Official Title: **PHASE I/IIA, OPEN-LABEL, SAFETY, TOLERABILITY, AND IMMUNOGENICITY STUDY OF INO-3112 DELIVERED BY ELECTROPORATION (EP) IN WOMEN WITH CERVICAL CANCER AFTER CHEMORADIATION FOR NEWLY DIAGNOSED DISEASE OR THERAPY FOR RECURRENT AND/OR PERSISTENT DISEASE**

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HPV-004

PHASE I//IIA, OPEN-LABEL, SAFETY, TOLERABILITY, AND IMMUNOGENICITY STUDY OF INO-3112 DELIVERED BY ELECTROPORATION (EP) IN WOMEN WITH CERVICAL CANCER AFTER CHEMORADIATION FOR NEWLY DIAGNOSED DISEASE OR THERAPY FOR RECURRENT AND/OR PERSISTENT DISEASE

Sponsored by:

Inovio Pharmaceuticals, Inc.

BB-IND # 15,946

Version 2.1

27 April 2016

PHASE I/IIA, OPEN-LABEL, SAFETY, TOLERABILITY, AND IMMUNOGENICITY STUDY OF INO-3112 DELIVERED BY ELECTROPORATION (EP) IN WOMEN WITH CERVICAL CANCER AFTER CHEMORADIATION FOR NEWLY DIAGNOSED DISEASE OR THERAPY FOR RECURRENT AND/OR PERSISTENT DISEASE

Biologic Products:	INO-3112 (VGX-3100 and INO-9012)
Protocol Number:	HPV-004
Sponsor:	Inovio Pharmaceuticals, Inc. 660 West Germantown Pike, Suite 110 Plymouth Meeting, PA 19462
Principal Investigator:	[redacted], MD
Medical Monitor:	[redacted], MD
Version and Date:	Version 2.1 27 April 2016

CONFIDENTIAL

SUMMARY OF CHANGES

The following is a list of significant protocol changes from v2.0 dated 12 June 2015 to v2.1 dated 27 April 2016. All other changes are administrative and do not significantly affect the safety of subjects, study scope, or scientific quality of the protocol.

1. The duration of the study changed from 3 years from last study treatment/EP to 36 weeks. This change still fulfills the study primary objectives, which include safety, tolerability and immunogenicity in subjects with cervical cancer and received INO-3112/EP treatment.
2. Updated the estimated number of Study Centers
3. Number of subjects to be enrolled in the study changed from 30 to 10 subjects. This is mainly due to study primary objectives and the challenge in trial operation/enrollment.
4. Specified in section 6.1.1 and 6.7 that the subjects with HPV-16 and/or HPV-18 positive from In-situ hybridization (ISH) or polymerase chain reaction (PCR) assays will be eligible for the study.
5. Added the option to conduct Weeks 2, 6, 8 and 10 visits as phone visit or in-person office visit. This change intends to be more convenient for study subjects.
6. Eliminated collection of the blood samples at Weeks 2, 4, 6, 10 and 14.
7. The medical monitor and associated contact information was updated to reflect a resourcing update by the Sponsor. All responsibilities of the updated medical monitor will remain the same.

PROTOCOL ACKNOWLEDGEMENT

I have read this Protocol and agree that it contains all necessary details for carrying out the study described. I understand that it must be reviewed by the Institutional Review Board or Independent Ethics Committee overseeing the conduct of the study and approved or given favorable opinion before implementation.

The signature of the Principal Investigator and Sponsor below constitute their approval of this protocol and proved the necessary assurances that this study will be conducted according to The Declaration of Helsinki, GCP, ICH guidelines, local legal and regulatory regulations as well as to all stipulations of the protocol in both the clinical and administrative sections, including statements regarding confidentiality.

_____ _____
Investigator's printed name and signature Date

_____ _____
[redacted], MD Date
Medical Monitor

Protocol Number: HPV-004
Site Number:
Version Number/Version Date: v2.1/27 April 2016

TABLE OF CONTENTS

CLINICAL PROTOCOL SYNOPSIS

Title of Study: Phase I/IIA, Open-Label, Safety, Tolerability, and Immunogenicity Study of INO-3112 Delivered by Electroporation (EP) in Women with Cervical Cancer after Chemoradiation for Newly Diagnosed Disease or Therapy for Recurrent and/or Persistent Disease
Estimated Number of Study Centers and Countries/Regions: 2 sites (United States)
Number of Subjects : Approximately 10 subjects
Study Phase: I/IIa
Research Hypothesis: Immunotherapy with INO-3112 delivered by intramuscular (IM) injection followed by EP with CELLECTRA®-5P will be immunogenic and well tolerated in women with newly diagnosed, inoperable cervical cancer associated with HPV-16 and/or HPV-18 after completion of standard chemoradiation therapy with curative intent (Cohort 1) or in women with persistent and/or recurrent cervical cancer associated with HPV-16 and/or HPV-18 following salvage therapy (Cohort 2) and will not be associated with any significant increased toxicity compared to that expected/reported with "standard" therapy alone.
Primary Objective: • Evaluate the safety and tolerability of immunotherapy with INO-3112 when delivered IM followed by EP with CELLECTRA®-5P in women with newly diagnosed, inoperable cervical cancer associated with HPV-16 and/or HPV-18 after completion of standard chemoradiation therapy with curative intent (Cohort 1) or in women with persistent and/or recurrent cervical cancer associated with HPV-16 and/or HPV-18 following salvage therapy (Cohort 2) compared to that expected/reported with "standard" therapy alone. **Secondary Objective:** • Evaluate the cellular and humoral immune responses to immunotherapy with INO-3112 delivered IM followed by EP with CELLECTRA®-5P in women with newly diagnosed, inoperable cervical cancer associated with HPV-16 and/or HPV-18 after completion of standard chemoradiation therapy with curative intent (Cohort 1) or in women with persistent and/or recurrent cervical cancer associated with HPV-16 and/or HPV-18 following salvage therapy (Cohort 2). **Exploratory Objective:** • Evaluate clinical responses (disease-free survival and progression-free survival) following treatment with INO-3112 delivered intramuscularly followed by EP with CELLECTRA®-5P in women with newly diagnosed, inoperable cervical cancer associated with HPV-16 and/or HPV-18 after completion of standard chemoradiation therapy with curative intent (Cohort 1) or in women with persistent and/or recurrent cervical cancer associated with HPV-16 and/or HPV-18 following salvage therapy (Cohort 2).

Study Design: This is a Phase I/IIa, open-label study to evaluate the safety, tolerability, and immunogenicity of INO-3112 [6 mg of VGX-3100 (2 separate DNA plasmids encoding E6 and E7 proteins of HPV 16 and HPV 18) and 1 mg of INO-9012 (DNA plasmid encoding human interleukin 12)] delivered IM by EP in approximately 10 female subjects with biopsy-proven, Stage IB-IVB inoperable invasive cervical carcinoma associated with HPV-16 and/or HPV-18 who have completed treatment with standard chemoradiation therapy with curative intent (Cohort 1) or in subjects with persistent and/or recurrent cervical cancer associated with HPV-16 and/or HPV-18 following salvage therapy (Cohort 2).

Eligible subjects who consent to participate in the study will receive a 1.1 mL IM injection of INO-3112 in the deltoid followed immediately by EP with CELLECTRA®-5P. If the deltoid is not a suitable location, the IM injection should be in the lateral quadriceps followed immediately by EP with CELLECTRA®-5P. All subjects (Cohorts 1 and 2) will receive a 4-dose series of INO-3112. The first study treatment/EP after completion of standard chemoradiation (Cohort 1) or salvage therapy (Cohort 2) will be designated as "Day 0", the second dose will be administered at Week 4, the third dose at Week 8, and the fourth (final) treatment will be administered at Week 12.

Cohort 1:
Cohort 1 will include subjects with biopsy-proven, Stage IB-IVB inoperable, newly diagnosed, invasive cervical carcinoma associated with HPV-16 and/or HPV-18 treated with standard chemoradiation therapy with curative intent.

All subjects in Cohort 1 must receive their first study treatment (Day 0) within 2 weeks after completing a course of standard radiation therapy (external beam and brachytherapy) administered concurrently with platinum based therapy with curative intent. (Refer to Appendix 3: Standard Chemoradiation Guidelines)

Cohort 2:
Cohort 2 will include subjects with persistent and/or recurrent cervical carcinoma associated with HPV-16 and/or HPV-18 treated with salvage therapy (chemotherapy and/or radiation therapy).

All subjects in Cohort 2 must receive their first study treatment (Day 0) no sooner than 2 weeks and no later than 4 weeks after completing a course of salvage therapy. If in the investigators opinion, there are no additional salvage therapy options, the subject may be enrolled in Cohort 2 without having received salvage therapy immediately prior to enrollment.

Primary Safety Endpoints:
1. Incidence of adverse events (all, severe [graded per Common Toxicity Criteria for Adverse Events (CTCAE) v4.03], unexpected, serious) classified by system organ class (SOC), preferred term, severity, and relationship to study medication and schedule
2. Injection site reactions including pain, tenderness, erythema and induration at the administration site
3. Rates of acute gastrointestinal, genitourinary, or other chemoradiation side effects above the expected, graded per Acute Radiation Morbidity Scoring Criteria (RTOG)
4. Changes in laboratory parameters from baseline

Study Design Contd.:

Secondary Immunologic Endpoints:

1. Antigen-specific cellular immune responses to INO-3112 in blood samples obtained from subjects per study schedule:
   a. Interferon-γ secreting T lymphocytes in PBMC by ELISpot
   b. Flow Cytometry for T-cell activation, cytolytic phenotype, and memory phenotype in PBMC
2. Antigen-specific humoral responses to HPV–E6 and –E7 by ELISA per study schedule

Exploratory Clinical Endpoints:

1. Changes in standard uptake volume (SUV) on PET/CT scans performed at baseline vs follow-up PET/CT scans obtained at specified time points
2. Evaluation of subjects relative immune competence longitudinally throughout the study starting at the screening visit (for details refer to Section 6.7: Cervical Virologic and Peripheral Blood Immunogenicity Assessment)
3. Changes in cervical histology from the screening biopsy as compared to the week 16 biopsy
4. Local immune responses to INO-3112 in tumor tissue samples obtained at week 16
5. Disease-free survival assessed in accordance with RECIST v1.1 (refer to Appendix 10) as follows:
   - Clinical evaluations for disease response will be conducted at all study visits (as assessed by clinical signs and symptoms of disease progression)
   - A baseline PET/CT scan will be obtained on each subject within 4 weeks prior to Day 0 and then PET/CT scans for disease progression will be obtained for all subjects 3-4 months after Day 0 and 3-5 months thereafter per standard of care/in accordance with local guidelines and institutional practices. Additional PET/CT scans may be obtained at other time points if clinically indicated to confirm a clinical diagnosis of disease progression based on signs and symptoms.

