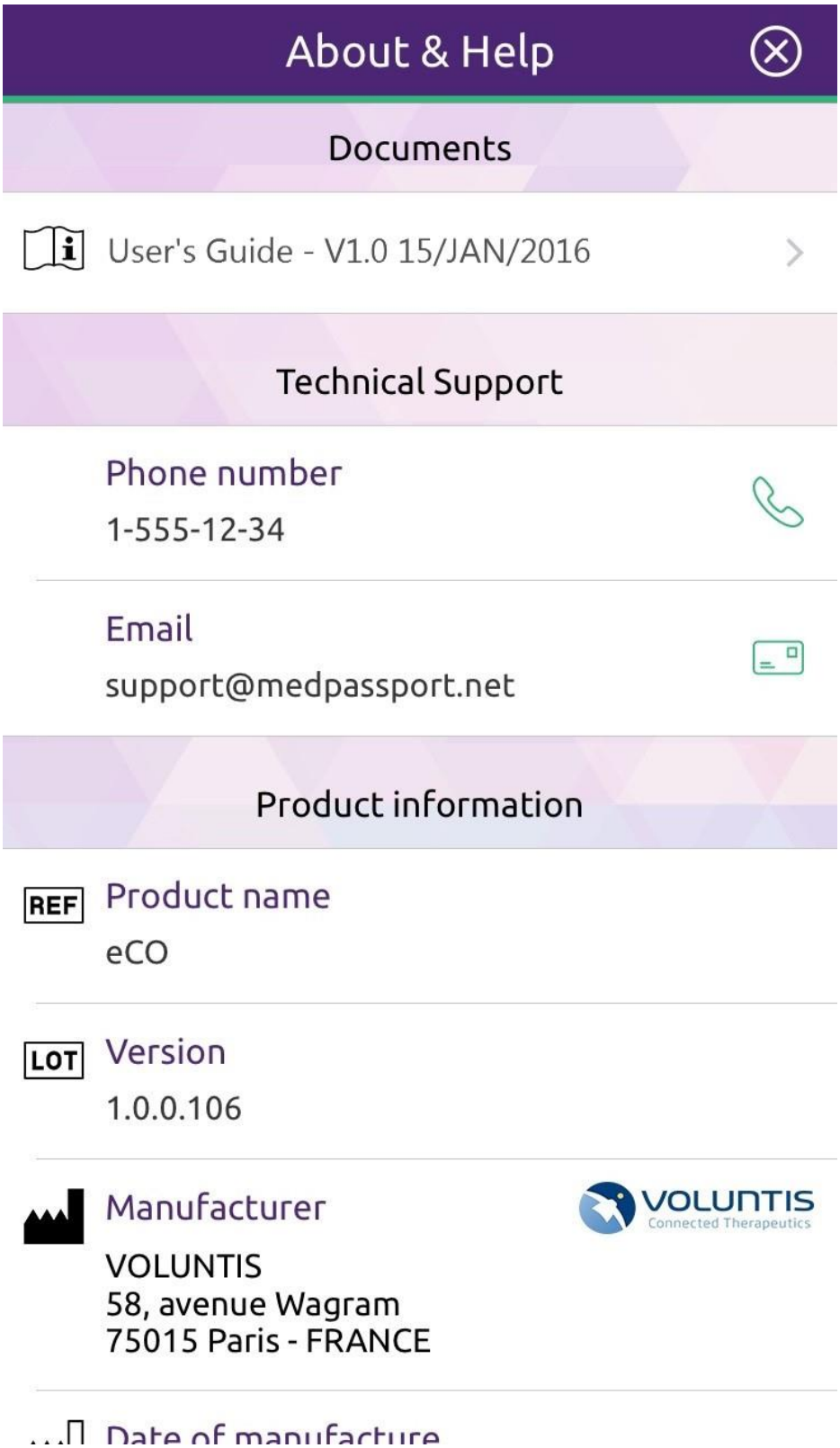
My Contacts:


My Contacts
Emergencies
Phone: 911
Research nurse
Dany WILSON
Phone: 555-012-3456
Pager: 555-789-1234
Oncologist
Nancy LOCKHEART
Phone: 555-888-9999
Pager: 555-111-2222
After Hours and Week-end
Phone: 555-632-2311
History
Home
Contact

Settings:


Settings
Emma JENKINS
70 Park Street
Somerville MAS 02144
Access code
Change access code
Blood Pressure Reminders
Every day at
8:00 am
6
7
8
00
am
9
01
pm
10
02
And
7:00 pm

Information:



eCo Mobile App User's Guide

User's Guide

Version 2017-06-30

How to Get Help: If you have difficulty installing, using, or understanding eCO, check with your health care provider to ensure that your account was set up correctly, and that use of the application is intended for you. Use of eCO is restricted to the person for whom it was prescribed.

eCO User Support
Toll free: 1-800-326-1448 (1-800-ECO-1HIT)
Email: support@ecostudy.us

CAUTION: Investigational device. Limited by Federal (or United States) law to investigational use.

Contents

ABOUT eCo

What is eCO?

eCO is medical software used to support symptom monitoring for women with recurrent ovarian cancer who are being treated with the investigational drug combination of Cediranib-Olaparib.

eCO is also used for remote patient monitoring by health professionals.

eCO is intended to provide secure capture, storage and transmission of blood pressure and diarrhea data, as well as other symptom-related data, to aid in remote monitoring of these symptoms by health care professionals.

eCO captures symptom data through manual entry by the patient and includes wireless connectivity to allow data capture via compatible Bluetooth enabled blood pressure monitors.

eCO supports symptom monitoring by health care providers through analysis and reporting of the symptom related data reported by the patient via the app. In addition, eCO provides directions to patients related to symptom management, which are the same as directions that physicians provide to patients as part of routine clinical practice.

eCO can be used at home or in a medical environment and includes a mobile application that can be accessed via iPhone 4s, 5, 5c, 5s, 6, 6+, 6s, 6s+, 7, 7+ or 7 SE running with iOS 8 or 9, or 10 (depending on availability of iOS version), and with 3G, 4G or Wifi connection.

Remark: eCO can only be used with a prescription from an authorized health care provider.

Caution:

- eCO is not intended to replace the care provided by a licensed healthcare professional, including prescriptions, diagnosis, or treatment.
- eCO is intended for prescription use and will not be indicated for over-the-counter use nor will it be available for download or use without activation by authorized clinical study staff.
- eCO should not replace a face-to-face consultation.
- eCO is not a tool for managing a medical emergency. **In case of emergency, dial 911.**

General Warnings and Precautions

1) Precautions for Use

eCO is to be:

- Used by patients who are have been enrolled in a clinical study aimed at studying the combination drugs Cediranib-Olaparib;
- Used by health care providers who are experienced in the management of hypertension and diarrhea symptoms;
- Used by patients who have the ability to regularly connect their mobile device to the Internet (3G, 4G, or wifi);
- Used by a single person with a personal access code which must not be shared;
- Used in conjunction with a mobile configuration (specific hardware and mobile operating system version) included on the list of compatible devices provided in the product information;
- Used by users who speak English;
- Installed on an operating system that runs in accordance with the manufacturer's instructions (e.g. no 'jail broken' or 'rooted' operating systems);
- Used by patients who have been trained in the use of the application and a compatible Bluetooth enabled blood pressure monitor;
- Used by patients who are deemed by their health care provider to possess:
  - An appropriate level of visual acuity and understanding to operate the product (able to read and understand English).
  - A sufficient intellectual capacity to use the product (e.g. able to understand recommendations for hypertension and diarrhea side effects management).
  - A sufficient level of understanding of the functionalities of the product.
  - A sufficient level of sensorial and motor capabilities (to handle the device giving access to the mobile application).

2) Compatible Equipment

The eCO mobile application requires an iPhone 4s, 5, 5c, 5s, 6, 6+, 6s, 6s+, 7, 7+ or 7 SE running with iOS 8 or 9, or 10 (depending on availability of iOS version), and with 3G, 4G or Wifi connection.

Contraindications

eCO is:

- Not to be used outside of a clinical study aimed at studying a combination of Cediranib-Olaparib.

- Not to be used by patients who haven't been trained on the application and trained with a compatible Bluetooth enabled blood pressure monitor.

First Steps with eCO

1) Prescription and registration information

During an appointment with your health care provider, s/he will:

- Identify a need for monitoring and support.
- Verify that you meet the acceptance criteria for using eCO.
- Prescribe eCO and establish your treatment plan, including:
  - Your diastolic blood pressure at baseline;
  - Your number of bowel movements per day at baseline.
  - (If you have had an ileostomy, this will be noted in your prescription.)

You will receive an email confirming the eCO registration. This email contains:

- Your login information (your user name).
- Your temporary password. This password, known to you alone, is strictly confidential. Do not share it with anyone.

2) Training

In order to use eCO, you must attend a training session. Once the training is complete, you will be able to connect to the mobile application.

3) Daily use

Each day you will use eCO to:

- Enter your blood pressure measures (either through a compatible Bluetooth enabled blood pressure monitor, or manually) with symptoms, if any.
- Enter diarrhea events as needed with symptoms, if any.
- Obtain recommendations based on the clinical study protocol.

4) Follow-up with your health care provider

Your health care provider also has an eCO web portal to monitor your blood pressure and diarrhea, should it occur.

When you use eCO on a mobile device, your data are saved on your device. The application must synchronize and transmit your data to your provider for it to be available to him/her. This synchronization requires an Internet connection (3G, 4G, or WIFI).

MOBILE APPLICATION

General technical Information

1) Compatible equipment

eCO is currently compatible with iPhone 4s, 5, 5c, 5s, 6, 6+, 6s, 6s+, 7, 7+ or 7 SE running with iOS 8, 9 or 10.

Caution: If you update your mobile device's operating system after eCO is installed, it is possible that eCO may stop working if the new operating system is incompatible with the version of the eCO mobile application installed on your device. You may need to update eCO from the App Store.

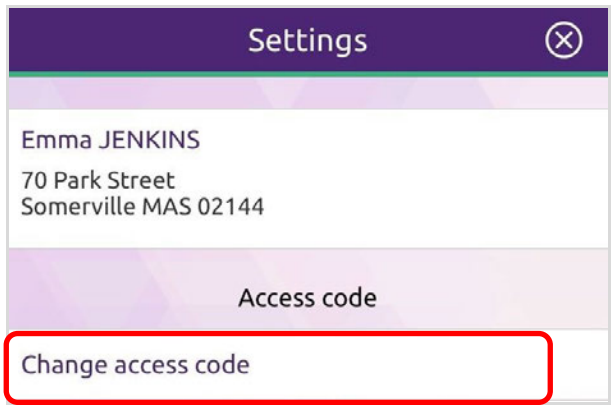
2) Connecting to eCO

When starting up eCO (or after a period of inactivity), the application will request your personal 4-digit access code. If you enter the wrong code 10 times, the application will be locked for 1 minute.

In the event of a forgotten access code, you may select "Forgot your code?" on the application entry page, and you will be able to reset your access code after entering your login and password.

3) Automatic locking

For your security, eCO will lock after one minute of non-use. To re-open the application, you will need to re-enter your four-digit access code. To change your access code, select the "Change access code" option under Settings.



4) Securing your device

Closing the application is not enough to protect your data. It is recommended that you your mobile device is protected by password.

5) Time settings on your device

eCO recommends that you utilize the automatic time settings of your mobile device for accurate synchronization.

Refer to your iPhone instructions for information about how to utilize the automatic time settings of your mobile device.

6) Errors

If an error occurs when opening eCO, an update may be needed. This can be done by going to the Appstore and updating eCO.

After updating eCO, if errors persist, contact eCO User Support (see Technical Support section in this document).

Installing eCO

To use eCO, download the application from the App Store and install it on your device.

Remark: An active Internet connection (3G, 4G, wifi) is required to download and install eCO.

App Store (for iPhone)

To download and install the application for iOS:

1. Go to the App Store on your device.
2. Search "eCO" in the search box.
3. Select the eCO application and tap "Install".

4. The download and installation take place automatically.

Caution: Although it is rare, it is possible for the version of your mobile device operating system to be incompatible with eCO. If this occurs, update to the most current operating system available. For more information on updating your operating system, please see your mobile device instructions and the manufacturer's recommendations.

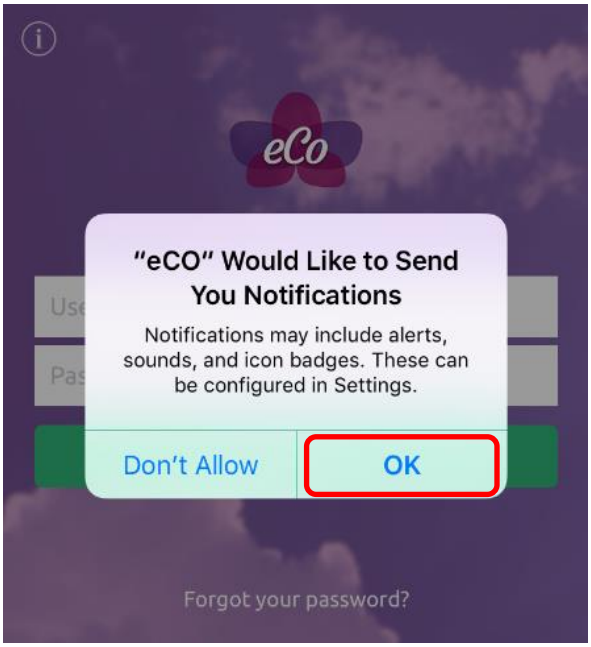
Connecting to eCO mobile for the first time

When your health care provider sets up your account, they will ask for your email address. eCO will send a confidential temporary password for your account to that email address. Do not give the eCO password to anyone.

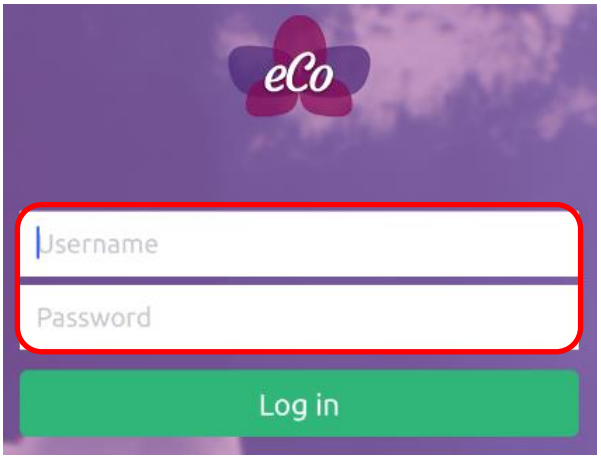
The temporary password will expire in seven (7) days, so you must download and install eCO during that time. If your password expires, contact eCO user support (see "Technical Support" section in this document).

After downloading and installing eCO on your device, you must go through a multi-step setup process:

1. Launch eCO and press "OK" for Notifications.



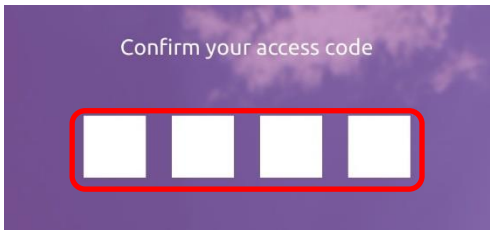
2. Enter your username and password and then tap "Log in"



3. Enter your new password.

Your new password must: – be at least 8 characters long, – contain at least one uppercase character (A - Z), at least one lowercase character (a - z) and at least one digit character (0 -9). It may contain non alphanumerical characters (for instance: *,-,+ «). It shall not be equal to or contain your username or full name. It must be different from the 5 previous passwords.

4. Create an access code by entering a 4-digit code, and confirm it by entering it again.



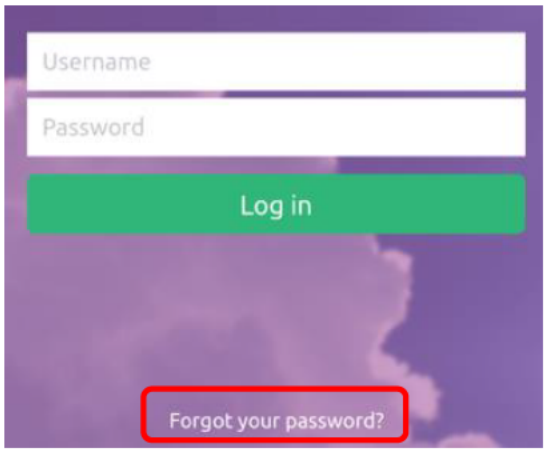
Remark: You must have an active and stable Internet connection (3G, 4G, WIFI) during the entire set-up process.

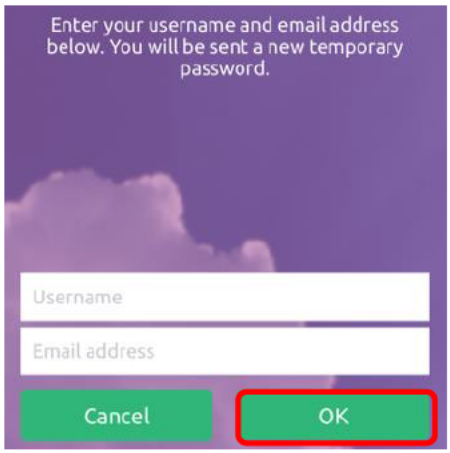
Remark: If your device is not compatible, you can:

- Update your device's operating system
- Install on another device

If compatibility issues persist, please contact User Support (see Technical Support section in this document).

If you forget your password, you can request a new one that will be automatically sent by email. Please enter the new password within 7 days.





Caution: If you are unable to connect, check your Internet connection, verify the email address and your temporary password, and try again.

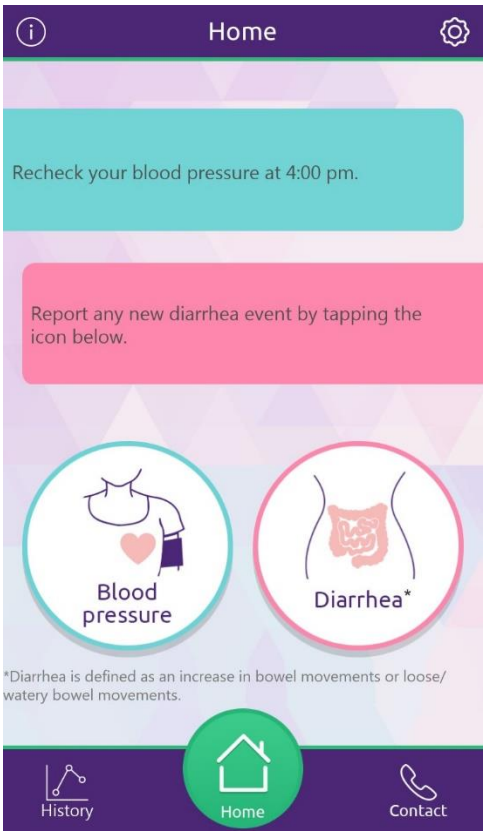
After ten failed attempts, your account will be blocked for 1 minute and will unlock automatically. If you have difficulty connecting, or questions about the process, please contact eCO User Support (see Technical Support section in this document).

Remark: If you encounter any issue while connecting, you can access the "About and Help" section by tapping the ⓘ icon. This section provides you with direct access to the User's guide and contact information for eCO's User Support.

Using eCO

The eCO mobile app Home has three sections:

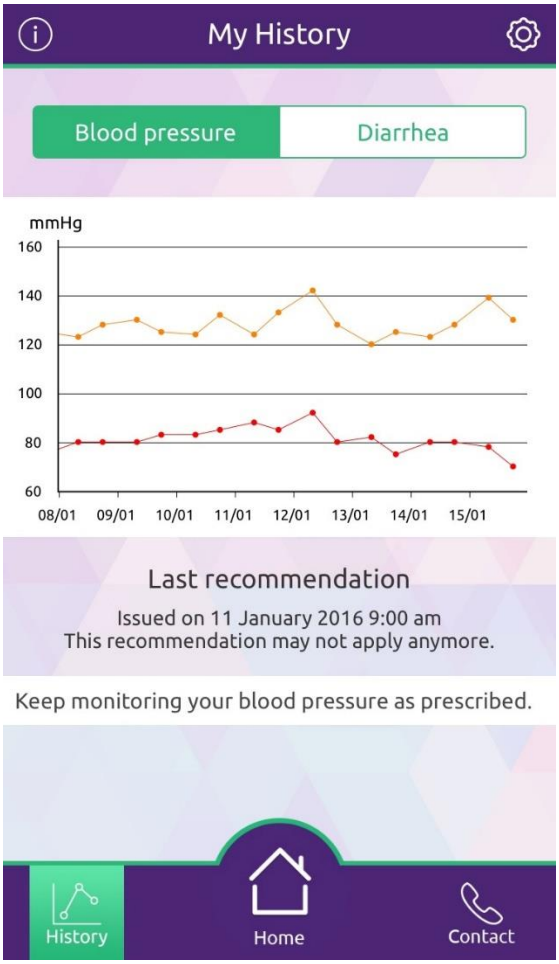
- Top section: The dark purple header provides access to app Information screen and Settings screen .
- Middle section: The center provides summaries of the most recent recommendations for blood pressure and diarrhea, and buttons to enter new blood pressure or diarrhea measures.
- Bottom section: The dark purple footer provides access to History, Home and Contact:
  - History: A summary of previous blood pressures and diarrhea recordings, as well as related recommendations.
  - Home: Main eCO page to enter new blood pressure or diarrhea recordings, and see summary of the recommendation for the previous entries.
  - Contact: List of Study Team contacts.

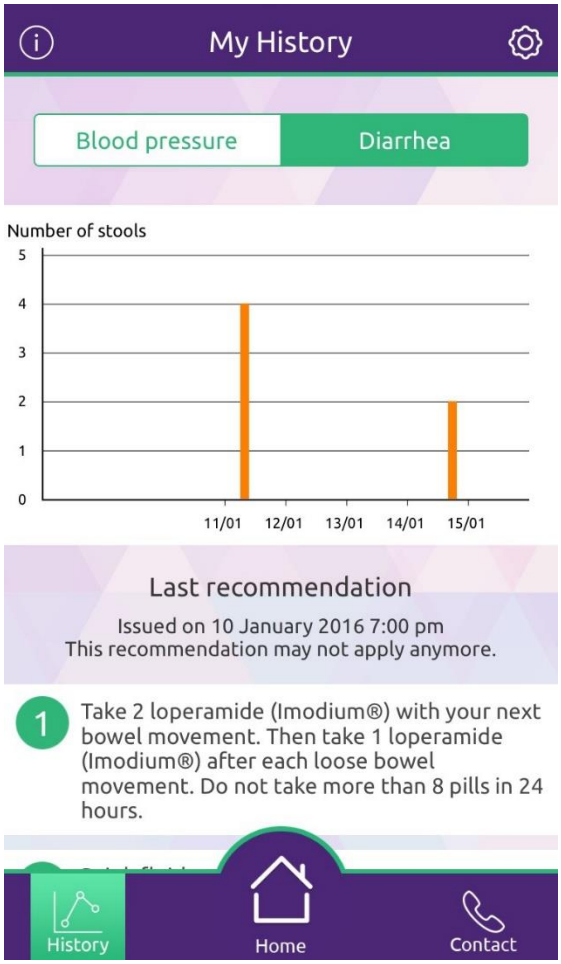


History

The Summary page displays a graph of your historical data for both blood pressure and diarrhea recordings and the recommendation related to the last recording.

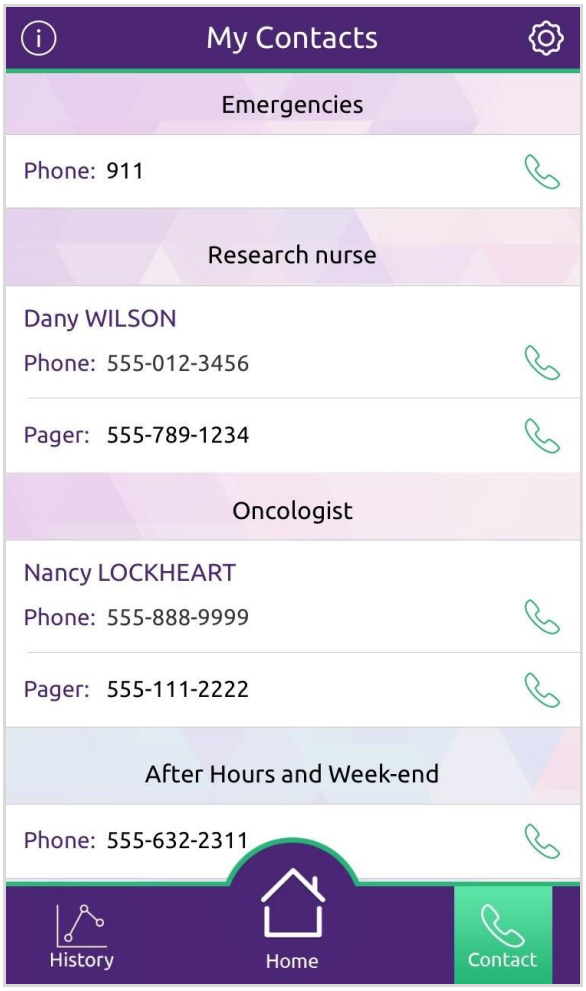
Select the corresponding tab to see the history and last recommendation made by eCO for blood pressure (left) and diarrhea (right).





Contacts

The Contacts page displays your list of contacts. tap on the icon to call a contact.

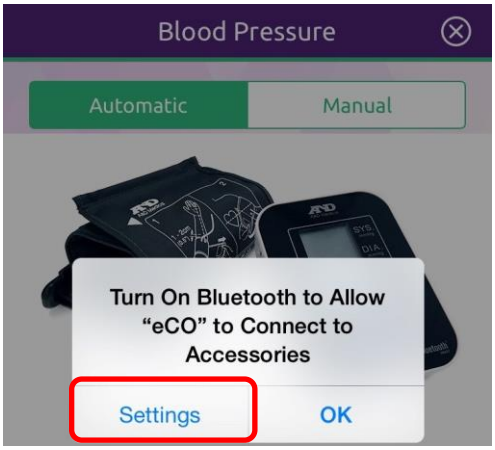


Caution: Your main Study Team contacts are displayed on this page (phone and/or pager). If you can't reach them, call **After Hours and Weekend contact or 911**.

Entering a blood pressure check

Pairing your Bluetooth-enabled blood pressure monitor

In the eCO app, if the Bluetooth connection is turned off on your iPhone, the eCO app will display a message asking you to turn on Bluetooth in your Settings. Press on "**Settings**" button.



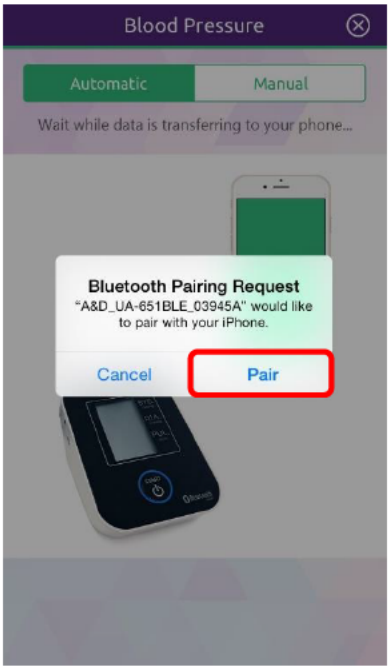
Caution: Do not press "OK". If you do press "OK", you will have to manually access your iPhone settings to enable Bluetooth connection.

- In your iPhone Settings: turn on Bluetooth.

- In the eCO app: tap the blood pressure icon to reach the Automatic Blood Pressure measure page.

- On the Bluetooth enabled BP monitor: press on the Start button for at least 4 seconds, until "**Pr**" (Pairing) is displayed.

- In the eCO app: a popup message "Bluetooth Pairing Request" is displayed; Press on "Pair" button.



- On the Bluetooth enabled BP monitor: the text "**Set**" must be displayed.

- Close the "Blood pressure" menu from the mobile with the top right close icon.

- If an error message appears, just confirm or ignore it.

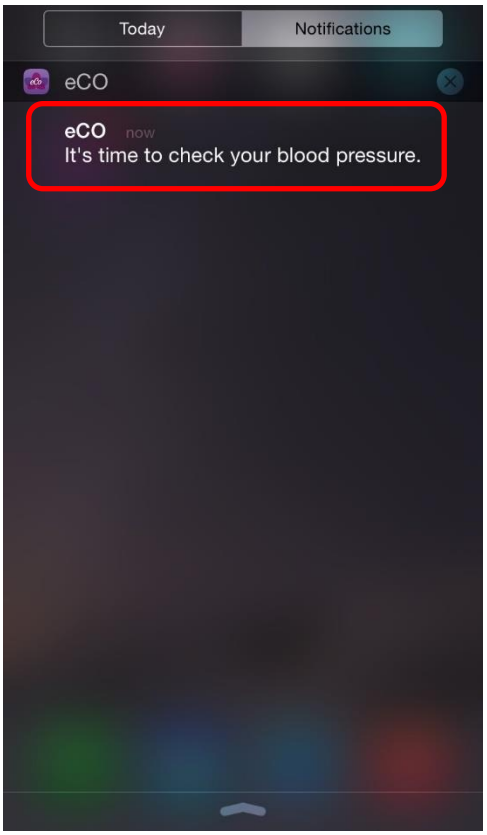
- The BPM displays "End".

- The pairing is now successfully completed, you can use the Bluetooth BP monitor to measure your blood pressure

Blood pressure reminders

eCO will send you a notification when a blood pressure check is needed. For routine monitoring, a blood pressure check is needed two times each day (or one time each day based on the recommendation from your health care provider). You may also be reminded to do more blood pressure checks depending on the blood pressure result.

To set your preferred times for routine monitoring, see the Settings section for instructions.



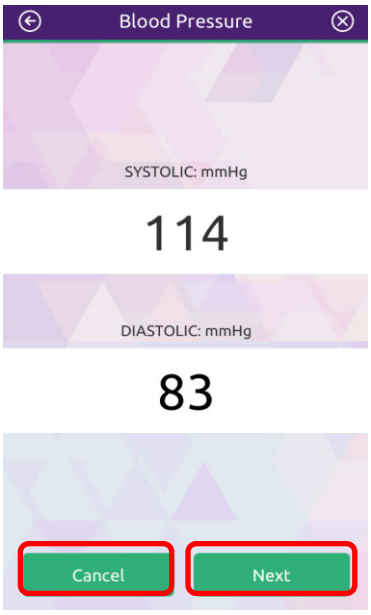
Using your Bluetooth enabled blood pressure monitor

Once your Bluetooth enabled blood pressure monitor is paired to your iPhone, you can record your blood pressure checks with it.

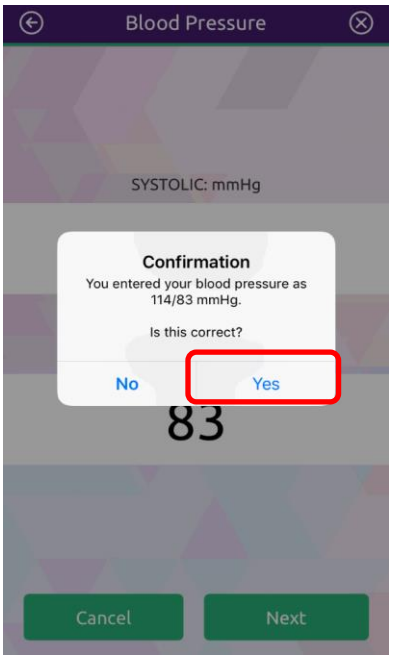
- Sit and put on the blood pressure cuff as instructed by your health care professional.
- Press on the "Blood pressure" icon on the eCO Home page.

- Press on the Start button of your blood pressure monitor. It should start measuring your blood pressure.
- After 30 to 60 seconds, eCO will indicate that a blood pressure measurement is being transferred from the blood pressure monitor.

- The blood pressure measurement will be displayed on eCO screen. Check to make sure the number displayed on the eCO screen is the same number displayed on the blood pressure monitor screen.
- Tap "Next" if the number is correct.
- If the number is incorrect, tap "Cancel" and do a new blood pressure check.



- In eCO, a confirmation message is displayed, tap "Yes" if your entry is correct.
- If your entry is incorrect, tap "No" then tap "Cancel" and do a new blood pressure check.

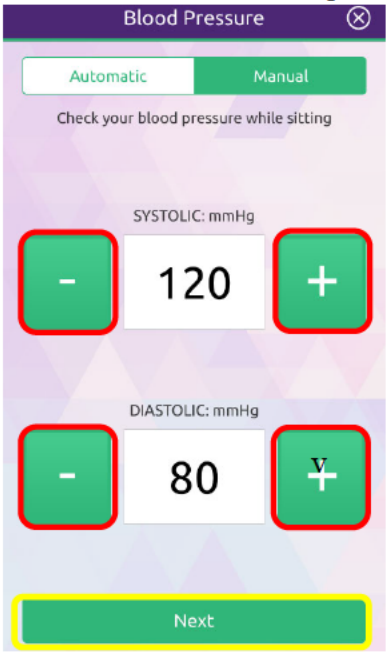


Entering data manually

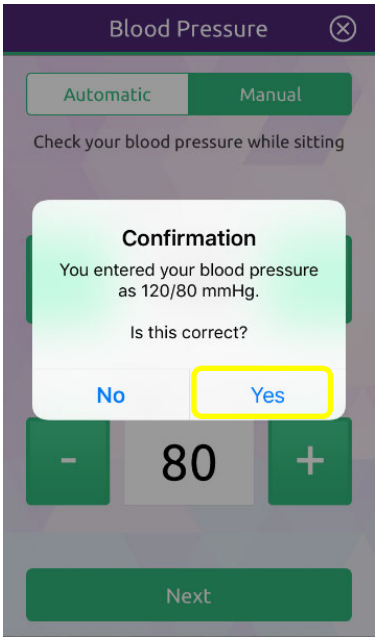
In case you have a problem with your Bluetooth-enabled blood pressure monitor and data aren't automatically transferred to eCO, you can enter your blood pressure measurements manually.

- Sit and put the blood pressure cuff on as instructed by your health care professional.
- Use your blood pressure monitor to check your blood pressure as usual.
- Press on the "Blood pressure" icon on the eCO Home page.