Inclusion Criteria

a) Written informed consent in accordance with institutional guidelines. If required by local law, candidates must also authorize the release and use of protected health information (PHI);

b) Female subjects age 18 years or older;

c) Histological diagnosis of squamous cell carcinoma, adenocarcinoma or adenosquamous cell carcinoma of the cervix. Not accepted are small cell, clear cell and other rare variants of the classical adenocarcinoma;

d) Histologically confirmed, Stage IB-IVB, invasive cervical carcinoma associated with HPV-16 and/or HPV-18 and meeting the following eligibility criteria for either Cohort 1 or Cohort 2;

Inclusion Criteria Contd.

1. Cohort 1

   - Newly diagnosed inoperable cervical cancer treated with chemoradiation therapy with curative intent and a life expectancy of at least 12 months as assessed by the investigator.
     - No CNS/spinal metastases
   - Able to initiate study treatment (Day 0) within 2 weeks of completion of last chemoradiation treatment;
     - Platinum based treatment (alone or in combination with other drugs); 5 weekly courses of Cisplatin 40 mg/m^2 completed within 10 weeks of its initiation
     - Standard radiation therapy (external beam and brachytherapy); completed within 10 weeks of its initiation
     - Brachytherapy; must be the last treatment if the subject is receiving sequential brachytherapy following the chemoradiation therapy

2. Cohort 2

   - Persistent and/or recurrent cervical cancer
     - No CNS/spinal metastases
   - Able to initiate study treatment (Day 0) at least 2 weeks after but no more than 4 weeks after completion of salvage therapy (If in the investigators opinion, there are no additional salvage therapy options, the subject may be enrolled in Cohort 2 without having received salvage therapy immediately prior to enrollment.)
   - Subject has a life expectancy of at least 12 months as assessed by the investigator

e) ECG with no clinically significant findings as assessed by the investigator performed within 30 days of signing the informed consent form (ICF);

f) Chemistry, liver function tests, renal function, total creatine phosphokinase (CPK) and hematology lab results must be ≤ Grade 1 at the time of screening, in accordance with the CTCAE v4.03;

g) Eastern Cooperative Oncology Group (ECOG) Performance status of ≤ 1;

h) Adequate venous access for repeated blood sampling according to study schedule;

i) Women of child-bearing potential must have a negative serum pregnancy test and agree to remain sexually abstinent, have a partner who is sterile (i.e., vasectomy), or use two medically effective methods of contraception (e.g., oral contraception, barrier methods, spermicide, intrauterine device (IUD)). This requirement should be followed from screening through 24 weeks after last study treatment/EP. Whole pelvis external beam radiation therapy (EBRT) followed by intracavitary (IC) therapy for cervical cancer is considered to be an irreversible form of contraception;

j) Able and willing to comply with all study procedures.

Exclusion Criteria:

a) Pregnancy or breastfeeding;

b) History of previous therapeutic HPV vaccination (individuals who have been immunized with licensed prophylactic HPV vaccines (e.g. Gardasil®, Cervarix®) are not excluded);

c) Prior exposure to an investigational agent or device within 30 days of signing the ICF. Of note, the subject may participate in observational studies;

d) Positive serological test for human immunodeficiency virus (HIV), Hepatitis B or Hepatitis C or history of HIV infection, Hepatitis B or Hepatitis C (women with cured HCV will be allowed; subject must have had an serologic test performed within 12 months of informed consent);

e) Prior major surgery within 4 weeks of first study treatment/EP from which the subject has not yet recovered to baseline;

f) High medical risks because of non-malignant systemic disease or with active uncontrolled infection;

g) Current malignancies at other sites, with the exception of adequately treated basal or squamous cell carcinoma of the skin;

- Cancer survivors, who have undergone curative therapy for a prior malignancy, have no evidence of that disease for five years and are deemed at low risk for recurrence, are eligible for the study;

h) Congestive heart failure or prior history of New York Heart Association (NYHA) class III/ IV cardiac disease (refer to Appendix 8);

i) Any concurrent condition requiring the continued use of systemic or topical steroids at or near the injection site, excluding non-systemic (e.g. inhaled and eye drop-containing) corticosteroids or the use of other immunosuppressive agents. All other corticosteroids must be discontinued > 4 weeks prior to Day 0 of study product administration;

j) Any cardiac pre-excitation syndromes (such as Wolff-Parkinson-White);

k) History of seizures (unless seizure free for 5 years);

l) Less than two acceptable sites exist for IM injection and EP between use of the deltoid and lateral quadriceps muscles. A site for injection/EP is not acceptable if there are tattoos or scars within 2 cm of the injection/EP site or if there is implanted metal within the same limb. Any device implanted in the chest (e.g., cardiac pacemaker or defibrillator) excludes the use of the deltoid muscle on the same side of the body;

m) Administration of any non-study related vaccine within 2 weeks of Day 0;

n) Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements;

o) Imprisonment or compulsory detainment (involuntary incarceration) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;

p) History of immunosuppressive or autoimmune disease;

q) Any other illnesses or conditions that in the opinion of the investigator may affect the safety of the subject or limit the evaluation of a subject or any study endpoint.

Table 1: HPV-004 Schedule of Events

Tests	S	D0	Weeks[a]										
			2	4	6	8	10	12	14	16	24	32	36
Study Procedures													
Informed consent	X												
Medical and CIN/Cancer history	X												
Inclusion/Exclusion criteria	X	X											
Physical exam/assessment[c]	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	X	X
Medical/Clinical assessment	X	X	X[b]	X	X[b]	X	X[b]	X	X[b]	X	X	X	X
Chemo/RT Effects/Adverse Events	X[m]	X	X[b]	X									
Adverse events	X	X	X[b]	X	X[b]	X	X[b]	X	X[b]	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Disease Status[d]	X									X		X	X
Vital signs (Height and Weight)[e]	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X												
Histologic HPV assessment[f]	X												
Tumor biopsy collection	X[l]									X			
ThinPrep™ sample (if obtainable)	X	X								X			X
Digene swab (2) (if obtainable)	X	X								X			X
PET/CT scan	X[n]									X[p]		X[q]	X[q]
Laboratory Procedures													
CBC w/ differential	X	X[o]		X[o]		X[o]		X[o]		X[o]			
Serum chemistry[g]	X	X[o]		X[o]		X[o]		X[o]		X[o]			
Urinalysis[h]	X												
CPK	X									X[o]			
Pregnancy Test[i]	X	X		X		X		X		X			
HIV/ hepatitis serology	X												
Blood immunologic samples[j,]	X	X				X				X	X	X	X
Immunotherapy Procedures													
Immunotherapy/EP		X		X		X		X					
Post treatment reaction[k]		X	X[b]	X	X[b]	X	X[b]	X	X[b]	X			
Download EP data		X		X		X		X					
Participant Reminder Card		X		X		X		X					
Review participant reminder card			X[b]	X	X[b]	X	X[b]	X	X[b]	X			

Wks 2, 6, 8 and 14 visits may be performed as an in-person office visit or a telephone call. After completing medical/clinical assessment, reviewing PRC and collecting information on AE with the subject on the phone, the investigator will determine whether an office visit is needed for further evaluation.

Cohort 1: Subjects in Cohort 1 can be screened either prior to initiation of chemoradiation, or during chemoradiation and should be enrolled such that their first study treatment (Day 0) will be delivered within 2 weeks of completing their chemoradiation therapy;

Cohort 2: Subjects in Cohort 2 can be screened and enrolled such that their first study treatment (Day 0) is no sooner than 2 weeks and no later than 4 weeks after completing the salvage therapy. If in the

investigators opinion, there are no additional salvage therapy options, the subject may be enrolled in Cohort 2 without having received salvage therapy immediately prior to enrollment.

[a] Procedures and visits scheduled from Day 0 through Wk 16 must occur ±1 week of scheduled time. Procedures and visits scheduled from Week 24 to Week 36 must occur ± 2 weeks of scheduled time.

[b] assessment to be performed if visit done as phone-call

[c] Targeted physical examination at all visits except full examination at screening (includes complete gynecological exam) and discharge visit

[d] Disease status should be categorized into 1) No evidence of disease (NED) 2) Partial Response 3) Stable disease 4) Progressive disease

[e]Temperature, respiratory rate, blood pressure, heart rate, weight and height. Height collected at screening only

[f] Paraffin embedded tissue obtained for diagnosis of cervical cancer must be available for HPV testing

[g] Serum chemistry includes glucose, albumin, total protein, SGPT, SGOT, alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), calcium, creatinine, electrolytes (sodium, potassium, chloride, carbon dioxide or bicarbonate)

[h] Urine samples will be tested by dipstick for glucose, protein, and hematuria.

i Serum pregnancy test required at screening. Urine pregnancy test should be used prior to tumor biopsy and prior to each study treatment/EP

[j] At least 34 mL (4 x 8.5 mL tubes) whole blood in Acid Citrate Dextrose tubes and 4 mL serum per time point. A total of at least 68 mL whole blood and 4 mL serum should be collected prior to dosing on Day 0

[k] Assessed 30 to 45 minutes after study treatment/EP and at post-treatment visits

[l] A tumor biopsy collection is required at screening if residual tissue and/or unstained slides are not available

[m] Chemo/RT effects to be assessed at screening if subject is screened during chemoradiation

[n] PET/CT to include standard uptake volume, must be performed within 4 weeks prior to Day 0

[o] All labs for Day 0 and those associated with any treatment visit should be available prior to treatment and collected no more than 48 hours prior to treatment

[p] PET/CT will be performed 3-4 months after Day 0

[q] Not required at study discharge if performed at wk 32

[r]Immune competence will be evaluated longitudinally throughout the study from the time of screening visit. No additional blood collection required.

1 INTRODUCTION

1.1 Background and Rationale

1.1.1 Epidemiology of HPV Infection and Cervical Cancer

More than 200 genotypes of human papillomavirus (HPV) are known, of which approximately 40 can infect the anogenital mucosa [World Health Organization 2008]. Persistent infection with oncogenic HPV genotypes is the proximate cause of virtually every squamous cervical cancer. HPV types 16 and 18 are the most prevalent types of highly oncogenic HPV associated with cervical cancer, accounting for approximately two-thirds of all cases of cervical cancer [Munoz 2003].

HPV infection is characterized by ongoing viral replication and shedding, and is associated with early pathologic changes (cervical intraepithelial neoplasia; CIN). Most genital HPV infections clear spontaneously. Persistent infection with a highly oncogenic HPV type is associated with integration of the viral genome into the host genome, with subsequent constitutive expression of the viral proteins, E6 and E7. Expression of these oncoproteins is functionally required for disease initiation and persistence, as E6 binds and targets p53 for degradation, and E7 targets pRb. Viral integration is found in high grade cervical dysplasia (CIN2/3), the intraepithelial lesion which is the immediate precursor to invasive disease. The vast majority of invasive cancers of the cervix are thought to arise from untreated CIN2/3 [Munger 2002]. Because these viral, non-'self' proteins are functionally required for disease, and are expressed only in diseased tissue, not in normal cells, they present compelling antigenic targets for therapeutic vaccination.