- In eCO, press on the "Manual" tab.
- In eCO, use the +/- arrows to enter your blood pressure as displayed on the monitor screen and press "Next".

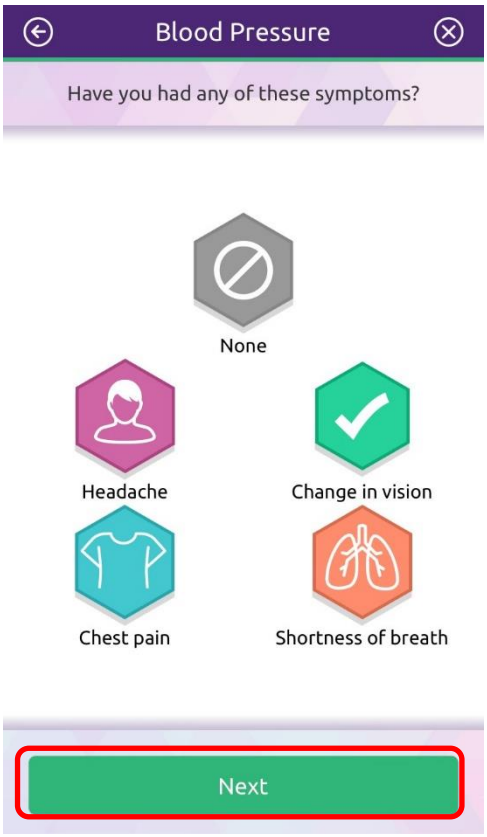


- In eCO, a confirmation message is displayed, tap "Yes" if your entry is correct.
- If your entry is incorrect, tap "No" and re-enter the correct measurement.



Adding symptoms

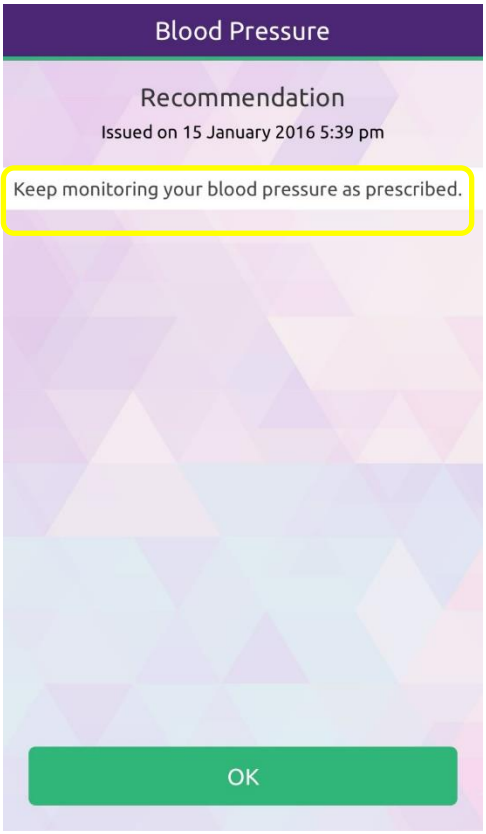
Based on the blood pressure entered (either using Bluetooth or manually), eCO may ask you if you have any symptoms such as headache, chest pain, change in vision or shortness of breath.

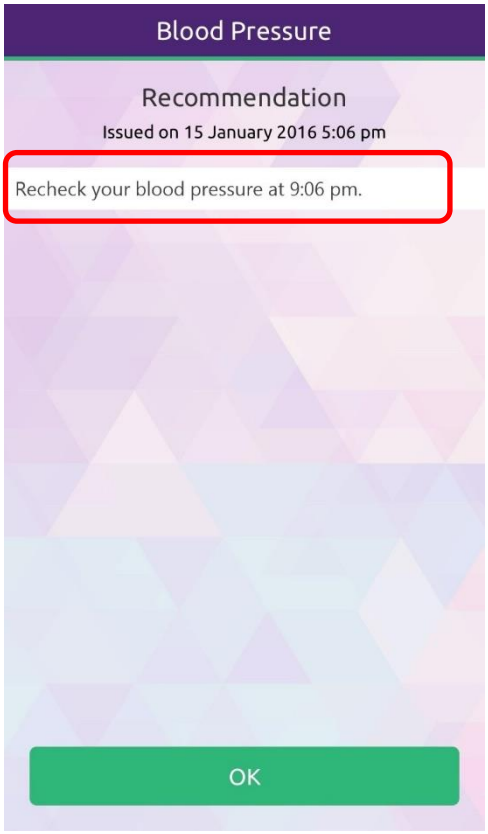


- Press "None" if you don't experience any of the symptoms listed.
- Press on the icon of the symptom(s) if you have any of those symptoms.
- Any symptom icon image you select will be replaced by a "Check" icon. See an example on the right screen above.
- If you press a symptom icon by mistake, press it again to turn it off.
- When your symptom entry is correct, press "Next".

Blood pressure recommendations

After each blood pressure measure (and any potential symptoms), a recommendation will be displayed. See examples below.

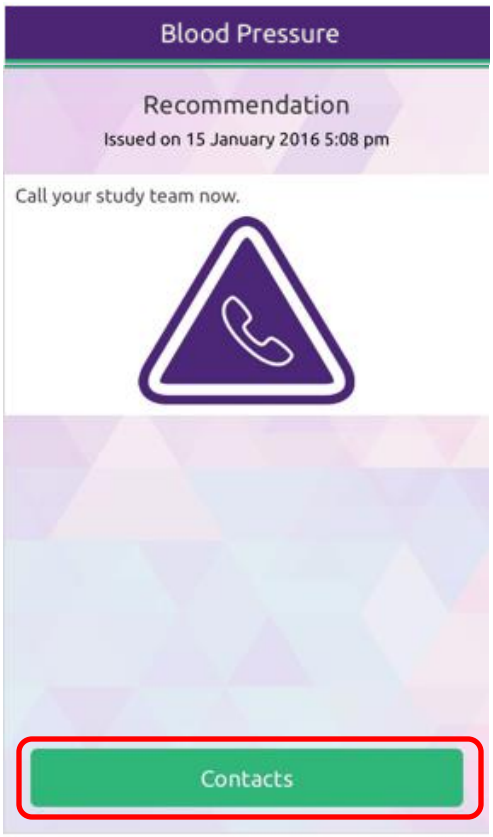


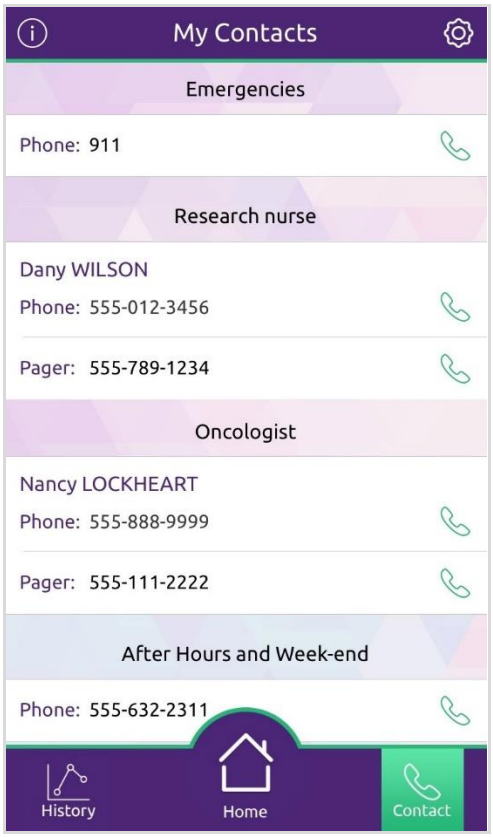


- Tap "OK" to return to the home screen.

If eCO recommends an additional blood pressure recheck, eCO will send you a reminder when this recheck is due.

If the eCO recommendation is to "Contact your study team now", tap "Contact" and the My Contacts screen will be displayed. Use the icon to make the call from your iPhone.





Caution:

- It is important for you to follow the recommendation provided by eCO.
- eCO is not intended to replace the care provided by a licensed healthcare professional, including prescriptions, diagnosis, or treatment.
- eCO should not replace a face-to-face consultation.
- eCO is not a tool for managing a medical emergency. **In case of emergency, dial 911.**

Entering diarrhea data

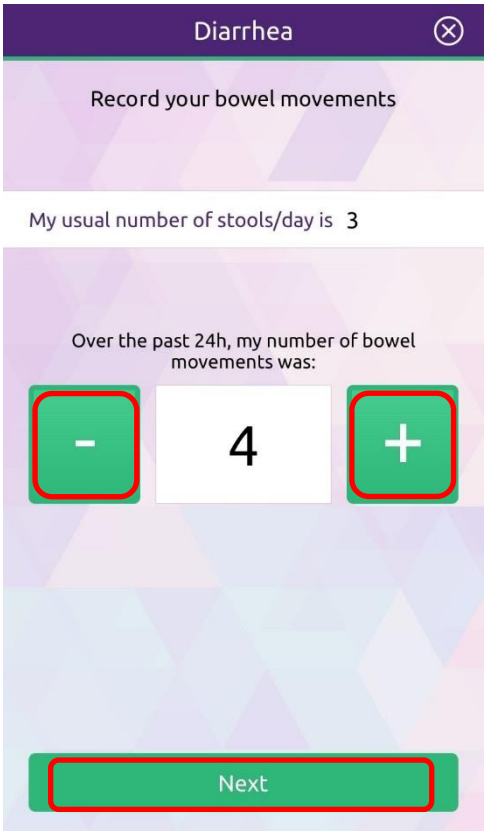
eCO allows you to enter diarrhea when it occurs and a recommendation will be provided, based on your baseline number of stools, and the number of bowel movements you enter. If you have an ileostomy, it will be based on the amount of output you enter. At your first visit, your health care provider indicated which way you will be entering diarrhea data.

Entering diarrhea data using number of bowel movements

Diarrhea is when you have an increase in the number of bowel movements from your usual number and/or if your bowel movements are loose or watery.

- Press on the diarrhea icon on the eCO Home page.

- Use the +/- buttons to enter the number of bowel movements in the last 24 hours, then press "Next" button.

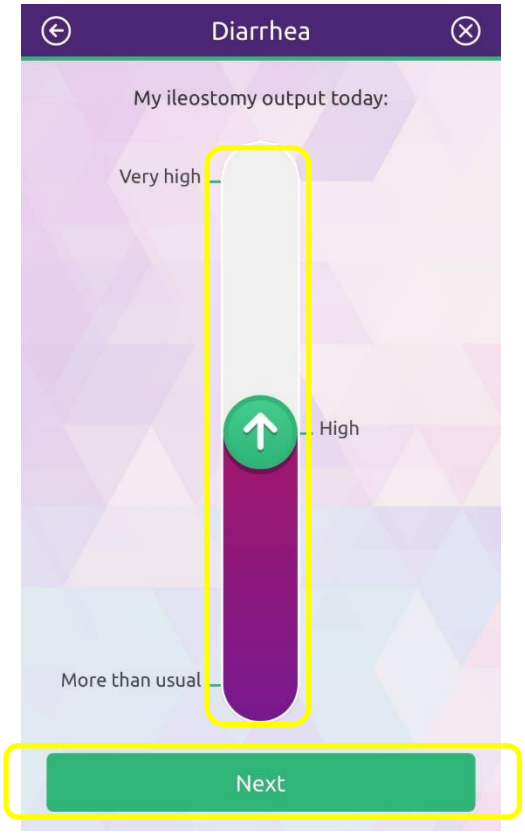


Entering diarrhea using ileostomy output.

If you have an ileostomy, diarrhea is when your ileostomy output is increased from your usual output.

- Press on the diarrhea icon on the eCO Home page.

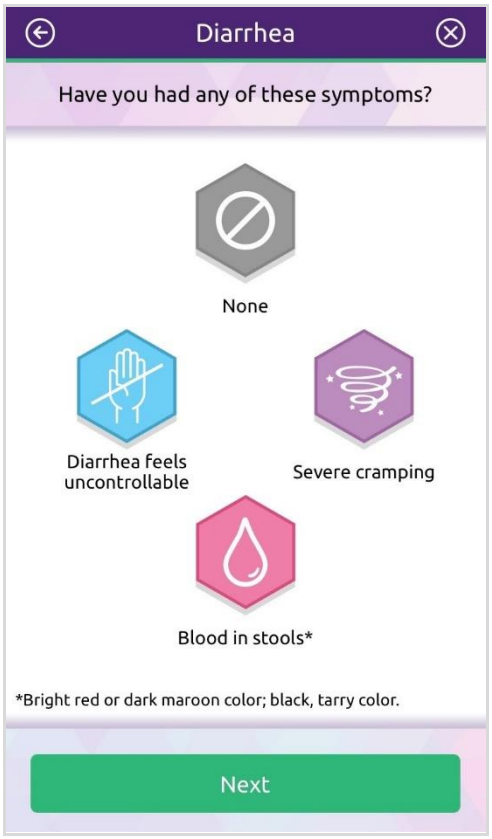
- Use the  slider to enter your ileostomy output in the last 24 hours, then press "Next".

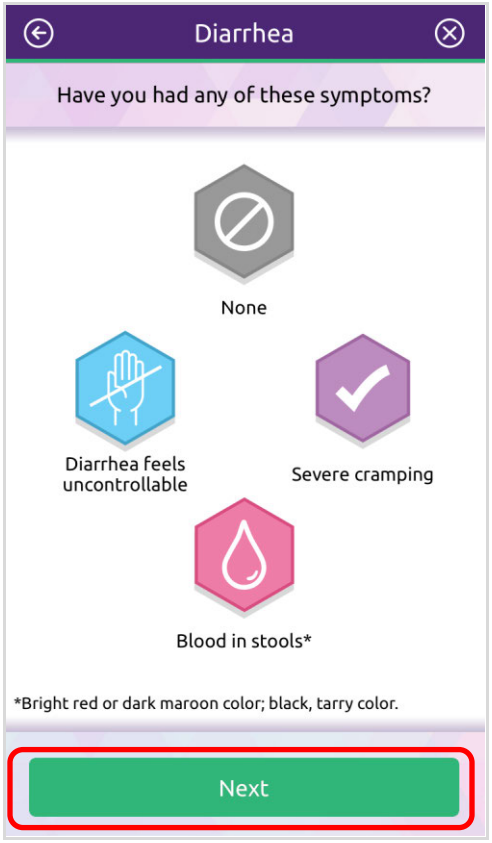

Diarrhea
My ileostomy output today:
Very high
High
More than usual
Next

Entering symptoms

In some cases of diarrhea, eCO might ask you if you have any symptoms, such as severe cramping, blood in stools (bright red, maroon or black, tarry color), or if your diarrhea feels uncontrollable.

- Select the symptoms you are having, if any. Press the "None" icon if you don't experience any of the symptoms listed.
- Any symptom icon image you select will be replaced by a "Check" icon. See an example on the right screen below.
- If you press a symptom icon by mistake, press it again to turn it off.
- When your symptom entry is correct, press "Next".



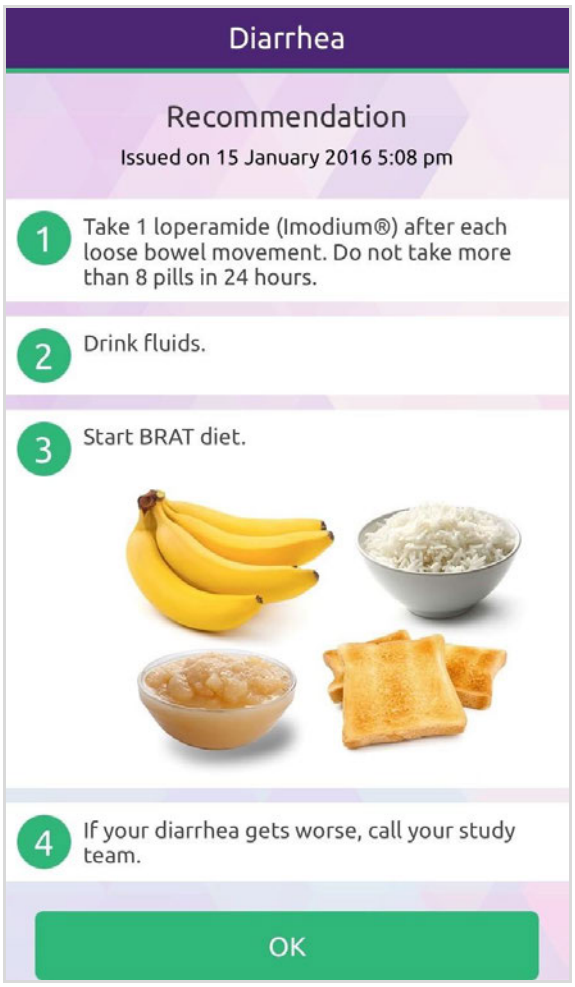


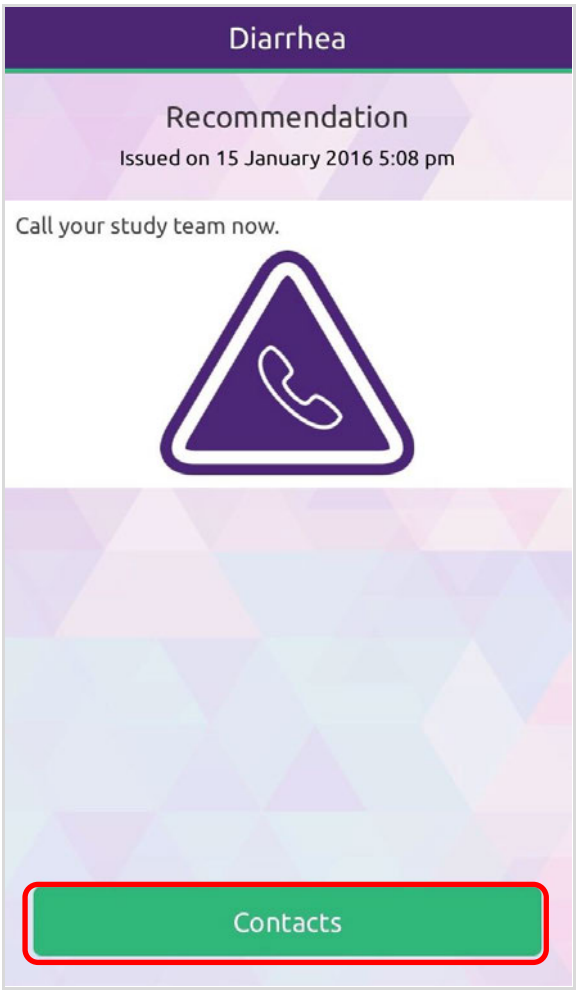
Remark: A new diarrhea event cannot be entered less than 18 hours after the last one. This is to allow time for the diarrhea self-management recommendations to work.