1.1.2 Primary Prevention of HPV Disease: Screening and Prophylactic Vaccination

Despite screening programs that have dramatically reduced the incidence of cervical cancer, approximately 12,900 American women are diagnosed with this disease annually, and 4100 die from it [ACS 2015]. Worldwide, cervical cancer is the fourth most common cancer in women resulting in approximately 268,000 deaths yearly [GLOBOCAN 2012].

In 2006, the U.S. Food and Drug Administration (FDA) licensed a quadrivalent HPV vaccine for use in females 9-26 years of age to prevent diseases caused by HPV types 6, 11, 16 and 18 [Centers for Disease Control and Prevention 2007]. The primary analysis of a prospective, randomized, double-blind, trial involving 10,565 women 15-26 years of age with no virologic evidence of infection by HPV 16 or 18, who were randomized 1:1 to receive a 3-dose course of vaccine or placebo, found the vaccine efficacy for prevention of the primary composite endpoint (prevention of HPV-16 or 18 infection resulting in CIN2 or 3) after 3 years to be 98% (95% C.I. 86%, 100%) [Future II Study Group 2007]. In October 2009, a bivalent vaccine was approved for use in women to prevent diseases caused by HPV types 16 and 18.

Recently available prophylactic HPV vaccines are unlikely to impact the burden of disease in the near future; protection is type-specific, and vaccine delivery requires intense infrastructure, including the need for three inoculations. Indeed, in the United States, only 44% of eligible teen (13-17 years) girls received any HPV vaccine, and ~27% completed the three-vaccination series in 2009. Furthermore, ensuring vaccination prior to HPV exposure can be challenging [CDC 2010].

1.1.3 Rationale for a HPV Immunotherapy

While the currently available prophylactic HPV vaccines are highly effective in preventing infection and the development of high-grade CIN caused by HPV types 16 and 18, these have no therapeutic effect, and therefore are of no value for women already infected with these oncogenic types. Treatment for CIN 2/3 usually consists of either surgical removal of the affected tissue by cone biopsy or a loop electrical excision procedure (LEEP), or ablative therapy via laser, or cryotherapy. Invasive cervical cancer may be treated by radical hysterectomy, and/or combination radiation and chemotherapy.

Intraepithelial HPV disease is indolent, and not all CIN 2/3 progress to invasive disease. In fact, in immune-competent subjects, spontaneous regression of CIN 2/3 over a relatively brief timeframe of 6 months is estimated at 30-40% [Trimble 2005, Castle 2009, Moscicki 2010]. In subjects with CIN 2/3 associated with HPV-16, the rate of spontaneous regression is lower, in the range of 25% [Trimble 2005, Castle 2009, Moscicki 2010]. Boosting cell-mediated immune responses to the early HPV E6 and E7 proteins may lead to elimination of immortalized cells and so prevent the development of invasive disease. [Kenter 2009]. The ability of immunotherapy with VGX-3100 delivered by EP to reverse high grade dysplasia is currently being studied in a prospective global, placebo-controlled, randomized phase 2 study in women with CIN2 and CIN3 associated with HPV-16 and/or HPV-18. A pre-planned interim analysis of the study data completed in July 2014 revealed that the study met its primary endpoint (histopathologic regression of lesions) and secondary endpoint (histopathologic regression of lesions in the context of elimination of HPV16 and/or 18 infection) demonstrating a highly statistically significant improvement in the VGX-3100 arm ($p<0.017$ and $p<0.001$ respectively). Treatment of HPV16 and/or 18 positive patients with CIN2 or 3 was generally safe as evidenced by the lack of statistical significance between the frequencies of adverse events reported in the placebo arm as compared to the VGX-3100 treated arm. Treatment with VGX-3100 was able to induce a robust immune response in the periphery as gauged by IFNg ELISpot as well as in the tissue as examined using immunohistochemistry. These data reveal the highly promising potential of therapeutic immunization with DNA followed by electroporation for the treatment of HPV-16 and/or HPV-18 related precancerous cervical disease in women.

There is early data regarding the use of therapeutic vaccines for cervical cancer which does appear to demonstrate some HPV-specific antibody response in pre-

clinical and early clinical studies [Borysiewicz 1996, Cui 2005, Cui 2006, Jochmus 1999, Liu 2000, Ohlschlager 2009, Welters 2008].

Some clinical studies have employed the combination of radiotherapy with immunotherapy and have been shown to induce tumor-specific and innate immunity [Chi 2005, Gulley 2005]. Radiation has been shown to increase immunogenicity of solid tumors by several mechanisms, including enhancing the expression of MHC class I molecules [Reits 2006], as well as increasing expression of adhesion molecules by endothelial cells [Gaugler 1997]. These and other phenotypic changes subsequent to radiation render established disease more susceptible to T-cell-mediated lysis [Garnett 2004]. Chemotherapeutic regimens, including cisplatin (CDDP) can also render solid tumors more susceptible to immunologic intervention [Gelbard 2006, Matsuzaki 2000].

However, to date, there are limited data investigating the use of a therapeutic vaccine for cervical cancer in the setting of chemoradiotherapy. Encouraging synergistic results have been demonstrated in animal models [Tseng 2009]. It was observed that TC-1 tumor-bearing mice treated with radiotherapy combined with CRT/E7(detox) DNA vaccination generated significant therapeutic anti-tumor effects and the highest frequency of E7-specific $CD8^+$ T-cells in the tumors and spleens of treated mice. Furthermore, treatment with radiotherapy was shown to render the TC-1 tumor cells more susceptible to lysis by E7-specific CTLs (cytotoxic T lymphocytes). In addition, it was observed that treatment with radiotherapy during the second DNA vaccination generated the highest frequency of E7-specific $CD8^+$ T-cells in the tumors and spleens of TC-1 tumor-bearing mice. Finally, TC-1 tumor-bearing mice treated with the chemotherapy in combination with radiation and CRT/E7(detox) DNA vaccination generated significantly enhanced therapeutic anti-tumor effects [Tseng 2009].

Rationale for DNA based Immunotherapy: DNA vaccines have several advantages over traditional vaccines such as live attenuated virus and recombinant protein-based vaccines (engineered specificity, production, safety). To date, DNA vaccines have been well-tolerated in humans. In fact, clinical data from hundreds of subjects vaccinated with DNA vaccines suggests that intramuscular administration alone elicits barely detectable systemic immune responses to vaccine antigens. Preclinical safety studies in the literature have not demonstrated evidence of plasmid integration [Martin 1999, Nichols 1995]. Similar results were obtained in the pre-clinical safety and toxicology studies performed with VGX-3100 in rabbits. In our studies with VGX-3100, the rates of plasmid clearance from the injection site skin and muscle were similar whether the plasmid was delivered with or without electroporation suggesting that the delivery method did not result in an increased persistence at the injection site.

Unlike viral vector-based constructs, DNA vaccines can be used for repeated administration as the efficacy of plasmid vectors are not influenced by pre-existing neutralizing antibodies [Chattergoon 1997]. Furthermore, the ability to engineer specific targeting of multiple antigenic components allows the inclusion of specific immunogens, adjuvants or targeting sequences. VGX-3100 is

comprised of plasmids targeting E6 and E7 proteins of both HPV subtypes 16 and 18, and is delivered via electroporation (EP) using the CELLECTRA®-5P constant current device.

Individual candidate vaccine plasmids were developed for both HPV-16 (pCon16E6E7) and HPV-18 (pCon18E6E7), pre-clinical expression and immunogenicity were demonstrated, and then the plasmids were combined and formulated to produce VGX-3100. Preclinical toxicology and biodistribution studies with VGX-3100 have demonstrated an acceptable safety profile in the New Zealand White Rabbit.

Several pre-clinical studies were performed to further characterize the two plasmids. The immunogenicity of DNA delivered by intramuscular (IM) injection alone was compared to DNA delivery via electroporation (IM+EP). Immunogenicity was compared to vector-alone controls in mice and non-human primates (rhesus macaques).

HPV-16 and HPV-18 E6 and E7 proteins were appropriately expressed and processed in two separate animal studies (mouse and rhesus macaques). Indeed in both cases, robust cell mediated immune (CMI) responses were elicited. CMI responses were enhanced by about 3-fold using EP delivery vs. DNA alone at doses as low as 10 µg when delivered by EP. Further, CMI was elicited for both the HPV-16 and 18 constructs based on similar ELISpot results.

A side-by-side comparison at the low DNA dose indicated that the responses were approximately 3-fold greater when delivered via IM+EP compared to IM alone. Similar levels of CMI responses were elicited when the plasmid DNA was delivered at a 10-fold higher dose using IM alone suggesting that the use of EP technology will pave the way for development of dose-sparing immunotherapy agents. Importantly, in both cases, the epitopes recognized were well characterized E6 and E7 epitopes suggesting that normal effective processing of antigens occurs following vaccination regardless of whether the antigens were delivered via IM+EP or IM alone. This phenomenon has been observed in pre-clinical studies with other DNA plasmid candidates as well (e.g. influenza, HIV), where the magnitude of response is increased when DNA vaccines are delivered via EP.

Finally, efficacy of the pCon16E6E7 plasmid was assessed in a mouse tumor challenge model using the TC-1 cell-line which expresses HPV-16 E6 and E7 proteins [Yan 2009]. Mice were challenged with TC-1 tumor cells at low dose ($5x10^4$) on Day 0. Three days after TC-1 cell implantation, ten mice were immunized with pVAX, a plasmid containing HPV16 E7 only (pE7) and pCon16E6E7 and boosted twice on day 10 and 17.

Only three out of ten mice in pCon16E6E7 vaccinated group developed tumors 49 days after initial tumor implantation. All mice in the pE7 group eventually developed tumors; however, the tumors in this group were smaller than those in the control group ($p<0.05$). In order to further assess the therapeutic potential of pCon16E6E7, we performed another tumor regression study by increasing the

challenge dose of TC-1 cells to $1x10^6$ and mice were not immunized with pCon16E6E7 until the average tumor size was about 6 mm (on day 7). After boosting four times, mice in pCon16E6E7 group developed significantly smaller tumors compared to those in the control group ($p<0.05$). Moreover, all mice in pCon16E6E7 group survived 49 days after tumor implantation. In contrast, none of the mice in the pVAX group survived 28 days after tumor implantation. These results indicate that the DNA vaccine pCon16E6E7 induced regression of well-established tumors in C57BL/6 mice. The efficacy of pCon18E6E7 was not assessed due to the lack of a suitable tumor challenge model for HPV-18 related tumors [Yan 2009].

VGX-3100, HPV therapeutic vaccine is a combination of two plasmids in equal quantities (*i.e.* the 6 mg dose will deliver 3 mg of each pGX3001 and pGX3002 plasmids):

a) pGX3001: p16ConE6E7, a plasmid encoding for a synthetic HPV16 consensus (SynCon™) E6 and E7 fusion gene into a pVAX1 backbone (Invitrogen, Carlsbad, CA) under the control of the cytomegalovirus immediate-early (CMV) promoter, and

b) pGX3002: p18ConE6E7, a plasmid encoding for a synthetic HPV18 consensus (SynCon™) E6 and E7 fusion gene into a pVAX1 backbone (Invitrogen, Carlsbad, CA) under the control of the cytomegalovirus immediate-early (CMV) promoter.