Diarrhea recommendations

After each diarrhea and symptom screen, a recommendation will be displayed. These recommendations are based on the information provided to you by your health care professional.

See a few examples below.



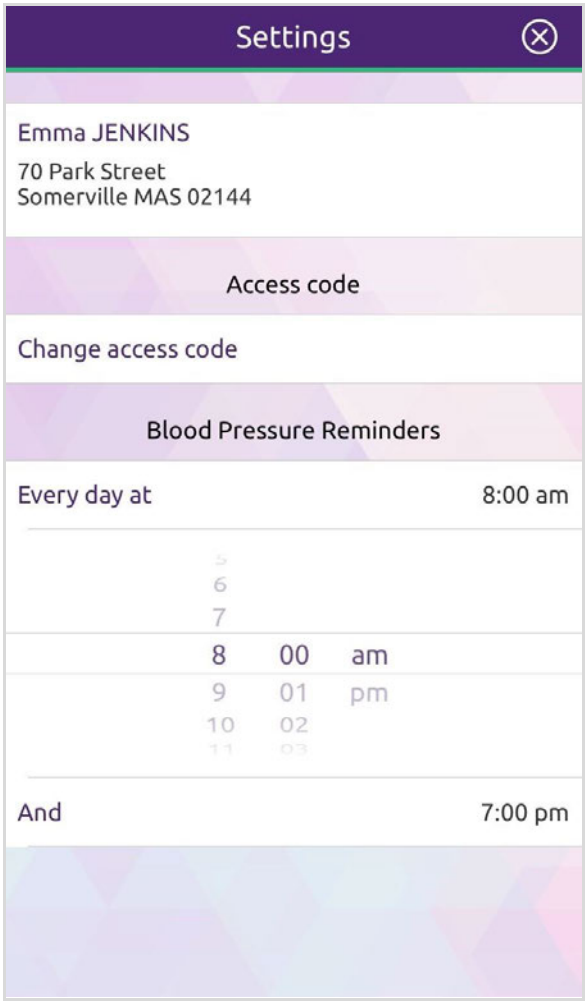


Caution:

- It is important for you to follow the recommendation provided by eCO.
- eCO is not intended to replace the care provided by a licensed healthcare professional, including prescriptions, diagnosis, or treatment.
- eCO should not replace a face-to-face consultation.
- eCO is not a tool for managing a medical emergency.
- **In case of emergency, dial 911.**

Settings

To access the Settings page in eCO, press on the  icon at the top right corner of the Summary, Home, or Contact pages.

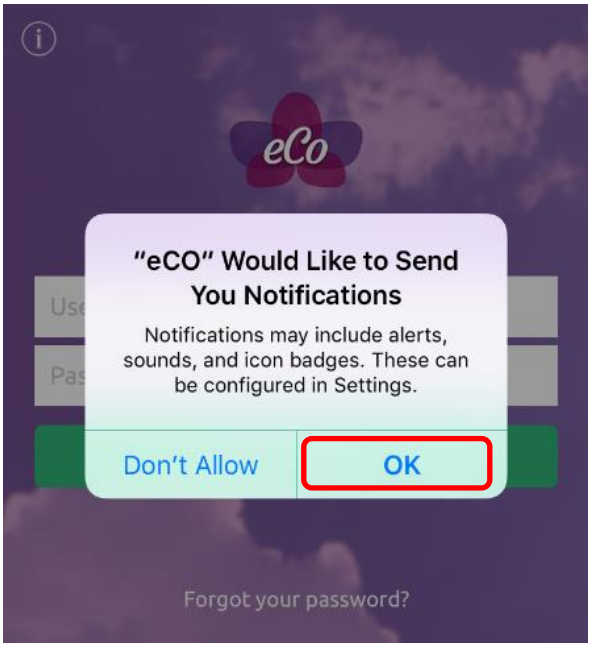


You can change the following items:

- **Change access code**: Change the access code by tapping here. eCO will ask you first for your current access code, then the new access code twice.

  Remark: After the application is put in background mode for more than one minute, you will be asked to enter your access code to unlock your application.

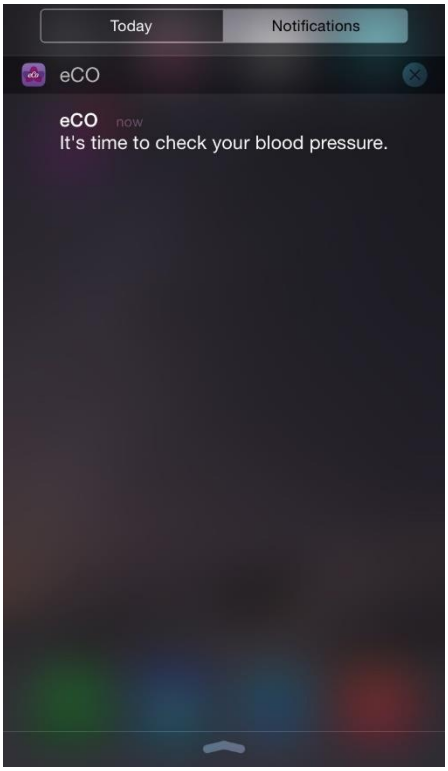
- **Reminders**: Change the blood pressure reminder times. The reminders will be displayed on your lock screen. Your notifications must be turned on to receive reminders.



Caution:

- Regular blood pressure monitoring is important and you must accept notifications upon first login, by tapping on "OK" button.
- Settings will not permit fewer than 8 hours separating the notifications.

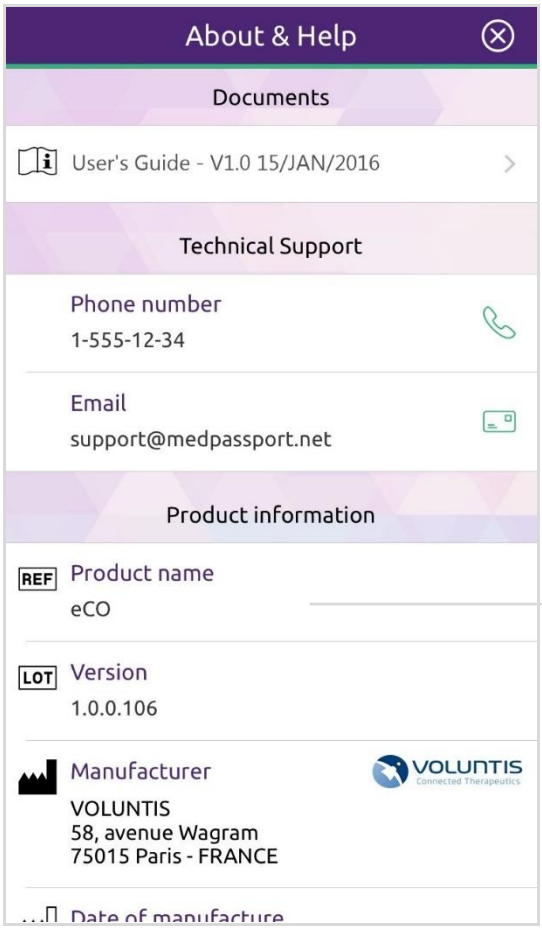
When notifications are sent, they are displayed on the iPhone lock screen, or in the notification list.


Today
Notifications
eCO
eCO now
It's time to check your blood pressure.

About and Help

The "About and Help" section provides important information about eCO including legal information, the license end date, support documents, and terms of use. This section allows access to an electronic version of the User Guide, which is regularly updated.

To access the "About and Help" section, press on the ⓘ icon at the top left corner of the eCO screen.



Documents

eCO's User's Guide is available in electronic format and can be accessed from here.

The "eCO Technical Support" line displays the user support email and toll free number to call if you are experiencing technical problems when using eCO (see Technical Support section in this document).

Remark: eCO user support provides technical support. For a **medical** problem, contact your

health care provider or for a medical emergency **call 911**.

Product information

The "Product Information" section displays the following information:

- Product name
- Version
- Manufacturer
- Release date
- Expiration date

TECHNICAL SUPPORT

For any technical question or issue, please contact the eCO User Support.

Toll free: 1-800-326-1448 (1-800-ECO-1HIT)

Email:**support@ecostudy.us**

HELP

Frequently Asked Questions

Compatibility

Which devices are compatible with eCO?

eCO is available on all iPhone devices from iPhone 4S to iPhone 7 SE Plus.

What should I do if eCO is not compatible with my iOS version or mobile device?

eCO is compatible with iOS 8, 9 and 10. Upgrade your iPhone's operating system and try connecting to the application again. If the problem persists, contact User Support.

I installed a new iOS version and eCO is not compatible anymore. What should I do?

After a new iOS version is released, a delay can exist before the application is available for this version. Contact User Support for more information.

Access to eCO

What should I do if I do not receive my password?

It is possible that the email confirming your registration has been identified as spam by your email software. Check your "Spam" folder, and if the email is not there, contact eCO User Support 1-800-326-1448 (1-800-ECO-1HIT) or by email: support@ecostudy.us.

What should I do if I have forgotten my temporary password?

If you have forgotten your temporary password, call your Study team in order to have your password generated again. You should receive this new password shortly after in your mailbox.

If you have forgotten your access code, tap on "Forgot your code?" in the Access code entry screen. Confirm that you want to reset your access code and authenticate again.

Internet connection

Do I need an active Internet connection to connect to eCO?

An active Internet connection is required during your first connection. Once you are logged in, you can open your application and enter your access code without being connected to Internet.

Do I need an active Internet connection to enter data?

eCO requires an active Internet connection to retrieve your contact information and your parameters. If you enter a blood pressure measure or report a diarrhea event without any internet connection, the recommendation may not take into account the settings made by your Study team.

Blood pressure entry

I forgot to enter my blood pressure when eCO asked me to do it. Should I enter it now?
Yes. The reminders are here to help you remember to enter your blood pressure. If you forgot to enter it before, you can still enter it now.

I cannot transfer the data from my blood pressure monitor to eCO. What can I do?
First, check that the Bluetooth function is activated on your iPhone. Then, check that your iPhone and your monitor are paired and try again. If the error persists, enter your BP manually and contact eCO User Support.

The symptoms I want to enter are not displayed in the list. How can I report them?
eCO displays the list of symptoms generally associated with hypertension. If the symptoms you want to report are not displayed in the list, it probably means that these symptoms are not related to your blood pressure. Select "None" and continue your blood pressure entry. If the symptoms worsen, contact your study team.

eCO asked me to call my Study Team. Who should I contact first?
Depending on the situation, you may prefer to call your research nurse or your oncologist. If your Study Team is not available, you can call the "After-hours and Weekend" number displayed in the application. In case of medical emergency, dial 911.

Diarrhea entry

a. **When should I report a diarrhea episode?**
You can report a diarrhea episode at any time. When you report a diarrhea episode, you will be asked to enter the number of bowel movements you have had over the past 24 hours.

b. **I have an ileostomy and eCO asks for my number of bowel movements. What should I do?**
If eCO asks you for the number of bowel movements you have had over the past 24 hours even if you have an ileostomy, it means that your profile was incorrectly set. Contact your study team to correct this.

c. **I don't have an ileostomy and eCO asks about my ileostomy output. What should I do?**
If eCO asks you about your ileostomy output even when you don't have an ileostomy, it means that your profile was incorrectly set. Contact your study team to correct this.

d. **I have had several diarrhea episodes over the past 24 hours. Why won't eCO let me enter several episodes in less than 24 hours?**
In order to provide you with the most accurate recommendation, eCO needs to know the number of bowel movements you've had over the past 24 hours. Once a recommendation is

made, it may take some time for the changes to be effective. Therefore, once you report a diarrhea episode, you must wait at least 18 hours to report another episode.

e. **The symptoms I want to enter are not displayed in the list. How can I report them?**
eCO displays the list of symptoms generally associated with diarrhea. If the symptoms you want to report are not displayed in the list, it probably means that these symptoms are not related to your diarrhea episode. Select "None" and continue your diarrhea report.

If the symptoms worsen, contact your study team.

Settings

a. **How can I update my personal information?**
Your personal information cannot be edited. If you want your personal information to be updated, call your study team.

b. **Can I change my number of daily blood pressure reminders?**
No. If you consider that you receive too many or not enough reminders, contact your study team to change this setting.

eCO in other countries

Does eCO work in other countries?
eCO works normally in all locations, but if you use the mobile app, you must continue to use the application on a regular basis with Internet access. Depending on your mobile plan, this could lead to a surcharge if you are outside of your normal usage area. You may use wifi for your Internet connection, if available.

Other questions

If your question has not been answered, please contact eCO User Support: 1-800-326-1448 (1-800-ECO-1HIT) or by email: **support@ecostudy.us**
.

Glossary and Abbreviations

Abbreviations

- **BP**: Blood pressure
- **eCO:** e Cediranib / Olaparib
- **mmHg**: millimeters of mercury