Both HPV type 16 and 18 E6 and E7 consensus nucleotide sequences were synthetically produced (GeneArt, Germany) after performing multiple alignments of the sequences described in the international genetic database (GenBank) for HPV type 16 and 18.

1.1.4 Target Organ for a Therapeutic HPV Immunotherapy – Skeletal Muscle

The skeletal musculature is an excellent candidate for the target tissue of gene expression, because muscle fibers have a long lifespan and can be transduced by circular plasmids, allowing the gene to be expressed efficiently in immunocompetent hosts [Davis 1993; Tripathy 1996]. Furthermore, muscle is well vascularized, allowing the newly produced transgene product to gain access to the circulation.

1.1.5 Delivery Method – Injection / Electroporation (EP)

The use of EP via the CELLECTRA®-5P device increases the expression of INO-3112. EP utilizes a transmembrane electric field pulse to induce microscopic pathways (pores) in a bio-membrane. The electric field allows macromolecules, ions, and water to pass from one side of the membrane to the other. The presence of a constant field influences the kinetics of directional translocation of the macromolecular plasmid, such that the plasmid delivery *in vivo* has been sufficient to achieve physiological levels of secreted proteins. Intramuscular injection of plasmid followed by EP has been used very successfully to deliver

therapeutic genes that encode for a variety of hormones, cytokines or enzymes in a variety of species [Prud'homme 2006, 2007]. The design of software that enables constant current EP to deliver plasmids allows for the individual resistance of the treated muscle to be taken into consideration and yields highly efficient *in vivo* plasmid expression [Khan 2005].

In a small (10 healthy volunteers) pilot study, pain was evaluated immediately, 5, 15, 30 minutes and 1 hour after EP with the CELLECTRA® device [Diehl 2013]. Subjects used a Visual Analog Scale (VAS) questionnaire, 10 cm in length, anchored by word descriptors at each end, "No Pain" and "Worst Pain", to mark their pain related to the treatment. Subjects reported a mean (±sem) score of 6.3 (±0.7) immediately after treatment and 2.8 (±0.5) approximately 5 minutes after the procedure. These data showed that the pain associated with electroporation was brief and diminished quickly [Diehl 2013].

1.2 Plasmid DNA Immunotherapy Agents (INO-3112)

1.2.1 VGX-3100

Chemical name: Circular, double stranded, deoxyribonucleic acid consisting of 3782 base pairs for the pGX3001 plasmid and 3824 base pairs for the pGX3002 plasmid.

Distinguishing name: Eukaryotic expression plasmids containing HPV 16 and 18-E6 & E7-encoding transcription unit controlled by a synthetic, CMV promoter, and elements required for replication and selection in *E. coli*, namely a pUC origin of replication (pUC Ori) and a kanamycin resistance gene (Kan R).

1.2.2 INO-9012

Chemical name: Circular, double stranded, deoxyribonucleic acid consisting of 6259 base pairs for the pGX6001 (also called *IL-12* DNA) plasmid.

Distinguishing name: Eukaryotic expression plasmids containing synthetic IL-12 p35 light chain and p 40 heavy chain (pGX6001) controlled by a dual promoter vector, a bGH poly A tract, bacterial origin of replication to support production of the plasmid in *E. coli*, and a kanamycin resistance gene (Kan R).

1.3 Dose and Regimen Rationale

The doses selected are based on previous human experience and preclinical data with VGX-3100 and other DNA vaccines. A total dose of 6 mg VGX-3100 DNA has been selected for this study based on the safety and immunogenicity data generated in the HPV-001 study, where 6 mg of DNA were delivered IM followed by EP, which showed trends toward higher response rates and magnitudes of IFN-γ ELISpot responses in the high dose cohort compared to the low (0.6 mg) and mid-dose (2 mg) cohorts (Table 1.1) without significant safety issues [Bagarazzi, 2012].

This dose-trend was consistent with prior expectation, a feature of the finding that suggests it is a "real" effect rather than random variation. Adverse events from

previous human studies with closely related DNA plasmid products have been limited to injection site pain from the injection and electroporation procedure. No unexpected or severe adverse events were observed in any of the three dose cohorts.

Table 1.1: Percent of subjects responding and average SFU/10^6 PBMC in responders for each antigen by cohort in Protocol HPV-001 Interferon-γ ELISpot

Cohort	Low		Mid		High	
Antigen	%RESP	AVG	%RESP	AVG	%RESP	AVG
16E6	33%	107	50%	243	50%	1341
16E7	17%	198	50%	104	67%	143
18E6	50%	359	50%	338	83%	664
18E7	33%	159	17%	179	50%	834
Any	67%	221	67%	210	83%	556

The IL-12 plasmid dose is based on previous experience in the HVTN-080 study, where 1 mg was co-administered with PENNVAX®-B followed by EP. HIV-specific CD4+ T cell responses were generated in ~81% of PENNVAX®-B + IL-12 recipients after three vaccinations, compared to 44% with PENNVAX®-B alone. Delivery of PENNVAX®-B via EP also increased the frequency of CD8+ T cell responses. CD8+ responses were detected in 33% of PENNVAX®-B and 52% of PENNVAX®-B + IL-12 recipients after 3 vaccinations. Six months after the third vaccination 43% of individuals were still able to respond to HIV peptide pools. Overall, 89% of individuals vaccinated with PENNVAX®-B + IL-12 plasmid followed by EP developed either a CD4+ or CD8+ T-cell response after the third vaccination. No unexpected or severe adverse events were observed in HVTN-080 or earlier studies of IL-12 DNA delivered without electroporation.

In summary, a total of 7 mg VGX-3100 + INO-9012 DNA was selected for this study based on the safety and immunogenicity data generated in HPV-001, the follow-on study HPV-002, and HVTN-080. Additional human experience with related DNA plasmids informing the dose is described below.

1.3.1 Previous Human Experience with VGX-3100

The clinical experience with VGX-3100 is demonstrated in two phase 1 studies, HPV-001 and HPV-002 which enrolled 18 and 13 women, respectively, and a phase 2 study, HPV-003, which enrolled 167 women. There have been no significant safety findings with very few related Grade 3 Adverse Events (AE's) and no related Grade 4 AE's or Serious Adverse Events (SAEs) after 551 doses in 185 subjects. Importantly, the safety profile of the DNA immunogen /electroporation technology platform employed in this study has been consistently unremarkable in the 580 subjects and 1,548 doses in 16 different studies as of

February 4, 2015. (Refer to INO-3112 Investigator's Brochure v3.0 for additional information)

There were no significant safety findings in the 18 subjects enrolled in HPV-001, the phase 1 study of VGX-3100, with only mild to moderate adverse events, injection site reactions and laboratory abnormalities which resolved without sequelae. All subjects returned home after at least 30 minutes observation in the study unit post injection/EP. CPK and ECGs were unremarkable post electroporation. Study participants judged the injection/EP to be relatively painful (mean VAS score 6.2 immediately after and 2.8 approximately 5 minutes after EP) but transient, but did not preclude subsequent injection/EP administration. There were no serious adverse events attributed to treatment in any of the subjects and there were no early discontinuations in the study. Thirteen women participated in HPV-002 in which a fourth dose (6 mg only) of VGX-3100 was evaluated and the safety findings were consistent with those observed in the parent study, HPV-001.

The clinical trial experience in HPV-003 with the investigational product to date is consistent with those reported previously. No new safety issues have been identified with VGX-3100 delivered IM followed by EP with CELLECTRA®-5P, and no serious unexpected drug related adverse events, or other events requiring expedited reporting, have been reported for subjects dosed with VGX-3100 delivered IM followed by EP with CELLECTRA®-5P.

The mechanism of action of VGX-3100 delivered using EP is expected to be mediated through a Th1-biased cytolytic T-cell response against the HPV16 and HPV18 E6 and E7 proteins. Strong antigen-specific T-cell immune responses were observed in not only the phase 1 HPV studies but also in the previous studies using the same technology with different antigens for several disease indications (*e.g*. influenza, HIV) [Bagarazzi 2012]. The cellular immunity has also been demonstrated to be durable up to 25 months from the initiation of therapy [unpublished data]; strongly suggesting the development of long term memory cells in the immunized volunteers. In addition, the antigen-specific T-cells have been shown to exhibit a memory phenotype by flow cytometry [Bagarazzi 2012]. Immunoglobulin G-based antibodies have also been measured in a high percentage (>90%) of immunized volunteers in the previous human studies with this technology [Bagarazzi 2012, unpublished data].

<u>Ongoing study of VGX-3100 in subjects with for high grade CIN associated with HPV-16 and/or HPV-18 (HPV-003)</u>

All current therapeutic options for cervical dysplasia are destructive, have adverse sequelae, and furthermore are not always curative. Among treated high grade CIN in immunocompetent women, the overall risk of recurrence is less than ten percent when all surgical margins are clear, but increases to approximately 25% in women with positive margins. About 90% of recurrences will occur within the first year after treatment [Felix 1994]. Moreover, tissue destruction from therapeutic interventions can make subsequent detection and treatment of recurrent disease difficult, as the healing process draws the transition zone of the

cervical epithelium proximally, into the endocervical canal [Ferris 1995]. Effective immunotherapy would obviate the need for surgery, to say nothing of preventing progression to cervical cancer. Consequently, a placebo-controlled phase 2 study is under way to determine if VGX-3100 delivered by EP will result in immune-mediated regression of high grade cervical dysplasia when administered prior to surgical intervention. The study, known as HPV-003 will evaluate histologic regression 6 months after completion of the three dose series. A pre-planned interim analysis of the study data completed in July 2014 revealed that the study met its primary endpoint (histopathologic regression of lesions) and secondary endpoint (histopathologic regression of lesions in the context of elimination of HPV16 and/or 18 infection) demonstrating a highly statistically significant improvement in the VGX-3100 arm ($p<0.017$ and $p<0.001$ respectively). Treatment of HPV16 and/or 18 positive patients with CIN2 or 3 was generally safe as evidenced by the lack of statistical significance between the frequencies of adverse events reported in the placebo arm as compared to the VGX-3100 treated arm. Treatment with VGX-3100 was able to induce a robust immune response in the periphery as gauged by IFNγ ELISpot as well as in the tissue as examined using immunohistochemistry. These data reveal the highly promising potential of therapeutic immunization with DNA followed by electroporation for the treatment of HPV-16 and/or HPV-18 related precancerous cervical disease in women.

A logical next step is to determine if INO-3112 delivered by EP could also provide clinical benefit for patients with invasive squamous cell carcinoma of the cervix. In this setting, the DNA immunogen/EP platform would need to generate HPV-specific immune responses to help eliminate residual neoplastic cells after standard therapy. This study is designed to assess potential toxicity and secondarily immune responses to specific antigens in both blood and locally in the cervix, and whether the immune responses are associated with subsequent regression of neoplastic cells.

1.3.2 Previous Human Experience with INO-9012

The safety profile associated with IM administration of IL-12 plasmid DNA alone or followed by EP has been acceptable in clinical studies. Clinical results from three different studies substantiate the safety and tolerability profile of IL-12 plasmid DNA. IL-12 plasmid DNA has been used in several cohorts in the following four phase I clinical protocols.