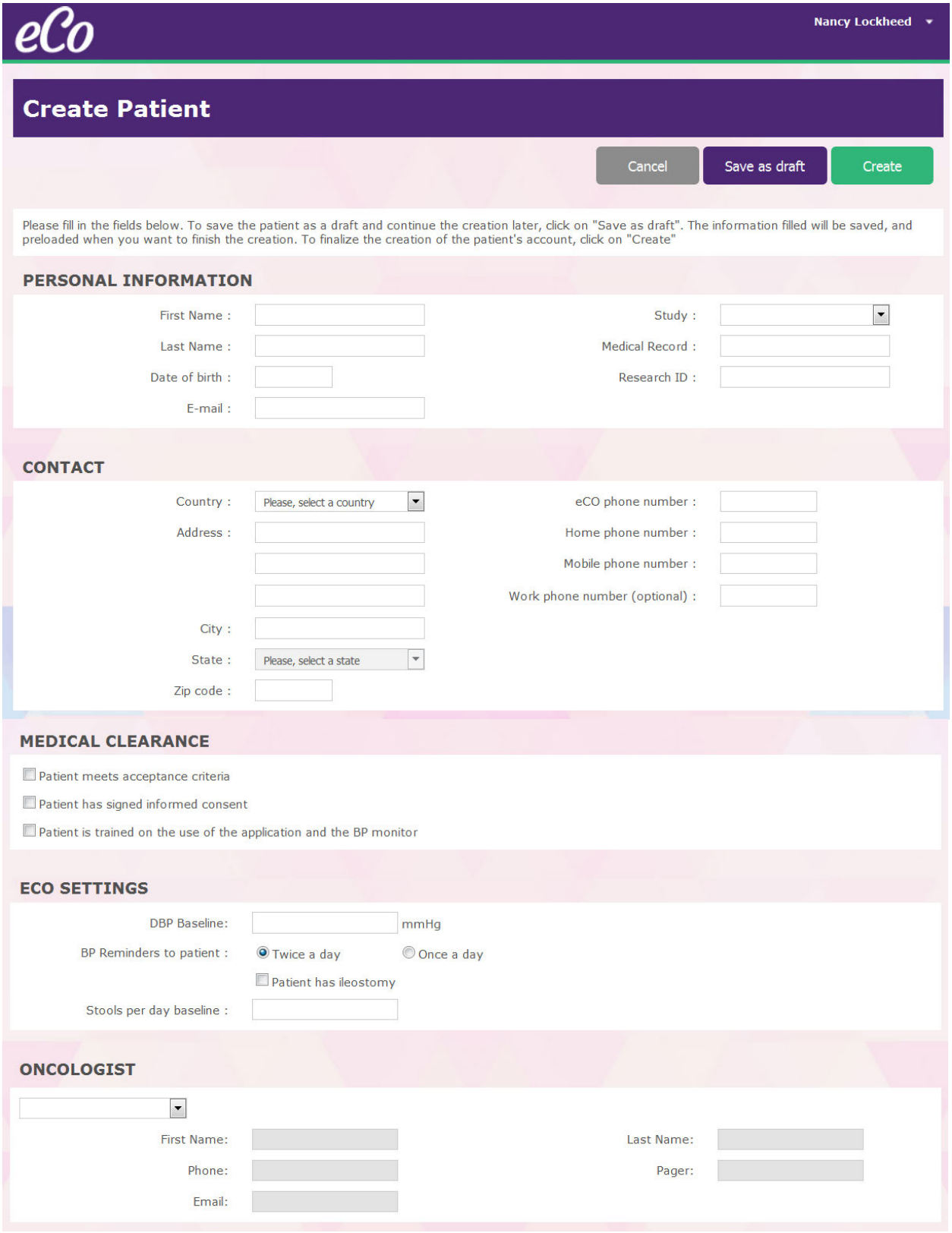
Technical terms

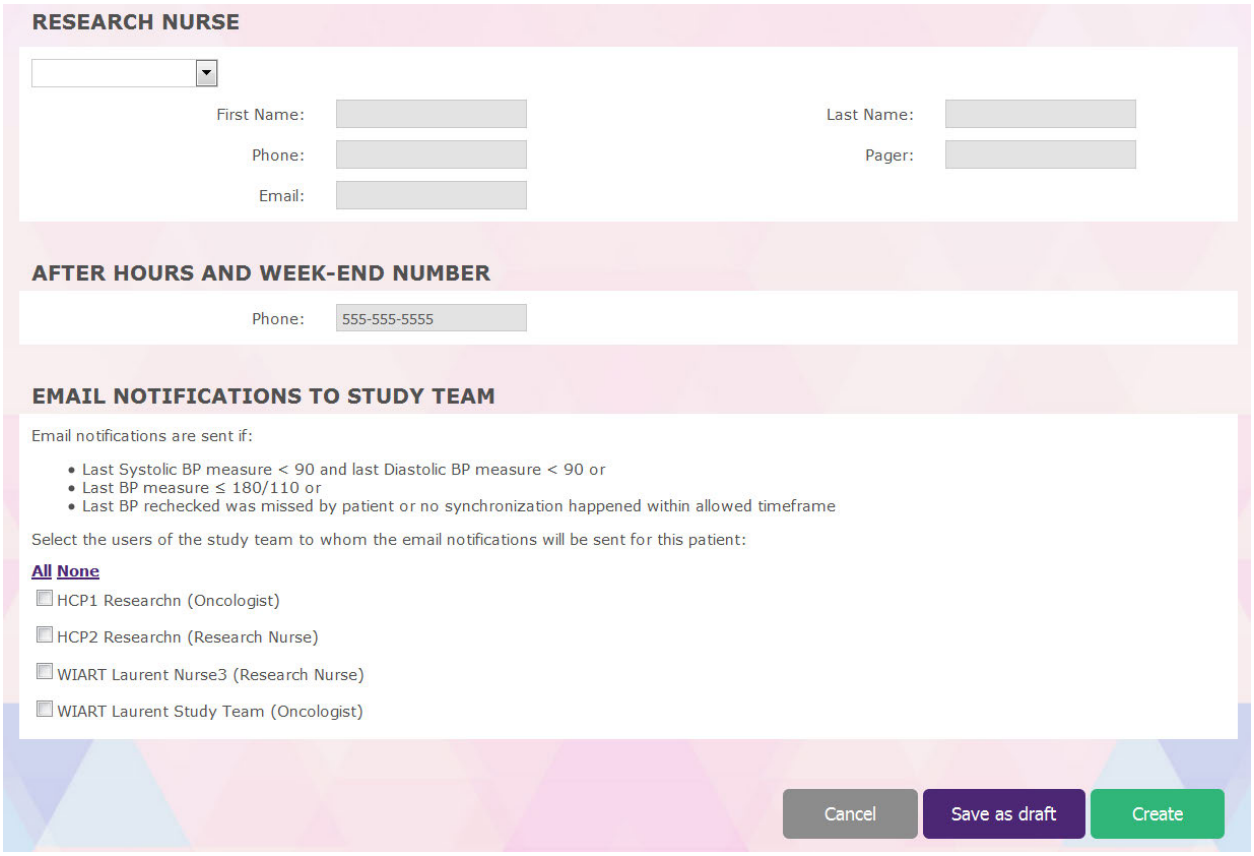
- **iOS**: An operating system found on several types of mobile devices made by Apple.
- **Synchronization**: Transfer of data between eCO mobile and the server.

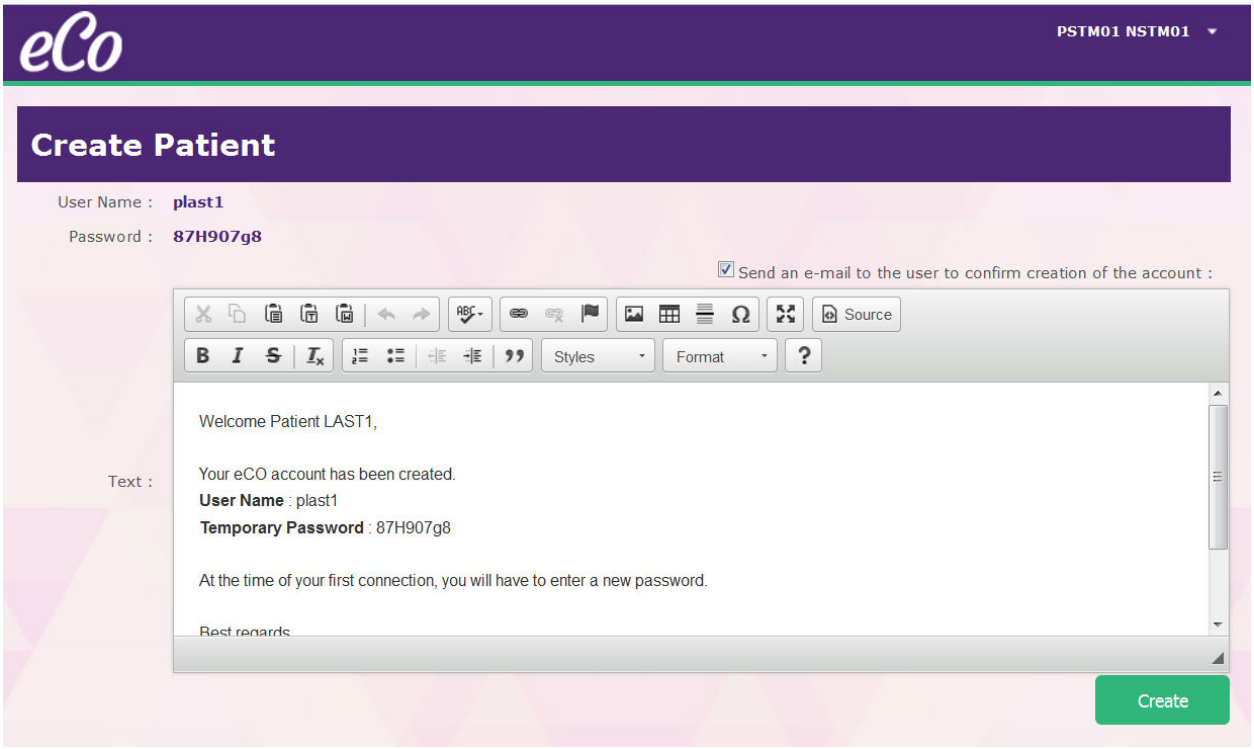
Legal information

Voluntis S.A.
58, avenue Wagram
75017 Paris
FRANCE
www.voluntis.com

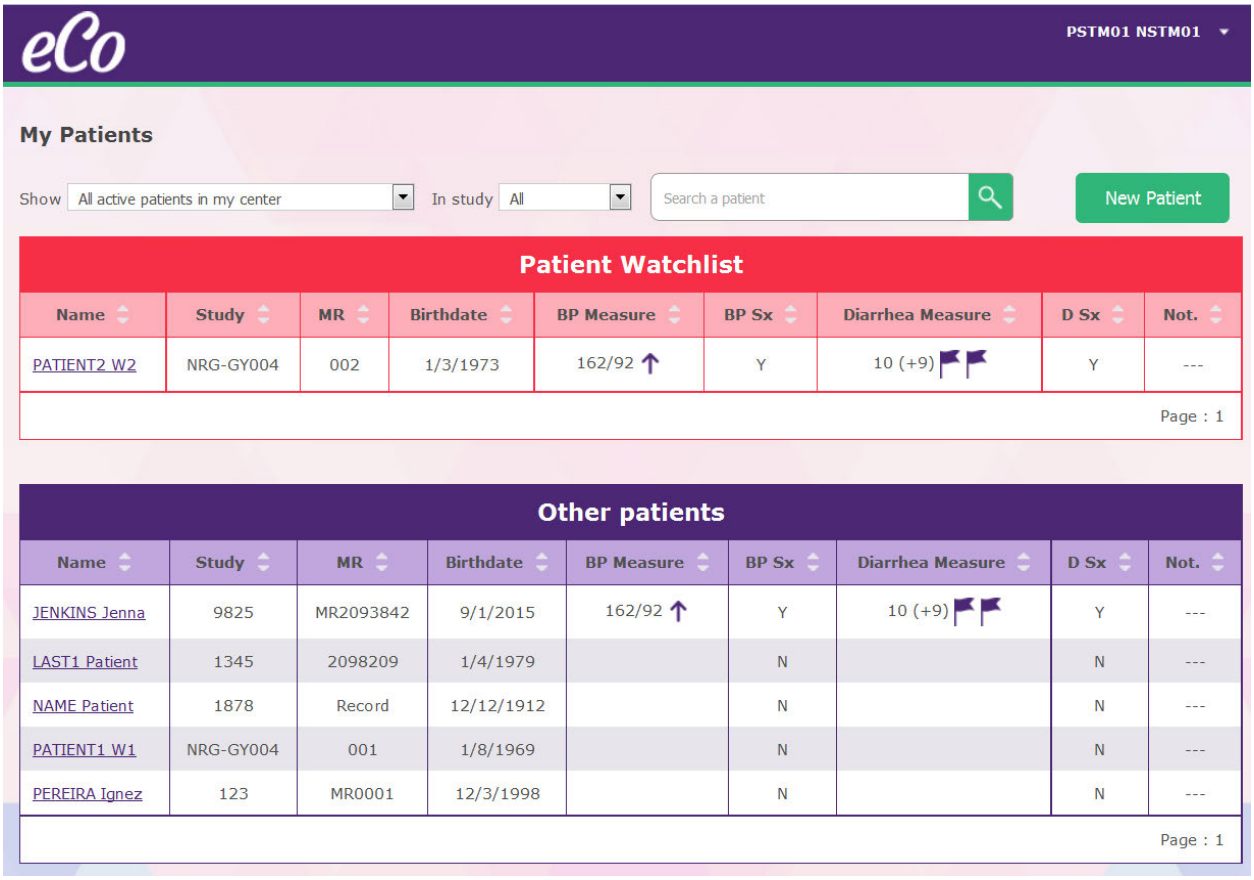
eCO Web Portal – Study Team Screenshots


eCo
Nancy Lockheed
Create Patient
Cancel
Save as draft
Create
Please fill in the fields below. To save the patient as a draft and continue the creation later, click on "Save as draft". The information filled will be saved, and preloaded when you want to finish the creation. To finalize the creation of the patient's account, click on "Create"
PERSONAL INFORMATION
First Name :
Last Name :
Date of birth :
E-mail :
Study :
Medical Record :
Research ID :
CONTACT
Country :
Please, select a country
Address :
City :
State :
Please, select a state
Zip code :
eCO phone number :
Home phone number :
Mobile phone number :
Work phone number (optional) :
MEDICAL CLEARANCE
Patient meets acceptance criteria
Patient has signed informed consent
Patient is trained on the use of the application and the BP monitor
ECO SETTINGS
DBP Baseline:
mmHg
BP Reminders to patient :
Twice a day
Once a day
Patient has ileostomy
Stools per day baseline :
ONCOLOGIST
First Name:
Last Name:
Phone:
Pager:
Email:

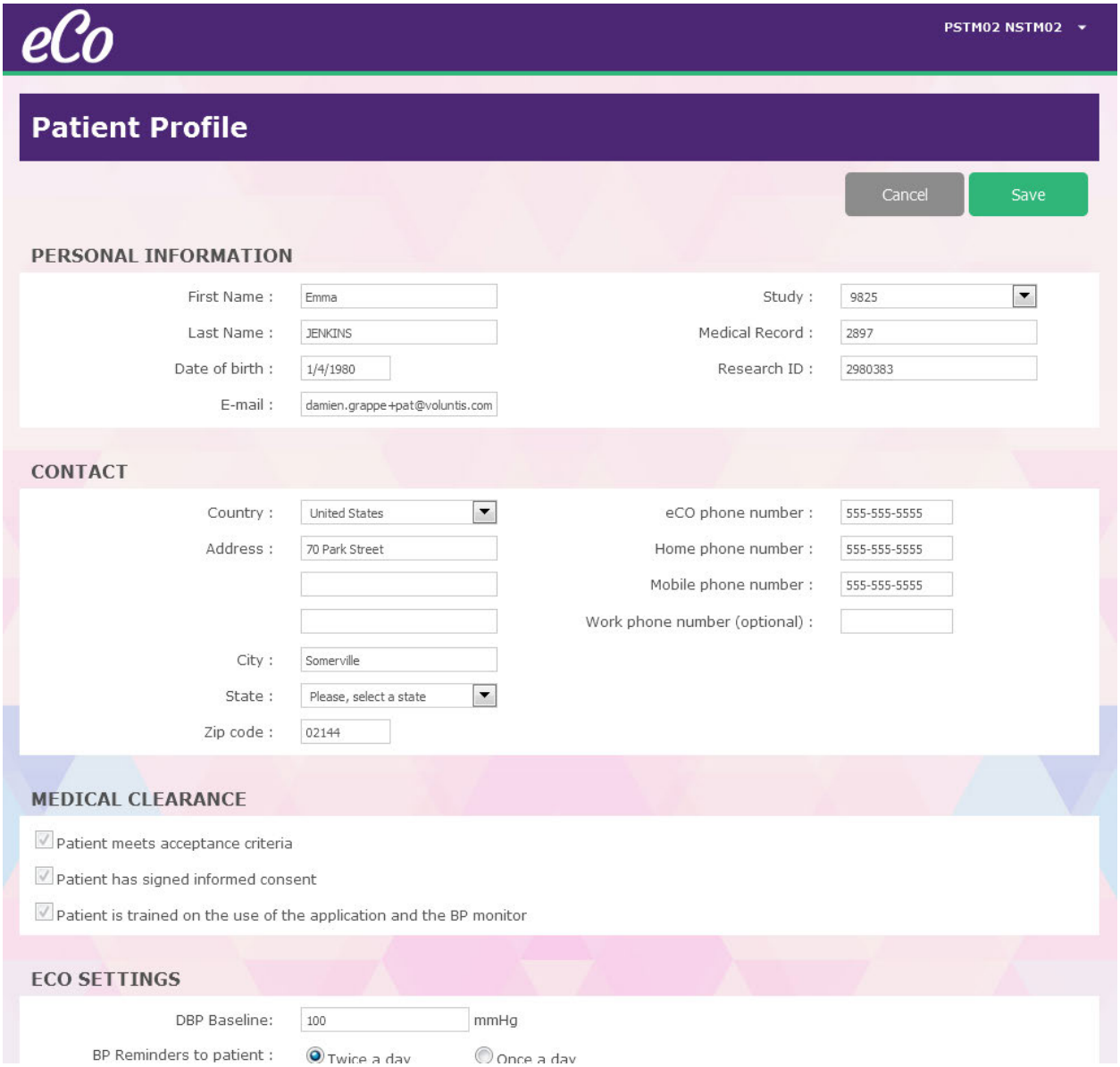

RESEARCH NURSE
First Name:
Last Name:
Phone:
Pager:
Email:
AFTER HOURS AND WEEK-END NUMBER
Phone:
555-555-5555
EMAIL NOTIFICATIONS TO STUDY TEAM
Email notifications are sent if:
• Last Systolic BP measure < 90 and last Diastolic BP measure < 90 or
• Last BP measure ≤ 180/110 or
• Last BP rechecked was missed by patient or no synchronization happened within allowed timeframe
Select the users of the study team to whom the email notifications will be sent for this patient:
All None
HCP1 Researchn (Oncologist)
HCP2 Researchn (Research Nurse)
WIART Laurent Nurse3 (Research Nurse)
WIART Laurent Study Team (Oncologist)
Cancel
Save as draft
Create


eCo
PSTM01 NSTM01
Create Patient
User Name : plast1
Password : 87H907g8
Send an e-mail to the user to confirm creation of the account :
Source
Styles
Format
Text :
Welcome Patient LAST1,
Your eCO account has been created.
User Name : plast1
Temporary Password : 87H907g8
At the time of your first connection, you will have to enter a new password.
Best regards
Create