Protocol #	**Co-administered with**	**# subjects received IL-12 DNA**
HVTN-060	HIV-1 gag p37	80
HVTN-063	HIV-1 gag p37	30
HVTN-070	PENNVAX®-B (gag, pol, env)	30

HVTN-080	PENNVAX®-B (gag, pol, env)	30

IL-12 DNA was delivered without EP in HVTN-060, -063 and -070 but was followed by EP in HVTN-080. In this protocol, PENNVAX®-B or placebo were delivered via IM injection followed by electroporation with the CELLECTRA®-5P device in 48 healthy volunteers. The regimen consisted of 3 mg of PENNVAX®-B with or without plasmid encoding IL-12 at months 0, 1 and 3. This study established that a highly engineered DNA vaccine delivered intramuscularly followed by EP can induce frequent and robust T-cell responses in humans.

In summary of above clinical studies, no pattern of systemic AEs emerged, and no SAEs related to the study products were observed. The plasmid DNA vaccine co-administered with IL-12 plasmid DNA as a cytokine adjuvant were well-tolerated. (See Section 5 of the INO-3112 IB for details for HVTN-080 study)

1.4 Risks/Benefit Assessment

1.4.1 Current Therapy for Stage IB-IVB Cervical Cancer

All current therapeutic options for cervical cancer involve either surgery with or without adjuvant chemotherapy and/or radiation therapy, or definitive radiation therapy, or definitive chemoradiation. Current outcomes with either radical surgery or standard chemoradiation for invasive cervical cancer results in cure rates of approximately 80 to 95 percent in early stage disease (stage I and non-bulky stage II disease) and approximately 40 to 60 percent for bulky stage II and stage III disease [Quinn 2006].

Table 1.3: Survival by FIGO stage for patients with cervical cancer: 1999 to 2001 FIGO statistics

FIGO stage	# of patients	Overall survival, %		
		1 year	2 years	5 years
IA1	829	99.8	99.5	97.5
IA2	275	98.5	96.9	94.8
IB1	3020	98.2	95	89.1
IB2	1090	95.8	88.3	75.7
IIA	1007	96.1	88.3	73.4
IIB	2510	91.7	79.8	65.8
IIIA	211	76.7	59.8	39.7
IIIB	2028	77.9	59.5	41.5
IVA	326	51.9	35.1	22
IVB	343	42.2	22.7	9.3

Original table modified for this publication. From: Quinn MA, Benedet JL, Odicino F, et al. Carcinoma of the cervix uteri. Int J Gynaecol Obstet 2006; 95:S43.

Recurrence rate by stage is as follows: for FIGO stage IB around 10%, for stage IIA 17%, for stage IIB 23%, and for stages III and IVA 42% and 74% respectively [Perez 1992].

For early stage disease, the predominant site of disease recurrences is local (*i.e.* at the vaginal apex) or regional (*i.e.* pelvic sidewall). The risk of persistent or recurrent pelvic disease increases with more advanced initial disease stage [Morely 1976, Hopkins 1991, Estape 1998].

The most frequent distant sites of recurrence are the para-aortic lymph nodes (81%), lungs (21%), and supraclavicular lymph nodes (7%), whose incidence relates to the stage of disease: it is 0–3% in stage IA, 13–16% in stage IB, 22–31% in stage IIA, 22–26% in stage IIB, 32–39% in stage III and 75% in stage IVA [Perez 1995].

The outcomes for inoperable cervical cancer have improved with the use of concurrent chemotherapy during radiation and this multi-modality approach is now standard of care [Rose 1999, Morris 1999, Grigsby 2001]. However, as noted above, recurrence rates are significant and impact not only survival but also quality of life.

Clearly, there is room to decrease recurrence rates at all stages of disease and additional investigations are warranted to further improve outcomes for this population.

1.4.2 Rationale for Study Design

There are data in patients with pre-invasive lesions that demonstrate the safety of immune-based therapy in immune-competent patients.

In otherwise healthy women whose CIN 2/3 lesions had already been resected, treatment with VGX-3100 delivered by EP stimulated both antibody and T-cell responses that were detectable in over 80% of subjects, without significant side effects. The potential benefit of taking part in this study is that INO-3112 could stimulate the immune system to eliminate residual neoplastic cells after standard therapy. This study is designed to assess primarily toxicity of treatment with INO-3112 delivered by EP after such standard therapy and secondarily, immune responses to the HPV antigens encoded by VGX-3100 in both peripheral blood and locally in the cervix.

Subjects enrolled in this protocol will undergo close clinical surveillance by experienced gynecologic oncologist, radiation oncologists and oncologists. Participants will be seen at screening to determine eligibility. Two cohorts will be enrolled.

In Cohort 1, prior to dosing, all subjects will have undergone standard external beam radiation therapy administered concurrently with cisplatin over 5 to 6 weeks, followed by brachytherapy and then a brief rest period (2 weeks or less) prior to the study treatment/EP (Day 0) regimen with INO-3112. The first study treatment/EP treatment (Day 0) will be administered within two weeks of completion of chemoradiation, the second study treatment/EP at Week 4

following Day 0, the third at Week 8 and the fourth (final) treatment will be administered at Week 12 following Day 0.

In cohort 2, subjects with persistent and/or recurrent disease will be treated with study treatment/EP following salvage therapy. The first study treatment/EP treatment (Day 0) will be administered no earlier than 2 weeks after completing salvage therapy, the second study treatment/EP at Week 4 following Day 0, the third at Week 8 and the fourth (final) treatment will be administered at Week 12 following Day 0.

Participants will be followed as part of this study for 6 months after the last study treatment/EP (i.e. Week 12) with INO-3112.

Radiation therapy has been shown to induce a variety of immune effects within the radiation field, including up regulation of major histocompatibility complex class I (MHC-I) expression and increased activation of CD8+ cytotoxic T lymphocytes (CTL) [Nikitina 2001]. Changes in cytokine and adhesion molecule expression facilitate homing of antigen-presenting cells and effector immune cells to the induced area [Hong 1995, Hong 1999, Hallahan 1996, Tanigawa 2001]. Decreases in CD4+ CD25+ regulatory T cells and myeloid-derived suppressor cells (MDSC) have also been noted, which leads to a more robust immune response in the irradiated area [Sutmuller 2001]. Apoptotic and necrotic tumor cells within the radiation field provide sources of antigens for dendritic cells, which in turn activate T cell maturation [Rock 2005]. The dying cells also release "danger factors" which can act as immunologic adjuvants to prevent immune tolerance to tumor antigens [Matzinger 1994, Galucci 1999, Shi 2002].

Studies revealed that radiation induces up regulation of death receptors, particularly Fas, in tumor cells, which further sensitizes them to the killing action of CTL [Sheard 1997, Chakraborty 2002, Garnett 2004]. Fractionated radiotherapy is hypothesized to impair the immune response due to deleterious effects on infiltrating immune cells whereas hypo-fractionated ablative dosing resulted in a superior immune response [Lee 2009]. Thus, concurrent vaccination at the end of brachytherapy may have a similarly activating effect on the local immune system. Previous murine studies have shown that radiation can heighten the immune response to vaccination against HPV oncogenes E6 and E7, and post-radiation vaccination with a recombinant HPV E6/E7 vector results in a significant increase in long-term survival due to cell-mediated killing [Tseng 2009].

Delivering the vaccine immediately after the conclusion of brachytherapy to harness the immunologic priming effects of radiation and complement the in situ immunization may initiate a sustained adaptive immune response against the E6 and E7-expressing tumor cells.

Monitoring will include HPV typing at screening/entry. Tumor biopsy, ThinPrep™ samples for HPV testing and cytology, and Digene swabs will be collected at screening (pre or post-chemoradiation), Day 0 and at Week 16 (one month post-dose 4) and week 36. Physical exam, vital signs, ECOG performance status and laboratory evaluations will be performed at screening and prior to first

study treatment/EP on Day 0 and at specified visits throughout the study. Imaging with PET/CT scans will be performed within 4 weeks prior to Day 0 (baseline) and 3-4 months after Day 0 and 3-5 month thereafter or at study discharge per standard of care or in accordance with local guidelines and institutional practices. Investigators will be instructed to use their clinical judgment throughout the study.

1.4.3 Potential Risks of DNA Immunotherapy Delivery with Electroporation

The underlying basis for all studies of plasmid DNA vaccines is the fairly substantial safety database that exists for the varied plasmid DNA vaccine candidates that have now been studied in both animals and humans. The plasmid DNA platform has been utilized for vaccine candidates for a variety of disease indications and infectious agents (*e.g.*, HIV, HPV, Influenza, SARS, West Nile virus, Ebola among others) in addition to plasmid cytokine adjuvants such as IL-2, IL-12 and IL-15.

In two companion papers by Sheets *et. al*, potential toxicities (both intrinsic and immunotoxicities) and biodistribution profiles were compared for 21 different plasmid DNA constructs, in 9 separate GLP-compliant studies [Sheets 2006a, 2006b]. Despite differing plasmid DNA backbones, promoters, and sequence inserts, toxicity and biodistribution profiles were similar for all plasmid DNA constructs. With respect to the toxicity assessments, the authors reported that toxicity was localized to the site of the injection for all 21 plasmid DNA constructs. Similarly, all plasmid DNA constructs evaluated showed evidence to be localized to the injection site and surrounding tissue in all studies. Based on the results of these GLP toxicology and biodistribution studies, Sheets et. al post a case for "refinements of preclinical safety protocols over time" as it pertains to the development pathway for plasmid DNA vaccine candidates [Sheets 2006a, 2006b].

Further, four separate GLP toxicology and biodistribution studies have been performed for eight additional plasmid DNA vaccine candidates developed by Inovio with identical backbones delivered by electroporation yielding similar toxicity and biodistribution profiles. Intramuscular co-administration of IL-12 plasmid was evaluated in nonclinical studies to support the studies of intramuscular IL-12 plasmid in humans.

DNA vaccines developed by Inovio have been delivered without electroporation (1 study) or using Inovio electroporation devices (11 studies) as shown in Table 1.4. Inovio electroporation devices have also been used to deliver DNA vaccines developed outside of Inovio in three different studies and two studies have evaluated the tolerability of Inovio electroporation devices with normal saline.

Based on clinical experience with INO-3112 from similar protocols using electroporation-mediated drug delivery and the overall safety database encompassing all studies of Inovio DNA delivered by electroporation with CELLECTRA®-5P, we do not expect to observe any severe or dose-limiting side

effects or toxicities. Side effects of vaccination with INO-3112 may include discomfort related to the electroporation technique, such as transient local edema, swelling, or pain.

In the phase I studies of VGX-3100 delivered by EP in women with a history of treated CIN 2/3 there were no serious adverse events attributed to treatment in any of the subjects enrolled and no participants discontinued early.

2 HYPOTHESIS AND STUDY OBJECTIVES

2.1 Hypothesis

Immunotherapy with INO-3112 delivered by IM injection followed by EP with CELLECTRA®-5P will be immunogenic and well tolerated in women with newly diagnosed, inoperable cervical cancer associated with HPV-16 and/or HPV-18 after completion of standard chemoradiation therapy with curative intent (Cohort 1) or in women with persistent and/or recurrent cervical cancer associated with HPV-16 and/or HPV-18 following salvage therapy (Cohort 2) and will not be associated with any significant increased toxicity compared to that expected/reported with "standard" therapy alone.

2.2 Primary Objective

Evaluate the safety and tolerability of immunotherapy with INO-3112 when delivered IM followed by EP with CELLECTRA®-5P in women with newly diagnosed, inoperable cervical cancer associated with HPV-16 and/or HPV-18 after completion of standard chemoradiation therapy with curative intent (Cohort 1) or in women with persistent and/or recurrent cervical cancer associated with HPV-16 and/or HPV-18 following salvage therapy (Cohort 2) compared to that expected/reported with "standard" therapy alone.

2.3 Secondary Objective

Evaluate the cellular and humoral immune responses to immunotherapy with INO-3112 delivered IM followed by EP with CELLECTRA®-5P in women with newly diagnosed, inoperable cervical cancer associated with HPV-16 and/or HPV-18 after completion of standard chemoradiation therapy with curative intent (Cohort 1) or in women with persistent and/or recurrent cervical cancer associated with HPV-16 and/or HPV-18 following salvage therapy (Cohort 2).

2.4 Exploratory Objective

Evaluate clinical response (i.e. disease-free survival) following treatment with INO-3112 delivered IM followed by EP with CELLECTRA®-5P in women with newly diagnosed, inoperable cervical cancer associated with HPV-16 and/or HPV-18 after completion of standard chemoradiation therapy with curative intent (Cohort 1) or in women with persistent and/or recurrent cervical cancer associated with HPV-16 and/or HPV-18 following salvage therapy (Cohort 2).

3 STUDY DESIGN

This is a Phase I/IIa, open-label study to evaluate the safety, tolerability, and immunogenicity of INO-3112 [6 mg of VGX-3100 (2 separate DNA plasmids encoding E6 and E7 proteins of HPV 16 and HPV 18) and 1 mg of INO-9012 (DNA plasmid encoding human interleukin 12)] delivered IM followed by EP in approximately 10 female subjects with biopsy-proven, Stage IB-IVB inoperable invasive cervical carcinoma associated HPV-16 and/or HPV-18 who have completed treatment with standard chemoradiation with curative intent (Cohort 1) or in subjects with persistent and/or recurrent cervical cancer associated with HPV-16 and/or HPV-18 following salvage therapy (Cohort 2).

Eligible subjects who consent to participate in the study will receive a 1.1 mL IM injection of INO-3112 in the deltoid followed immediately by EP with CELLECTRA®-5P. If the deltoid is not a suitable location, the IM injection should be in the lateral quadriceps followed immediately by EP with CELLECTRA®-5P. All subjects (Cohorts 1 and 2) will receive a 4-dose series of INO-3112. The first study treatment/EP after completion of standard chemoradiation (Cohort 1) or salvage therapy (Cohort 2) will be designated as "Day 0", the second dose will be administered at Week 4, the third dose at Week 8, and the fourth (final) treatment will be administered at Week 12.

Cohort 1:

Cohort 1 will include subjects with biopsy-proven, Stage IB-IVB inoperable, newly diagnosed invasive cervical carcinoma associated with HPV-16 and/or HPV-18 treated with standard chemoradiation therapy with curative intent.

All subjects in Cohort 1 must receive their initial study treatment (Day 0) within 2 weeks after completing a course of standard radiation therapy (external beam and brachytherapy) administered concurrently with platinum based therapy with curative intent.

Subjects will have received standard external beam radiation therapy administered concurrently with cisplatin at 40 mg/m^2/week followed by their brachytherapy prior to the study treatment with INO-3112. The chemoradiation must be completed within 10 weeks of initiation. Standard external beam radiation therapy should be delivered to the pelvis +/- para-aortic nodal chain to a total dose of 45 Gy in 25 fractions, in conjunction with high dose rate (HDR) or low dose rate (LDR) brachytherapy to the cervix to deliver a total dose of 80-90 Gy (LDR equivalent) to point A. Parametrial and nodal boost should be delivered as determined by the disease stage per sequencing outlined in Appendix 3, such that brachytherapy will be the last treatment administered.

Weekly cisplatin chemotherapy at 40 mg/m^2 should be administered during Weeks 1-5 of standard external beam radiation and during parametrial boost.

Cohort 2:

Cohort 2 will include subjects with persistent and/or recurrent cervical carcinoma associated with HPV-16 and/or HPV-18 who have been treated with salvage therapy (chemotherapy and/or radiation therapy).

All subjects in Cohort 2 must receive their initial study treatment (Day 0) no sooner than 2 weeks and no later than 4 weeks after completing a course of salvage therapy. If in the investigators opinion, there are no additional salvage therapy options, the subject may be enrolled in Cohort 2 without having received salvage therapy immediately prior to enrollment.

Primary Safety Endpoints:

1. Incidence of adverse events (all, severe [graded per CTCAE v4.03], unexpected, serious) classified by system organ class (SOC), preferred term, severity, and relationship to study medication and schedule
2. Injection site reactions including pain, tenderness, erythema and induration at administration site
3. Rates of acute gastrointestinal, genitourinary, or other chemoradiation side effects above the expected, graded per Acute Radiation Morbidity Scoring Criteria (RTOG)
4. Changes in laboratory parameters from baseline

Secondary Immunologic Endpoints:

1. Antigen-specific cellular immune responses to INO-3112 in blood samples obtained from study subjects per study schedule:
    a) Interferon-γ secreting T lymphocytes in PBMC by ELISpot
    b) Flow Cytometry for T-cell activation, cytolytic phenotype, and memory phenotype in PBMC
2. Antigen-specific humoral responses to HPV–E6 and –E7 by ELISA per study schedule

Exploratory Clinical Endpoints:

1. Changes in standard uptake volume (SUV) on PET/CT scans performed at baseline vs follow-up PET/CT scans obtained at specified time points.
2. Evaluation of subjects relative immune competence longitudinally throughout the study starting at the screening visit (for details refer to Section 6.7: Cervical Virologic and Peripheral Blood Immunogenicity Assessment)
3. Changes in cervical histology from the screening biopsy as compared to the week 16 biopsy
4. Local immune responses to INO-3112 in tumor tissue samples obtained at week 16
5. Disease-free survival assessed in accordance with RECIST v1.1 (Refer to Appendix 10) as follows:
    - Clinical evaluations for disease response will be conducted at all study visits, (as assessed by clinical signs and symptoms of disease progression).

- A baseline PET/CT scan will be obtained on each subject 1 to 2 weeks prior to Day 0 and then PET/CT scans for disease progression will be obtained for all subjects 3-4 months after Day 0 and every 3-5 months thereafter per standard of care/in accordance with local guidelines and institutional practices. Additional PET/CT scans may be obtained at other time points if clinically indicated to confirm a clinical diagnosis of disease progression based on signs and symptoms.

4 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion Criteria

a) Written informed consent in accordance with institutional guidelines. If required by local law, candidates must also authorize the release and use of protected health information (PHI);
b) Female subjects age 18 years or older;
c) Histological diagnosis of squamous cell carcinoma, adenocarcinoma or adenosquamous cell carcinoma of the cervix. Not accepted are small cell, clear cell and other rare variants of the classical adenocarcinoma;
d) Histologically confirmed, Stage IB-IVB, invasive cervical carcinoma associated with HPV-16 and/or HPV-18 and meeting the following eligibility criteria for either Cohort 1 or Cohort 2;

1. Cohort 1
   - Newly diagnosed inoperable cervical cancer treated with chemoradiation therapy with curative intent and life expectancy of at least 12 months as assessed by the investigator
     - No CNS/spinal metastases
   - Able to initiate study treatment (Day 0) within 2 weeks of completion of last chemoradiation treatment;
     - Platinum based treatment (alone or in combination with other drugs); 5 weekly courses of Cisplatin 40 mg/m^2 completed within 10 weeks of its initiation
     - Standard radiation therapy (external beam and brachytherapy); completed within 10 weeks of its initiation
     - Brachytherapy; must be the last treatment if the subject is receiving sequential brachytherapy following the chemoradiation therapy

2. Cohort 2
   - Persistent and/or recurrent cervical cancer
     - No CNS/spinal metastases
   - Able to initiate study treatment (Day 0) at least 2 weeks but no more than 4 weeks after completion of salvage therapy (If in the investigators opinion, there are no additional salvage therapy options, the subject may be enrolled in Cohort 2 without having received salvage therapy immediately prior to enrollment.)
   - Subject has a life expectancy of at least 12 months as assessed by the investigator

e) ECG with no clinically significant findings as assessed by the investigator performed within 30 days of signing the informed consent form (ICF);
f) Chemistry, liver function tests, renal function, total CPK and hematology lab results must be ≤ Grade 1 at the time of screening, in accordance with the CTCAE v4.03;
g) Eastern Cooperative Oncology Group (ECOG) Performance status of ≤ 1; ;
h) Adequate venous access for repeated blood sampling according to study schedule;
i) Women of child-bearing potential must have a negative serum pregnancy test and agree to remain sexually abstinent, have a partner who is sterile (i.e., vasectomy), or use two medically effective methods of contraception (e.g., oral contraception, barrier methods, spermicide, intrauterine device (IUD)). This requirement should be followed from screening through 24 weeks after last study treatment/EP. Whole pelvis external beam radiation therapy (EBRT) followed by intracavitary (IC) therapy for cervical cancer is considered to be an irreversible form of contraception;
j) Able and willing to comply with all study procedures.

4.2 Exclusion Criteria

a) Pregnancy or breastfeeding;
b) History of previous therapeutic HPV vaccination (individuals who have been immunized with licensed prophylactic HPV vaccines (e.g. Gardasil®, Cervarix®) are not excluded);
c) Prior exposure to an investigational agent or device within 30 days of signing the ICF. Of note, the subject may participate in observational studies;
d) Positive serological test for human immunodeficiency virus (HIV), Hepatitis B or Hepatitis C or history of HIV infection, Hepatitis B or Hepatitis C (women with cured HCV will be allowed; subject must have had an serologic test performed within 12 months of informed consent);
e) Prior major surgery within 4 weeks of first study treatment/EP from which the subject has not yet recovered to baseline;
f) High medical risks because of non-malignant systemic disease or with active uncontrolled infection;
g) Current malignancies at other sites, with the exception of adequately treated basal or squamous cell carcinoma of the skin;
    - Cancer survivors, who have undergone curative therapy for a prior malignancy, have no evidence of that disease for five years and are deemed at low risk for recurrence, are eligible for the study;
h) Congestive heart failure or prior history of New York Heart Association (NYHA) class III/ IV cardiac disease (refer to Appendix 8);
i) Any concurrent condition requiring the continued use of systemic or topical steroids at or near the injection site, excluding non-systemic (e.g. inhaled and eye drop-containing) corticosteroids or the use of other immunosuppressive agents. All other corticosteroids must be discontinued > 4 weeks prior to Day 0 of study product administration;
j) Any cardiac pre-excitation syndromes (such as Wolff-Parkinson-White);

k) History of seizures (unless seizure free for 5 years);
l) Less than two acceptable sites exist for IM injection and EP between use of the deltoid and lateral quadriceps muscles. A site for injection/EP is not acceptable if there are tattoos or scars within 2 cm of the injection/EP site or if there is implanted metal within the same limb. Any device implanted in the chest (e.g., cardiac pacemaker or defibrillator) excludes the use of the deltoid muscle on the same side of the body;
m) Administration of any non-study related vaccine within 2 weeks of Day 0;
n) Active drug or alcohol use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements;
o) Imprisonment or compulsory detainment (involuntary incarceration) for treatment of either a psychiatric or physical (i.e. infectious disease) illness;
p) History of immunosuppressive or autoimmune disease;
q) Any other illnesses or conditions that in the opinion of the investigator may affect the safety of the subject or limit the evaluation of a subject or any study endpoint.