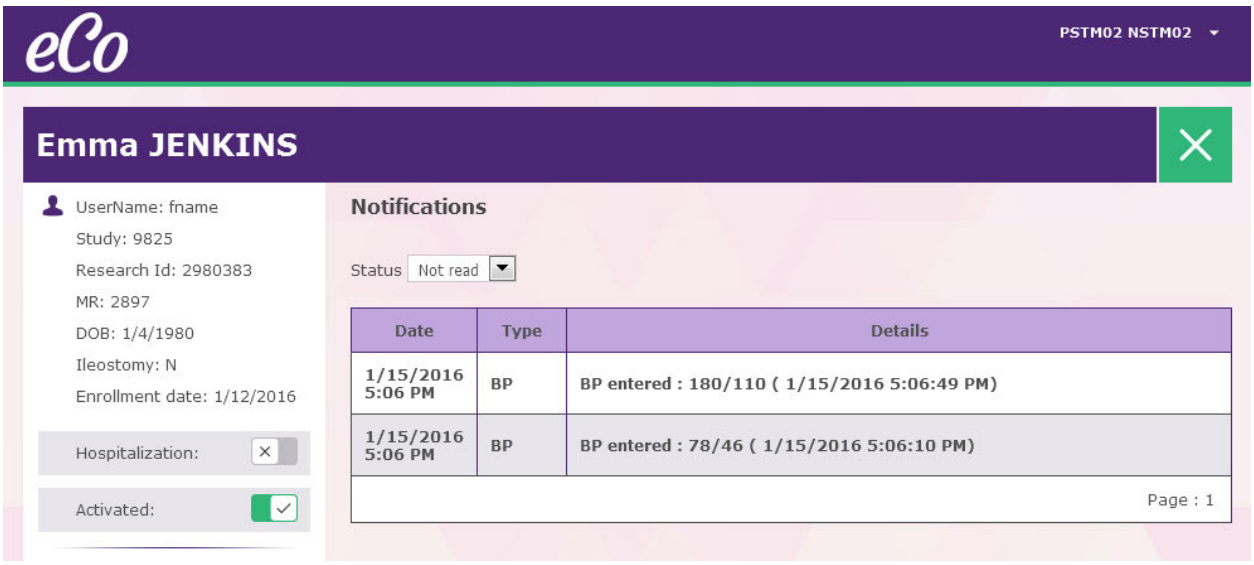
Patient Watchlist



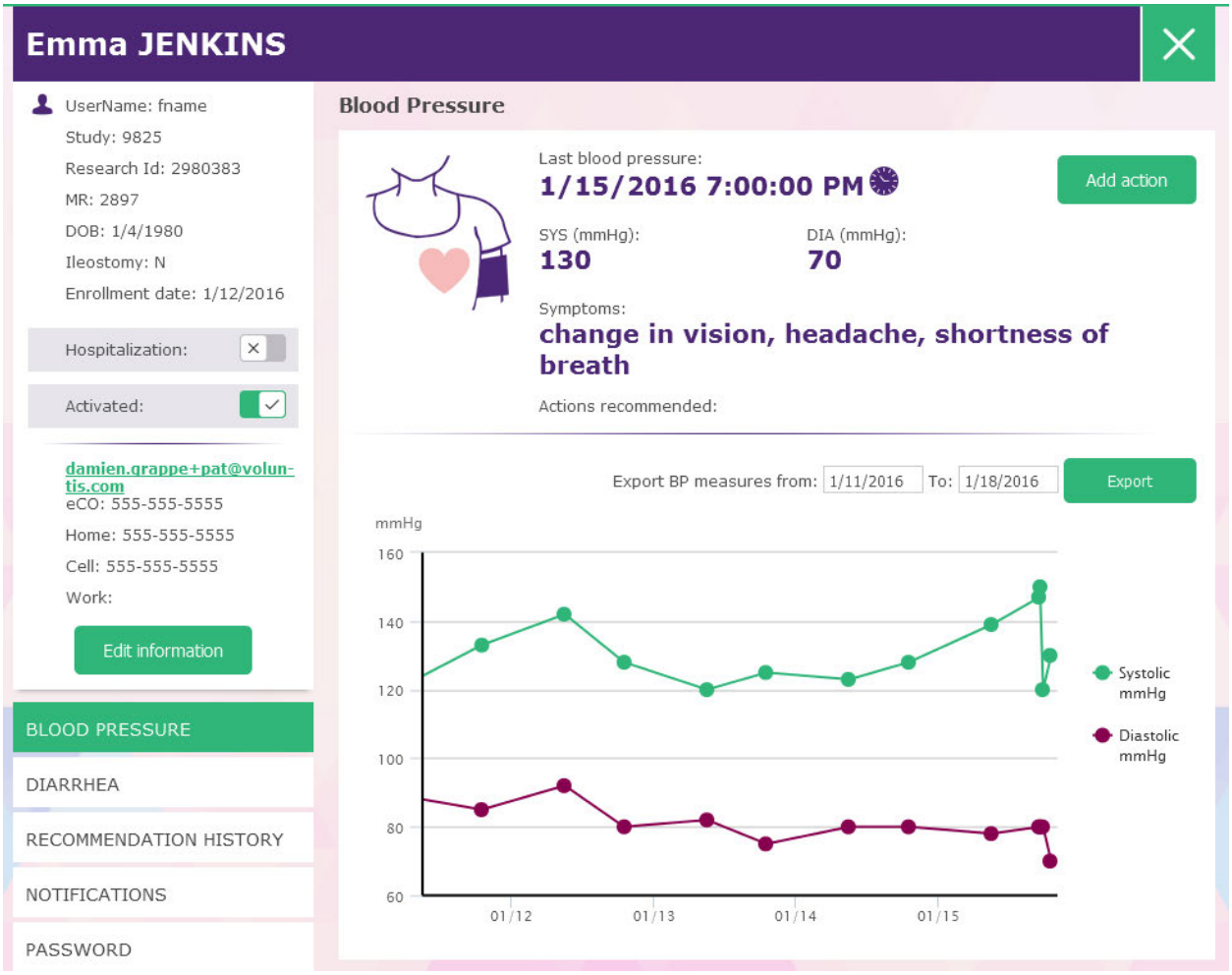
Example Completed Patient Profile



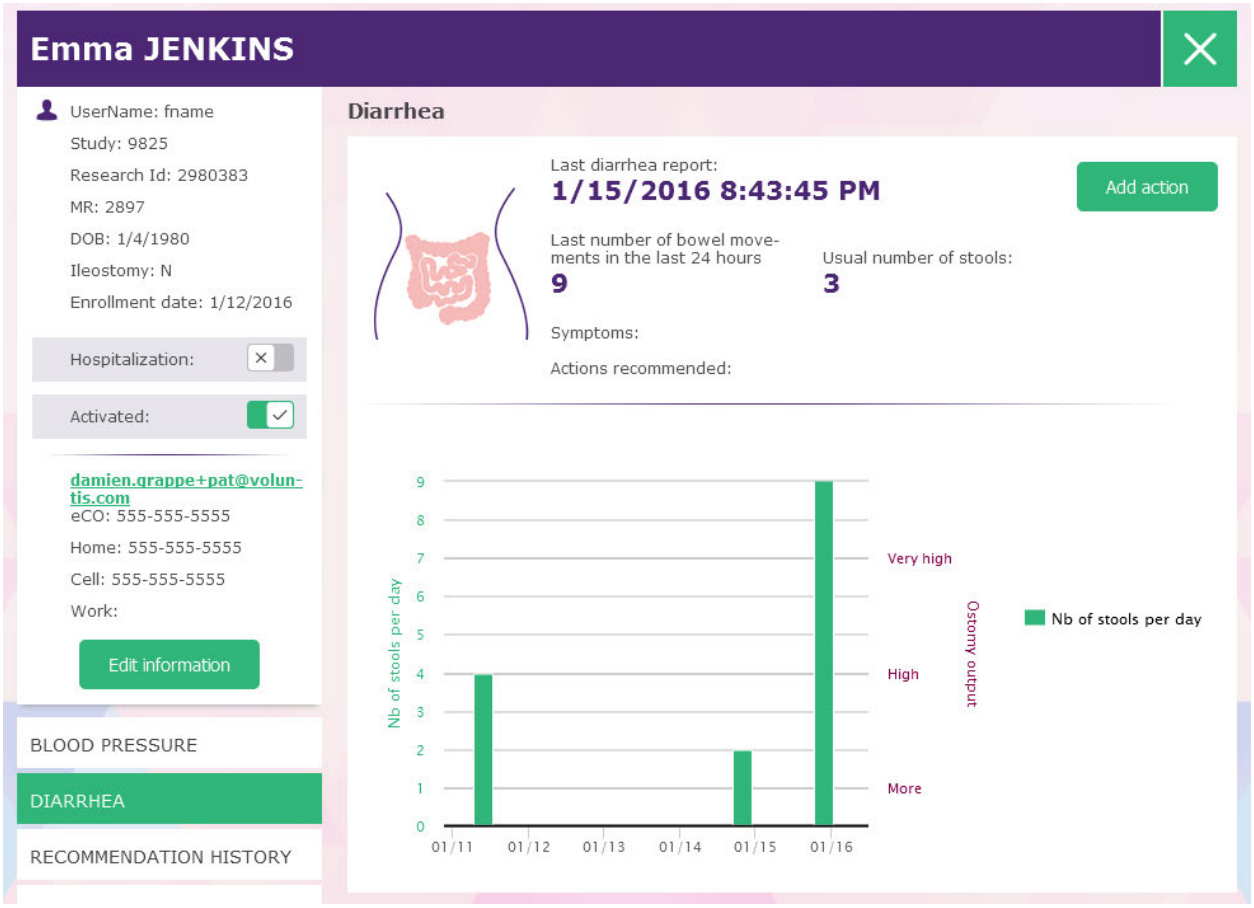
Example of Notifications



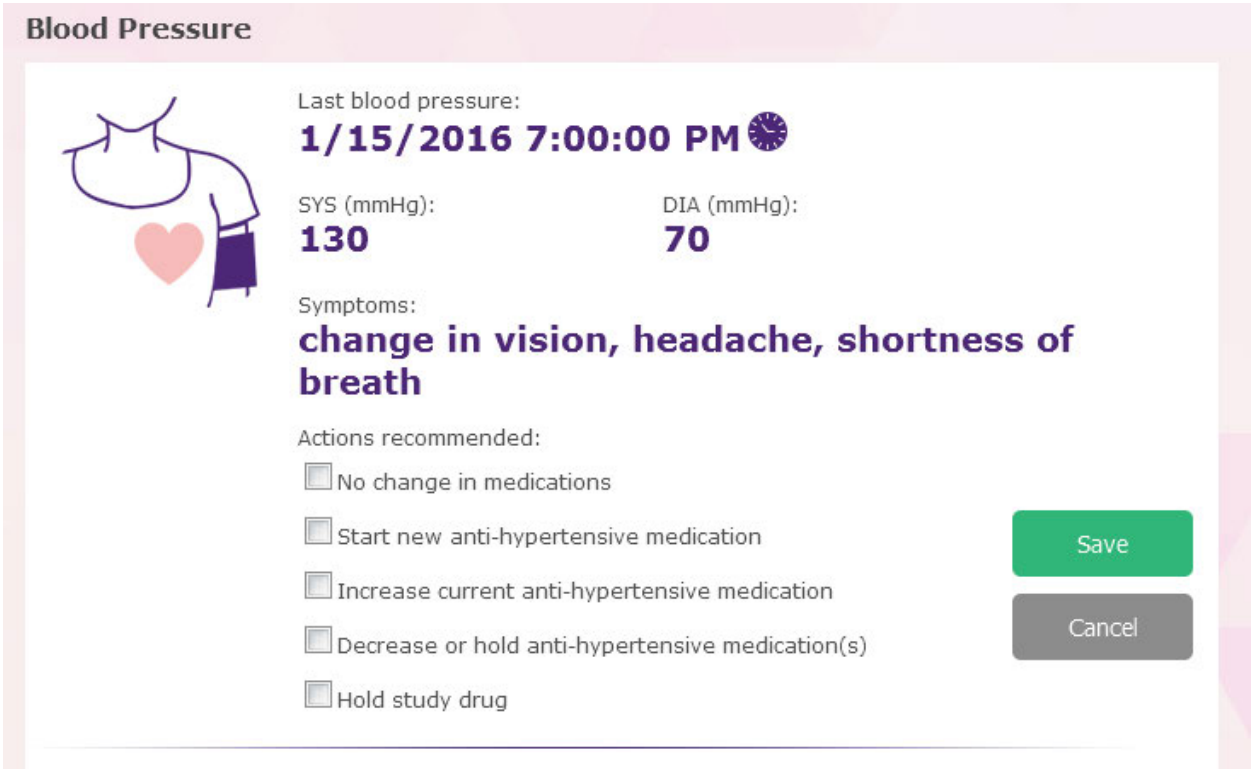
Blood Pressure History

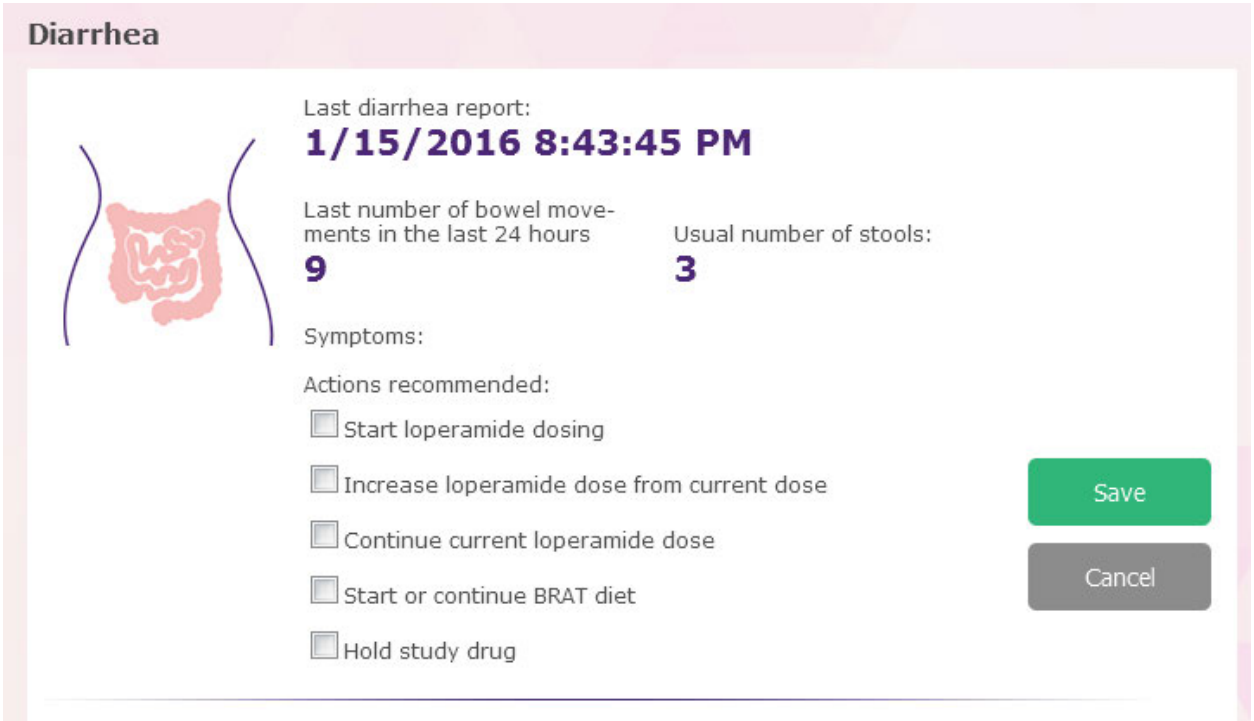


Diarrhea History



Add Recommended Action by Study Team





View Protocol

Blood pressure

Protocol Reminder Download complete protocol

- Increases in BP and cases of hypertension have been associated with many drugs acting on the VEGF pathway. The proposed mechanism for this increase is through inhibition of VEGF-induced peripheral vasodilation. Hypertension following cediranib treatment has been seen in animal studies as well as clinical trials.

Only doses of cediranib will be modified for hypertension; olaparib doses will not be reduced unless other toxicities are experienced. Patients receiving cediranib will be provided with blood pressure monitors for home use and will check and record their blood pressures at least twice daily while on study treatment.

See the tables below for guidelines on hypertension management and Appendix G for suggested antihypertensive medications by class.