4.3 Supplementation of Study Subjects

Additional subjects may be enrolled with the approval of medical monitor, if subjects withdraw prior to completion of the study treatment.

4.4 Discontinuation/Withdrawal of Study Subjects

The subject will be considered to have completed the study when she completes all scheduled Study Treatments and follow-up visits or death, whichever occurs first. The discharge visit will be the last follow-up visit. If subject discontinues or is withdrawn at any time after receipt of Study Treatment, the investigator should make every effort to have the subject complete all assessments designated for the discharge visit. The investigator will make every effort to have all scheduled immune assessment blood sample collected as indicated in the Schedule of Events, Table 1 of the Clinical Synopsis. Any adverse events (AEs) present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.1 – Safety Parameters.

If the subject manifests Grade 4 toxicity attributable to study treatment/EP, she will not receive further study treatment/EP but will be encouraged to continue follow-up safety assessment through study discharge and not discontinue from the study. If a subject manifests Grade 3 toxicity attributable to study treatment/EP, the medical monitor and PI will discuss whether further treatment should be continued for that participant.

Subjects will be discontinued from the study if there is confirmed disease progression or if subject starts new anti-cancer therapy.

The reason for any discontinuation of study treatment should be discussed with the Sponsor's Medical Monitor within 24 hours. The primary reason for the subject discontinuing further study treatments or withdrawal from the study itself should be selected from the following standard categories:

- Adverse Event (Adverse Reaction): Clinical or laboratory events occurred that, in the medical judgment of the investigator for the best interest of the subject, are grounds for discontinuation. This includes serious and non-serious adverse events regardless of relation to study treatment.
- Death: The subject died.
- Withdrawal of Consent: The subject desired to withdraw from further participation in the study in the absence of an investigator-determined medical need to withdraw. If the subject gave a reason for withdrawal, it should be recorded on the Case Report Form (CRF). This reason does not allow for further data collection and should not be selected if follow-up data collection of this subject is anticipated by the subject.
- Protocol Violation: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g., treatment noncompliance, failure to return for defined number of visits). The violation should be discussed with the Sponsor's Medical Monitor prior to discontinuation of Study Treatments or study withdrawal.
- Lost to Follow-up: The subject fails to attend study visits and study personnel are unable to contact the subject after repeated attempts including letter sent by certified mail or equivalent.
- Physician Decision: The subject was terminated for a reason other than those listed above by the physician caring for the subject.
- Other: The subject was terminated for a reason other than those listed above, such as termination of study by the Sponsor.

5 INVESTIGATIONAL PRODUCTS

5.1 Investigational Product

Investigational product is defined as a pharmaceutical form of an active ingredient being tested or used as a reference in the study, whether blinded or unblinded.

INO-3112 is combination of VGX-3100 and INO-9012.

VGX-3100, the active investigational product to be used in this study, is a mixture of two separate DNA plasmids encoding E6 and E7 proteins of HPV types 16 and 18. A second investigational product being evaluated for use in combination with VGX-3100 is known as INO-9012. INO-9012 is a DNA plasmid expressing the p35 and p40 human IL-12 subunits off of separate promoters within the same plasmid.

INO-3112 will be provided by Inovio or its designee. The site pharmacist or designee will combine VGX-3100 and INO-9012 into a single syringe to create a 1.1 mL IM formulation of INO-3112 (see Appendix 6 for details).

Table 5.1 Investigational Products

VGX-3100	The plasmid pGX3001 and pGX3002
Volume per container	1.0 mL minimum/vial

Concentration	6.0 ± 0.4 mg/mL
Container Size and Type	10 mL glass vial
INO-9012	The plasmid pGX6001
Volume per container	0.2 mL minimum/vial
Target Concentration	10.0 ± 0.5 mg/ml
Container Size and Type	2 mL glass vial

5.2 Packaging and Labeling

This study is open label. Therefore the subject, the Investigator's site personnel and the Sponsor are not blinded to treatment. Each vial will be labeled with a single panel label. The following shows text that may be included on the vial labels:

Biologic Product	Specimen Label
VGX-3100	SynCon™ VGX-3100 [6mg/mL] 1 mL/vial Lot: VGX-3100. xxxxxx Date of Manufacture: DD MMM YY Final Retest Date: DD MMM YY Store frozen at or below -15C CAUTION: New Drug – Limited by Federal Law to Clinical Trial Use Only Inovio Pharmaceuticals Inc 660 W Germantown Pike, Plymouth Meeting, PA 19462 USA
INO-9012	SynCon™ INO-9012 [10 mg/mL] 0.2 mL/vial Single Use Vial Lot: INO-9012.xxxxxx Date of Manufacture: DD MMM YY Final Retest Date: DD MMM YY Store frozen at or below -15°C CAUTION: New Drug – Limited by Federal Law to Investigational Use. Inovio Pharmaceuticals Inc. Rev 000

5.3 Handling of INO-3112

Inovio will be responsible for assuring that the quality of the investigational products is adequate for the duration of the trial. All study products will be shipped frozen on dry ice. If there is no dry ice remaining in the shipment container when the shipment is received, the Sponsor or designee should be contacted immediately.

In addition, a temperature monitor will track the temperature of vials and will indicate any excursions during shipment to the site.

Investigational product(s) should be stored in a secure area according to local regulations. Vials must be stored at -20 °C upon receipt at the clinical site. The Sponsor should be notified of any deviations from this recommended storage condition.
A freezer temperature log must be monitored daily and maintained at the site.

5.4 Dispensing of INO-3112

It is the responsibility of the Investigator to ensure that INO-3112 is dispensed to study participants. It must be dispensed only from official study sites by authorized personnel according to local regulations and must be recorded appropriately on the investigational product accountability record.

Vial contents must be thawed at ambient room temperature and must be administered within 4 hours of removal from freezer.

VGX-3100 and INO-9012 will be combined by the site pharmacist into a single syringe for subjects using the procedure outlined in Appendix 6.

The syringe must be labeled with the date and time it was removed from the freezer and a four-hour expiration date and time from the time the vial is removed from the freezer. The label should also contain the words “administer as soon as possible”.

5.5 Records of INO-3112 Disposition at Investigational Sites

It is the responsibility of the Investigator to ensure that a current record of investigational product disposition is maintained at each study site where investigational product is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area;
- Amount currently in storage area;
- Label ID number or batch number and use date or expiry date;
- Dates and initials of person responsible for each investigational product inventory entry/movement;
- Amount dispensed to each subject, including unique subject identifiers;
- Amount transferred to another area/site for dispensing or storage;
- Amount returned to Sponsor;
- Amount destroyed at study site, if applicable.

5.6 Return and Destruction of Investigational Products

Upon completion or termination of the study, all unused and/or partially used investigational product must be returned to Inovio, if not authorized by Inovio or local regulations to be destroyed at the site.

All investigational products returned to Inovio must be accompanied by the appropriate documentation. Returned supplies should be in the original containers. Empty containers should be retained until final reconciliation performed by the Study Monitor, but not be returned to Inovio. It is the Investigator’s responsibility to arrange for disposal of all empty containers,

provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The return of unused investigational product(s) should be arranged by the responsible Study Monitor.

If investigational products are to be destroyed on site, it is the Investigator's responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted by Inovio, procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused investigational products can only be destroyed after being inspected and reconciled by the responsible Inovio Study Monitor.

5.7 Use of CELLECTRA®-5P Electroporation Device

The instructions for use of the CELLECTRA®-5P device are located in the Operations Manual. Each clinical site will receive training for the use of the CELLECTRA®-5P device. The following specifications will be used during the study:

Number of pulses = 3
Current Strength = 0.5 Amp
Electroporation pulse duration = 52 milliseconds/pulse
Interval separating pulses = 1 second

The **injection/electroporation procedure** must be performed by qualified personnel. Any individual designated to perform the procedure should be permitted by the relevant local authorities to administer parenteral medications to patients (e.g. MD, DO, RN) in addition to receiving device training from sponsor personnel. Individuals whose credentials do not meet the relevant local requirements may perform the injection/electroporation procedure under the conditions below:

1. The procedure must be performed under the direct supervision of the Principal Investigator or an approved Sub-Investigator who has already been trained by sponsor personnel.
2. The CV and any relevant qualifications of the individual have been reviewed and approved by the sponsor or its designee to perform the procedure.

Any deviation from the above procedures must be approved by the sponsor or its designee.

5.8 Investigational Device Accountability

Each clinical site is responsible for maintaining investigational device accountability. This includes recording the CELLECTRA®-5P serial number, IM applicator serial number, and IM array lot number used for injection/EP of each

subject. Site personnel will be required to download electroporation data and provide to Inovio after each treatment.

6 STUDY PROCEDURES AND TREATMENTS

See **Table 1** for Schedule of Events showing study procedures and the times at which they are to be carried out.

6.1 Procedure by Visit

6.1.1 Screening Evaluations

Subjects who consent to participate in the study will be eligible for screening and will have a tumor biopsy sample (i.e. unstained slides) sent to laboratory for HPV assessment that will done either by ISH or PCR. If a subject has documented evidence of HPV-16 and/or HPV-18 infection results from cervical specimen obtained prior to anti-cancer treatment, then those results will be acceptable. If applicable, ThinPrep™ sample should also be sent simultaneously to the central lab for HPV assessment by PCR. Another cervical biopsy should be collected at screening if residual tissue is not available for additional assessment. The screening assessments, if required may be done in two parts. The first part will consist of consenting the subject and collecting cervical biopsy samples for HPV assessment. The second part of the visit will consist of performing the remaining screening assessment.

Subjects in Cohort 1 can be screened either prior to initiation of chemoradiation or during chemoradiation. Subjects should be screened and enrolled such that their first study treatment (Day 0) will be delivered within 2 weeks of completing their chemoradiation therapy.

Subjects in Cohort 2 can be screened at any time prior to the date of their first study treatment. Subjects should be screened and enrolled such that their first study treatment (Day 0) is no sooner than 2 weeks and no later than 4 weeks after completing the salvage therapy.