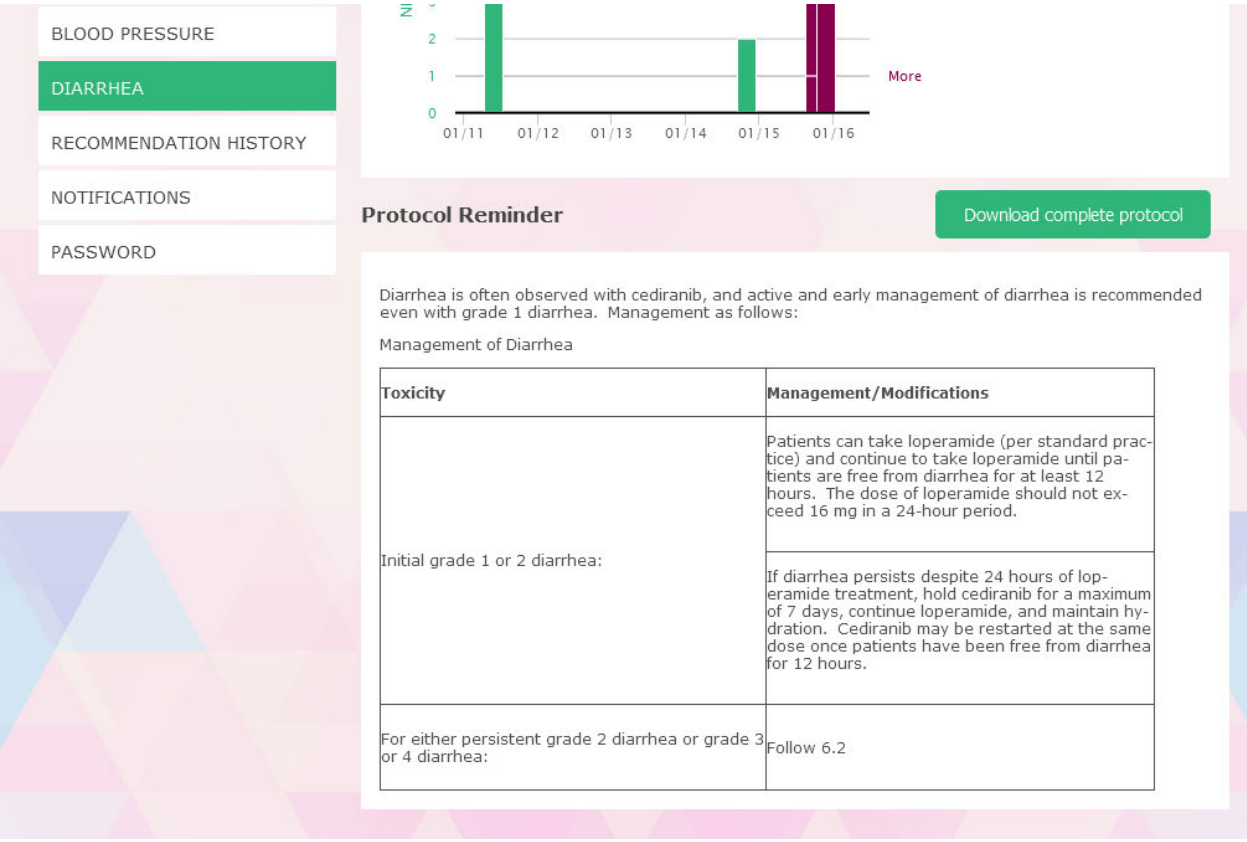
Note:

- If patients require a delay of >2 weeks for management of hypertension, management should be discussed with the overall PI and may require discontinuation from protocol therapy
- Patients may have up to 4 drugs for management of hypertension prior to any dose reduction in cediranib.
- Hypertension should be graded using the NCI CTCAE v4.0. Patients with baseline hypertension who require the addition of new medications for hypertension management while on study drug may not have an increase in CTCAE grade, but a change in attribution should be noted.
- Note: Stopping or reduce the dose of cediranib is expected to cause a decrease in BP. The treating physician should monitor the patient for hypotension and adjust the number and dose of antihypertensive medications accordingly.

Hypertension Monitoring and Management

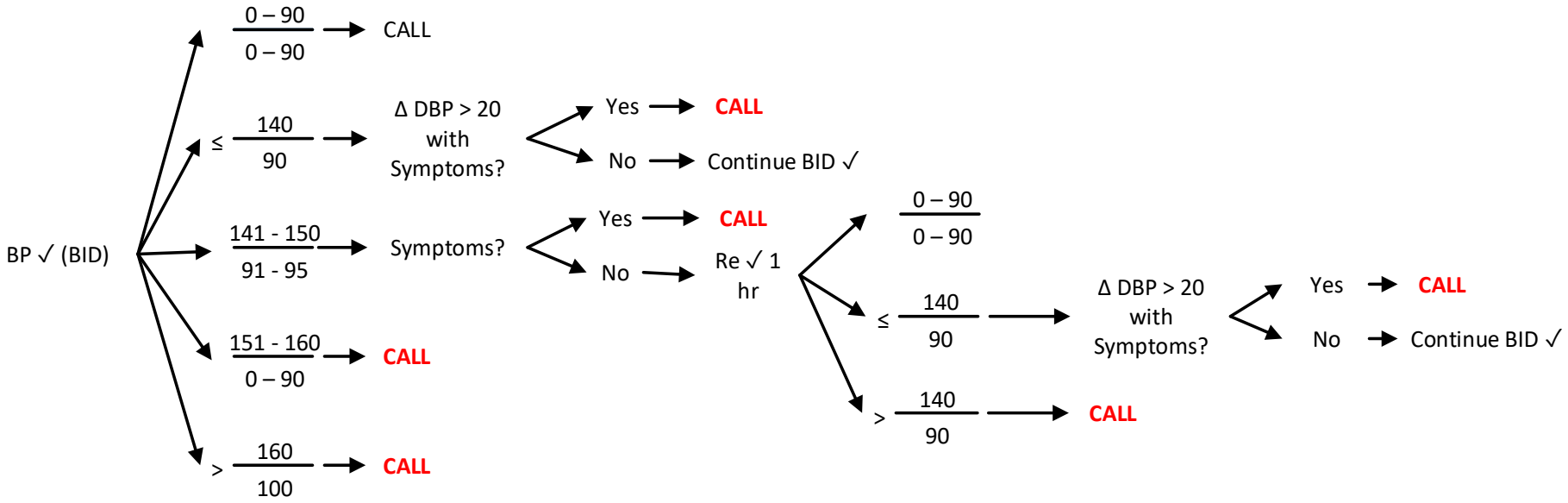
Event	Definition	Antihypertensive Therapy	Blood Pressure Monitoring	Cediranib Dose Modification
Grade 1	Asymptomatic transient (<24 hours) increase by >20 mmHg diastolic or to > 140/90 mmHg if previously within normal limits	None	Standard monitoring per treating MD	None
	Recurrent or persistent (>24 hrs) or symptomatic increase by >20 mmHg (diastolic) or	Initiate BP medication for first line treatment: • *Suggestion:* Calcium-channel blocker or ACE inhibitor Escalate dose of medication until BP is controlled or at a maximum dose	Increase frequency of	Do not hold cedi-

Diarrhea

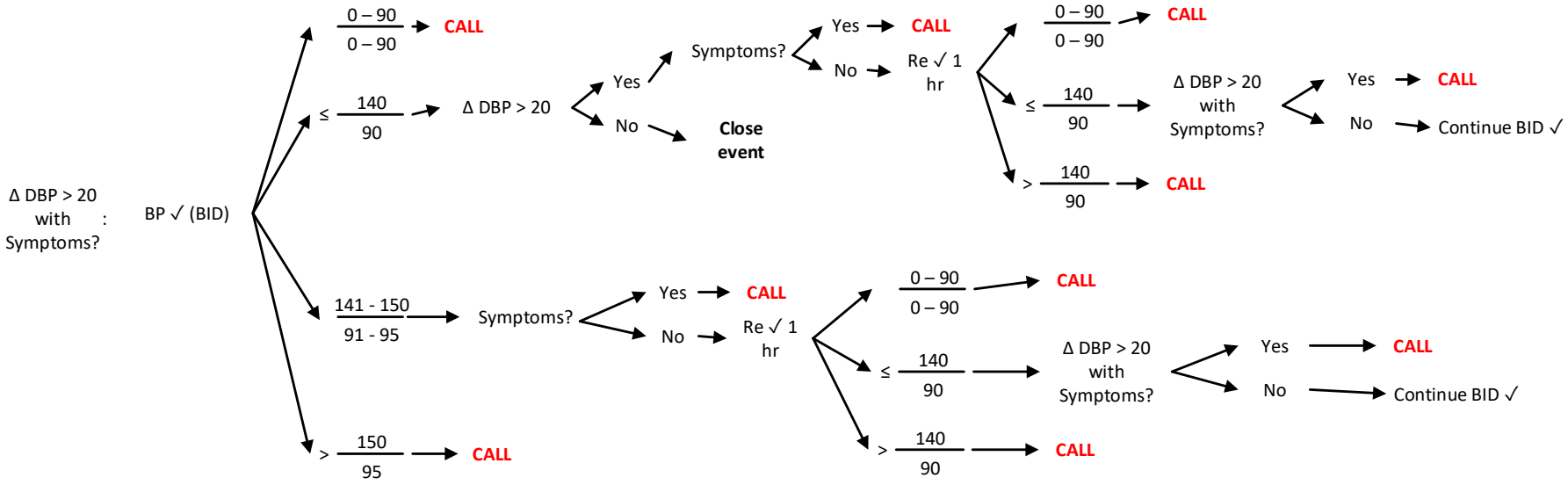

BLOOD PRESSURE
DIARRHEA
RECOMMENDATION HISTORY
NOTIFICATIONS
PASSWORD
NI
2
1
0
More
01/11
01/12
01/13
01/14
01/15
01/16
Protocol Reminder
Download complete protocol
Diarrhea is often observed with cediranib, and active and early management of diarrhea is recommended even with grade 1 diarrhea. Management as follows:
Management of Diarrhea
Toxicity
Management/Modifications
Initial grade 1 or 2 diarrhea:
Patients can take loperamide (per standard practice) and continue to take loperamide until patients are free from diarrhea for at least 12 hours. The dose of loperamide should not exceed 16 mg in a 24-hour period.
If diarrhea persists despite 24 hours of loperamide treatment, hold cediranib for a maximum of 7 days, continue loperamide, and maintain hydration. Cediranib may be restarted at the same dose once patients have been free from diarrhea for 12 hours.
For either persistent grade 2 diarrhea or grade 3 or 4 diarrhea:
Follow 6.2

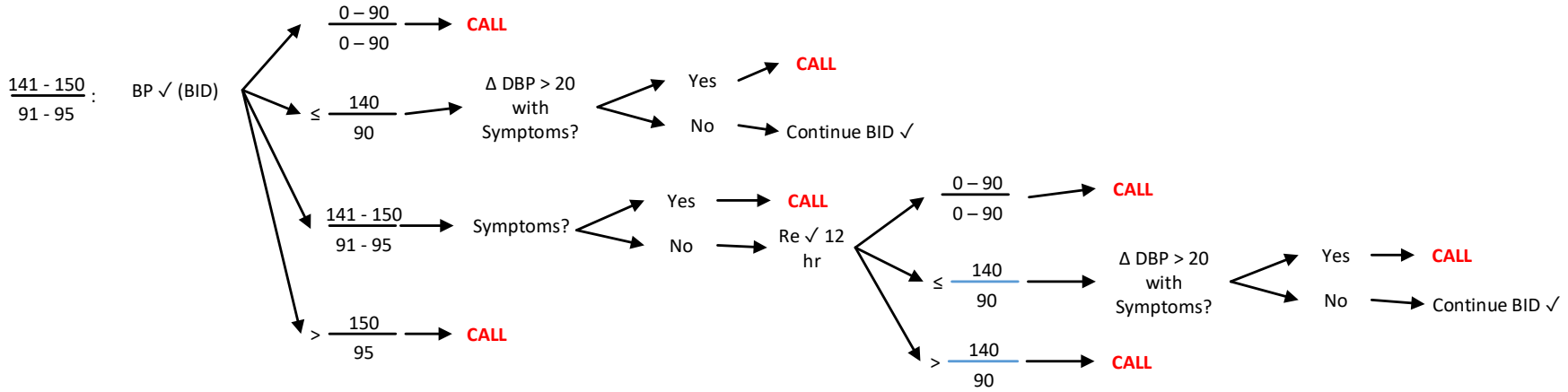
eCO Blood Pressure – Diarrhea Monitoring Data Collection

Not in BP event:

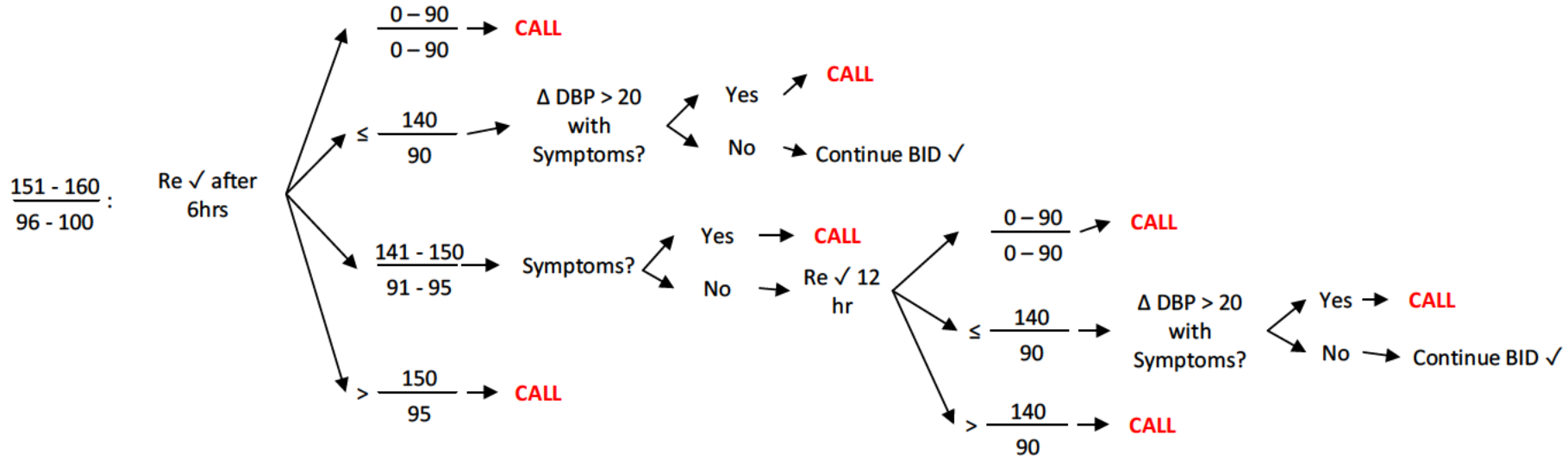


In BP event:

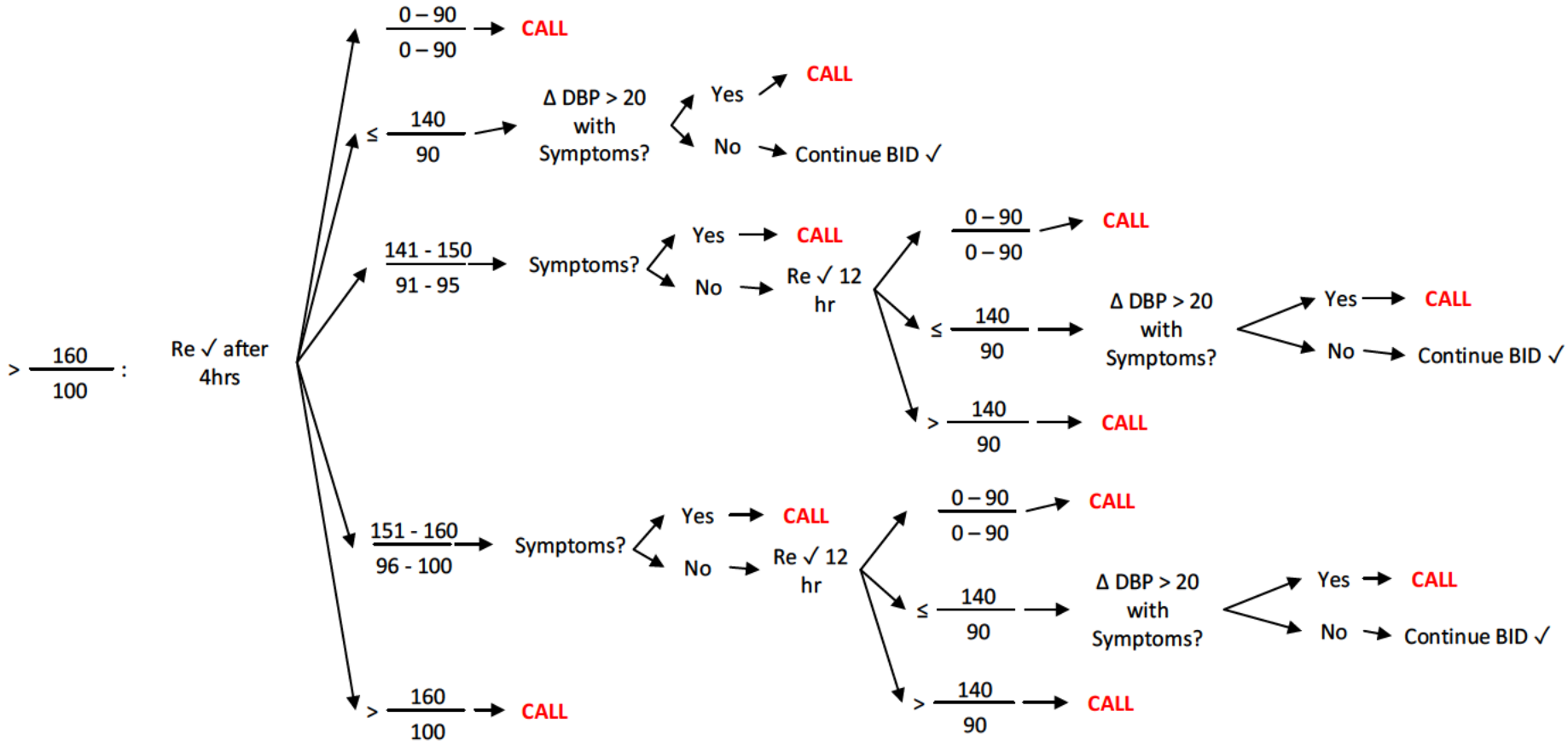

Δ DBP > 20 with Symptoms? :
BP ✓ (BID)
0 – 90 / 0 – 90 → CALL
≤ 140 / 90 → Δ DBP > 20
Yes
No
Close event
Symptoms?
Yes → CALL
No → Re ✓ 1 hr
0 – 90 / 0 – 90 → CALL
≤ 140 / 90 → Δ DBP > 20 with Symptoms?
Yes → CALL
No → Continue BID ✓
> 140 / 90 → CALL
141 - 150 / 91 - 95 → Symptoms?
Yes → CALL
No → Re ✓ 1 hr
0 – 90 / 0 – 90 → CALL
≤ 140 / 90 → Δ DBP > 20 with Symptoms?
Yes → CALL
No → Continue BID ✓
> 140 / 90 → CALL
> 150 / 95 → CALL


141 - 150 / 91 - 95 :
BP ✓ (BID)
0 – 90 / 0 – 90 → CALL
≤ 140 / 90 → Δ DBP > 20 with Symptoms?
Yes → CALL
No → Continue BID ✓
141 - 150 / 91 - 95 → Symptoms?
Yes → CALL
No → Re ✓ 12 hr
0 – 90 / 0 – 90 → CALL
≤ 140 / 90 → Δ DBP > 20 with Symptoms?
Yes → CALL
No → Continue BID ✓
> 140 / 90 → CALL
> 150 / 95 → CALL

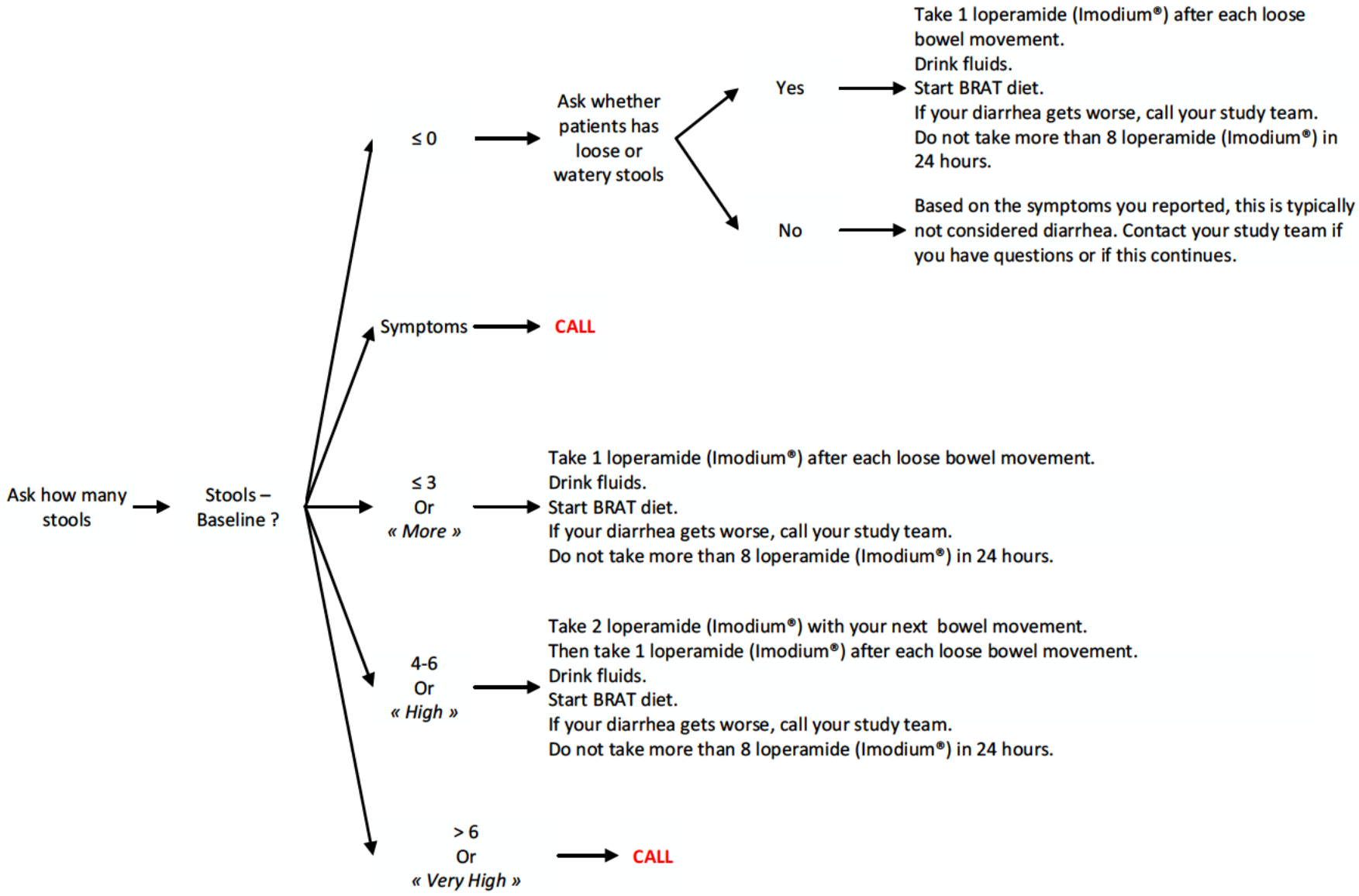
In BP event:


151 - 160 / 96 - 100 :
Re ✓ after 6hrs
0 – 90 / 0 – 90
CALL
≤ 140 / 90
Δ DBP > 20 with Symptoms?
Yes
CALL
No
Continue BID ✓
141 - 150 / 91 - 95
Symptoms?
Yes
CALL
No
Re ✓ 12 hr
0 – 90 / 0 – 90
CALL
≤ 140 / 90
Δ DBP > 20 with Symptoms?
Yes
CALL
No
Continue BID ✓
> 140 / 90
CALL
> 150 / 95
CALL

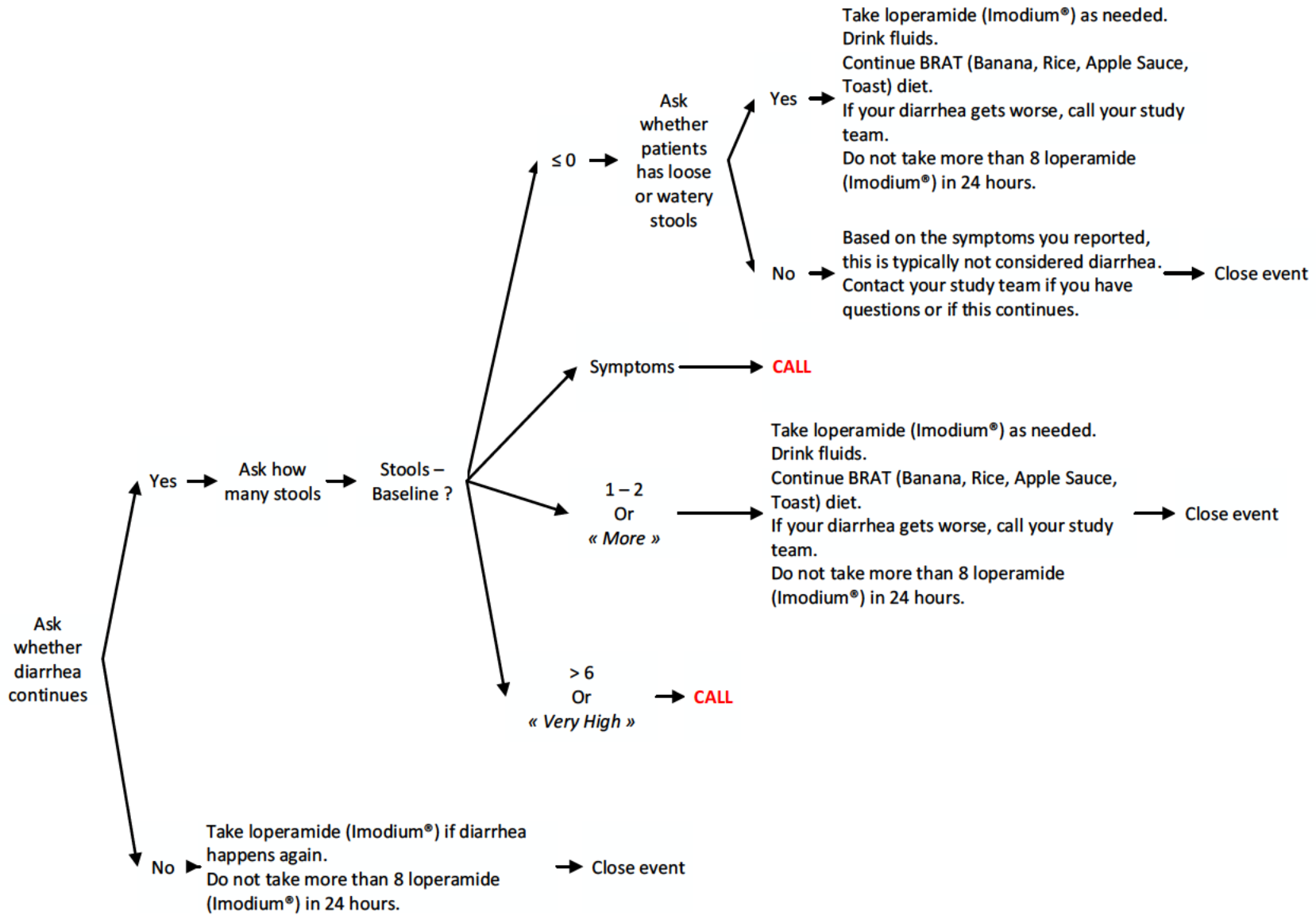
In BP event:


> 160/100 :
Re ✓ after 4hrs
0 – 90 / 0 – 90 → CALL
≤ 140/90 → Δ DBP > 20 with Symptoms? → Yes → CALL
No → Continue BID ✓
141 - 150/91 - 95 → Symptoms? → Yes → CALL
No → Re ✓ 12 hr
0 – 90 / 0 – 90 → CALL
≤ 140/90 → Δ DBP > 20 with Symptoms? → Yes → CALL
No → Continue BID ✓
> 140/90 → CALL
151 - 160/96 - 100 → Symptoms? → Yes → CALL
No → Re ✓ 12 hr
0 – 90 / 0 – 90 → CALL
≤ 140/90 → Δ DBP > 20 with Symptoms? → Yes → CALL
No → Continue BID ✓
> 140/90 → CALL
> 160/100 → CALL

Diarrhea initial:



Ongoing diarrhea:



Patient User Surveys and Phone Interview Guide

eCO Baseline Survey: Technology Use

Participant ID: _____ Site ID:_____

Date: _____

1. Which of the following items do you use?

   ☐ Desktop computer
   ☐ Laptop Computer
   ☐ Mobile Phone
   ☐ Tablet
   ☐ eBook Read (i.e., Kindle)

2. *Answer if you use a Mobile Phone or Tablet*

   What type of smart phone and/or tablet device type do you use?
   ☐ iPhone (Model: _____)
   ☐ Android (Model: _____)
   ☐ Other Phone (Model: _____)
   ☐ Tablet (Model: _____)

3. *Answer if you use a Mobile Phone, Tablet or eBook reader.*

   What type of activities do you use your phone or tablet for? Check all that apply.
   ☐ Phone calls
   ☐ Texting
   ☐ Playing games
   ☐ Browsing the internet
   ☐ Purchasing from the internet
   ☐ Downloading new applications

Facilitator's Guide for eCO Mobile App Phone Interviews

Submitted by:
User-Centered Design, Inc.
20548 Deerwatch Place
Ashburn, VA 20147
(703) 729-2370
www.user-centereddesign.com

[Note: The purpose of this document is to guide the moderator. The questions and tasks contained herein may not be asked as written. The facilitator often draws on participant comments and the natural flow of the testing process to determine the flow of the session. While the facilitator will try to follow the order of the guide, many times tasks will come up ahead of time or in different order. The facilitator may allow the order of the tasks to change in order to let the process flow naturally.]

Obtain consent

I need to ask you to formally agree to consent to participate in this interview. We are asking you for approximately 10 minutes of your time.

We won't be asking anything personal and no information identifying you will be shared with others.

Your participation is voluntary, and if you choose not to participate it will not affect your involvement in the clinical trial. You may ask questions at any time during the interview and you're free to stop the interview at any time without penalty and without any questions being asked of you. Do you have any questions for me before we start?

If you agree to participate, you are saying that you understand what I've told you and that any questions you have were satisfactorily answered. Do you agree to participate in the interview?

Interview

A. **INTRODUCTION**

Thank you for agreeing to talk to me today.

You've had the eCO application for about a week now and I wanted to follow up to see how it was going for you with the app since you left your doctor's office. I will only be asking about the mobile app and I will not be asking about your treatment.

There are only a few questions and as I said, the main purpose for the call today is to find out if the app is working alright for you this past week or if you are having any challenges with it. You can decline to answer any question and end this call when you want. I have one of my colleagues with us today taking notes for me Is it ok for my colleague to listen in to take notes for me? Are you ok with starting the questions?

Do you have any questions for me before we start?

B. Interview for Users (status predetermined by study team)

- Tell me about your use of the application. How often have you been using it? (Probe for type of activities)
    - [For each] How did the experience go for you?
        - Did you experience any problems or difficulties? [Discuss any issues raised; probe for monitoring blood pressure, diarrhea, etc.]
    - [If not mentioned] Have you reported a diarrhea event through the application yet?
- Have you ever received a recommendation from the application?
    - If so, was the recommendation clear?
- What parts of the application, if any, did you initially find difficult to learn how to use? Have you figured them out now?
- What parts of the application, if any, do you still find difficult or awkward to use now that you've figured out how to use the app?

- Do you have any questions about how to use the app that you would like to ask me?

C. **Interview for Non-Users**

- According to the information I have, you decided not to use the application.
    - Can you share with me the reasons why you decided not to use it? [Probe for technical and situational]
    - Is there anything that might have changed your mind about your decision not to use the application, even now?

D. Closure

- OK, those are the questions I have. Are there any questions you would like to ask me about the application or anything else you'd like to discuss about the application before I let you go?
- Thanks again for your participation.

eCO User Survey: Patients

Participant ID: ☐ Site ID: ☐

Date: ☐

	Strongly Disagree				Strongly Agree	
1. I liked using this app.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	
2. Using the app made me feel my care was being closely monitored.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	
3. Using the app made me feel more connected to the health care team.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	
4. The app made me feel involved in my own care.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	
5. It was hard for me to initially learn how to use the app.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	
6. I imagine most people would find it easy to learn how to use the app.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	
7. Even after learning how to use it, I found the app hard to use.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	
8. It was easy to find where to set the time(s) to receive reminders to take my blood pressure.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ N/A
9. The process of setting blood pressure reminders on the app was difficult.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ N/A
10. The process of reporting blood pressure side effects on the app was easy.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	
11. The process of recording blood pressure itself was difficult.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	
12. It was clear when I should report diarrhea.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	

13. The process of reporting diarrhea side effects on the app was difficult.

1	2	3	4	5	N/A
☐	☐	☐	☐	☐	☐

14. The process of reporting diarrhea on the app was easy.

1	2	3	4	5	N/A
☐	☐	☐	☐	☐	☐

15. Recommendations from the app were not very clear.

1	2	3	4	5
☐	☐	☐	☐	☐

16. It was easy to find the last recommendation made by the app.

1	2	3	4	5
☐	☐	☐	☐	☐

17. It was hard to find the Study Team Contact information.

1	2	3	4	5
☐	☐	☐	☐	☐

Comments

Feel free to add any additional comments you have about the application.

eCO User Survey: Study Team

○ MD ○ NP/PA ○ RN/Research Coordinator ○ Other_____

Site ID: ☐▽

Date: ☐

	Strongly Disagree				Strongly Agree
1. I liked using this website.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. It was hard for me to initially learn how to use the website.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3. I imagine that most people would find it easy to learn how to use the website.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4. Even after learning how to use it, I thought the website was hard to use.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5. The website made my work more efficient.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6. The amount of alerts generated were appropriate.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7. The content of the alerts were hard to understand.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
8. The content of the alerts were helpful.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
9. The tables on the “My Patients” page were hard to understand.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
10. The tables on the “My Patients” page had all the information I needed.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
11. I liked the separation of patients into a “watchlist” and a “non-watchlist”.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
12. The patient information section had all the information I needed.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
13. The patient information section was	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

hard to use.

Comments
Feel free to add any additional comments you have about the application.

eCO User Survey: Back-office

○ MD ○ NP/PA ○ RN/Research Coord.

Site ID: ☐▽

Date: ☐

	Strongly Disagree				Strongly Agree
1. I liked using this website.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
2. It was hard for me to initially learn how to use the website.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
3. I imagine that most people would find it easy to learn how to use the website.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
4. Even after learning how to use it, I thought the website was hard to use.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
5. Adding a new study center was easy to do	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
6. Managing existing study centers was hard to do.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
7. Adding a new study was easy to do.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
8. Managing existing studies was hard to do.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
9. Adding a study protocol to a study was easy to do.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
10. Adding new users was hard to do.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
11. Managing existing users was easy to do.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Comments

Feel free to add any additional comments you have about the application.