The following evaluations will be performed at **screening** visit prior to Day 0:

- Signed informed consent
- Histologic diagnosis of cervical cancer
- Collect demographic information
- Determination of eligibility per inclusion and exclusion criteria
- Medical and CIN/cancer history
- Medical/clinical assessment
- Adverse event (AE)/Serious adverse event (SAE) assessment
- Determine disease status
- Concomitant medications review
- Assessment of systemic reaction/toxicity/side effects of standard (chemoradiation) therapy (only if subject is screened during chemoradiation therapy)

- Full physical exam to include complete gynecological exam and ECOG performance status
- Vital Signs (including body temperature, respiratory rate, blood pressure, heart rate and height/weight)
- 12-lead ECG
- HPV assessment
- Tumor biopsy collection (required only if residual tissue or unstained slides are not available at screening)
- ThinPrep™ sample for HPV testing (if applicable)
- Digene swab (2 samples) (if applicable)
- Baseline PET/CT scan (must be performed within 4 weeks prior to Day 0)
- Complete blood count with differential
- Serum chemistry evaluation including glucose, albumin, total protein, SGPT, SGOT, alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), calcium, creatinine, electrolytes (chloride, carbon dioxide or bicarbonate, potassium, sodium)
- Baseline CPK
- Urinalysis
- Serum pregnancy test
- HIV, Hepatitis B and C serology (not required if performed within 12 months of signing of informed consent)
- Whole blood and serum for immunologic assays

6.1.2 Study Evaluations

Visit dates and windows must be calculated from the date of the Day 0 visit.

The following study evaluations will be performed on **Day 0 prior to study treatment/EP 1**:

- Determination of eligibility per inclusion and exclusion criteria
- Medical/clinical assessment
- Targeted physical assessment (including ECOG performance status)
- AE/SAE event assessment
- Assessment of systemic reaction/toxicity/side effects of standard (chemoradiation) therapy to be completed immediately prior to the first study treatment/EP on Day 0
- Concomitant medications review
- Vital Signs and Weight
- ThinPrep™ sample for HPV testing (if applicable)
- Digene swab (2 samples) (if applicable)
- Complete blood count with differential
- Serum chemistry evaluation including glucose, albumin, total protein, SGPT, SGOT, alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), calcium, creatinine, electrolytes (chloride, carbon dioxide or bicarbonate, potassium, sodium)
- Urine pregnancy test
- Whole blood and serum for immunologic assays

The following study evaluations will be performed on **Day 0, post study treatment/EP 1**:

- Post-treatment adverse event and injection site reaction assessment within 30-45 minutes after EP
- Distribute Participant Reminder Card (PRC)
- Download EP data

The following study evaluations will be performed at **Weeks 2, 6, 10 and 14 post study treatment/EP (± 1 week)**:

- Medical/clinical assessment *
- Targeted physical assessment (including ECOG performance status)
- Assessment of systemic reaction/toxicity/side effects of standard (chemoradiation) therapy
- Post-treatment injection site reaction assessment*
- AE/SAE assessment*
- Concomitant medications review*
- Review of PRC*
- Vital Signs and Weight

Weeks 2, 6, 10 and 14 visits may be performed as an in-person office visit or a telephone call. The type of visit will be documented on the case report form. All study procedures listed above should be performed for an in-person visit. The assessments that are required for a telephone call are indicated above with an asterisk (*).
If the visit will be conducted by telephone, the subject should submit their PRC (i.e. mail, fax, email) to site personnel prior to the phone visit. If the PRC is not received in advance, site personnel should review all PRC elements verbally (see Protocol Section 6.2.4.4). The hard copy of the PRC should be collected and reviewed at the next in-person study visit. After completing a medical/clinical assessment, reviewing the post-vaccination diary and assessing for adverse events and injection site reactions with the subject on the phone, the Investigator will determine whether an office visit is needed for further evaluation.

The following study evaluations will be performed on **Weeks 4, 8 and 12 prior to each study treatment/EP (±1 week)**:

- Medical/clinical assessment
- Targeted physical assessment (including ECOG performance status)
- Adverse event/serious adverse event assessment
- Assessment of systemic reaction/toxicity/side effects of standard (chemoradiation) therapy at Week 4 only
- Concomitant medications review
- Vital Signs and Weight

- Complete blood count with differential
- Serum chemistry evaluation including glucose, albumin, total protein, SGPT, SGOT, alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), calcium, creatinine, electrolytes (chloride, carbon dioxide or bicarbonate, potassium, sodium)
- Urine pregnancy test
- Whole blood and serum for immunologic assays at Week 8 only

The following study evaluations will be performed on **Weeks 4, 8 and 12 post study treatment/EP**:

- Post-treatment adverse event and injection site reaction assessment within 30-45 minutes after EP
- Distribute and review PRC
- Download EP data

The following study evaluations will be performed on **Week 16 (±1 weeks)**:

- Medical/clinical assessment
- Targeted physical assessment (including ECOG performance status)
- AE/SAE assessment
- Concomitant medications
- Determine disease status
- PET/CT scan (must be done EVERY 3-4 months after Day 0)
- Vital Signs and Weight
- Urine pregnancy test
- Tumor biopsy collection
- ThinPrep™ sample for HPV testing (if applicable)
- Digene swab (2 samples) (if applicable)
- Complete blood count with differential
- Serum chemistry evaluation including glucose, albumin, total protein, SGPT, SGOT, alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), calcium, creatinine, electrolytes
- CPK
- Whole blood and serum for immunologic assays

The following study evaluations will be performed on **Weeks 24 (±2 weeks)**:

- Medical/clinical assessment
- Targeted physical assessment (including ECOG performance status)
- AE/SAE assessment
- Concomitant medications
- Vital Signs and Weight
- Whole blood and serum for immunologic assays

The following study evaluations will be performed on **Weeks 32 (±2 weeks)**:

- Medical/clinical assessment with ROS
- Targeted physical assessment (including ECOG performance status)
- AE/SAE assessment
- Concomitant medications

- Vital Signs and Weight
- PET/CT scan
- Whole blood and serum for immunologic assays

The following study evaluations will be performed on **Week 36 or discharge visit (±2 weeks):**

- Medical/clinical assessment
- Full physical exam (including ECOG performance status)
- AE/SAE assessment
- Concomitant medications
- Determine disease status
- Vital Signs and Weight
- PET/CT scan (not required if performed at wk 32)
- ThinPrep™ sample for HPV testing (if applicable)
- Digene swab (2 samples) (if applicable)
- Whole blood and serum for immunologic assays

6.2 Timing and Evaluations

6.2.1 Informed Consent

No study specific-assessments or procedures can be conducted until a signed informed consent form (ICF) has been obtained from the subject.

Study personnel will meet with prospective study subjects, explain the study, and provide them with an ICF that describes the screening tests, eligibility criteria for entering the study, and study treatments and follow-up procedures.

6.2.2 Assignment of Screening/Allocation Numbers

Study personnel will screen subjects and assign unique subject identification number (SID). Subject ID numbers are a combination of site number plus a 3-digit number starting with XX1. Information regarding subject's screening number and screen date must be documented on a screening log.
When a subject has been deemed eligible by criteria listed in protocol Section 4 - Selection and Enrollment of Subjects, the clinical site will contact the Sponsor to register the subject and provide the required eligibility information. The site will complete a Subject Identification Form (Appendix 1) and fax or email to the Sponsor prior to enrolling the subject. The Sponsor will assign the subject a unique allocation number based on the cohort the subject will be enrolled and return via fax or email the completed form to the site. Once assigned, the allocation number cannot be reused for any reason.

6.2.3 Medical History

Subjects will be asked to report any current or past medical conditions and illnesses at their screening visit and should include treatment detailed information on all therapy directed against cervical cancer, or CIN, e.g. past surgical and/or

radiation regimens. Any prior chemotherapy or immunotherapies, adjuvants, etc. should be recorded on the CRFs.

Any worsening of a condition recorded in the medical history should be recorded as an Adverse Event on the CRFs.

6.2.4 Safety Assessments

Safety evaluations and management of toxicities are detailed in Section 7. Assessments for safety are described within this section.

6.2.4.1 Medical and Clinical Assessments

New onset disease and concomitant medications will be collected on Day 0 and at all subsequent study visits through discharge.

Assessment of systemic reaction/toxicity/side effects of standard (chemoradiation) therapy will be collected at specified visits and be reported using the "Acute Radiation Morbidity Scoring Criteria (RTOG)", (Appendix 5).

Assessment of all other adverse events will be collected form the time of informed consent through discharge and will be will be assessed using the CTCAE v4.03 issued by the US Department of Health and Human Services on June 14, 2010 (Appendix 4).

Clinical evaluations for disease response will be conducted at all of the study visits (as assessed by clinical signs and symptoms of disease progression). PET/CT scans for disease progression will be obtained for all subjects 3-5 months after Day 0 and every 3-5 months thereafter per standard of care or in accordance with local guidelines and institutional practices.

6.2.4.2 Physical Assessments

A full examination including complete gynecological exam and ECOG performance status will be conducted during screening and study discharge. A targeted physical assessment (including ECOG performance) will be performed at other visits as determined by the Investigator or directed per subject complaints.

6.2.4.3 Post-Treatment Reaction Assessment

The Investigator will assess local and systemic reactions post-treatment (within 30-45 minutes after study treatment/EP) and at specified visits. Any reported local post treatment reactions will be graded per the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials and any reported systemic post treatment reactions will be graded per CTCAE v4.03 and recorded on the CRFs (see Section 6.6 for more details).

6.2.4.4 Participant Reminder Card

Subjects will be given an oral thermometer and participant reminder card (PRC) at each study treatment/EP visit. Subjects will be instructed to take and record their temperature daily (at the same time each day). They will also be advised to record local and systemic events on a PRC as shown in Appendix 9.

If Weeks 2, 6, 10 and 12 visits are conducted by telephone, the subject should submit their PRC (i.e. mail, fax, email) to the site personnel prior to the phone visit. If the PRC is not received in advance, site personnel should verbally review all PRC elements listed above. The hard copy of the PRC should be collected at the next in-person study visit. Any entry on PRC determined to meet the criteria for a Grade 1 or higher adverse event should be documented as adverse event. If the PRC entry does not meet the criteria of a Grade 1 or higher AE as per the CTCAE v4.0, clinical judgment can be used to determine whether the entry should be recorded as an AE. For cases where the PRC entry and final AE reporting (i.e., grading) do not agree, the reasoning should be recorded in the source documents.

6.2.4.5 Vital Signs

Vital signs including body temperature, respiration rate, blood pressure and heart rate will be measured at all the study visits.

6.2.4.6 Weight and Height

Weight (kg) and height (cm) will be collected at the screening visit. Weight will be collected at each additional visit from Day 0 through discharge.

6.2.4.7 12-lead ECGs

An ECG will be performed at screening within 30 days of signing of ICF for all subjects to determine subject eligibility. Abnormal ECGs should be interpreted as clinically significant or not clinically significant.

6.2.4.8 Pregnancy Test

For women of reproductive potential, a negative result for serum pregnancy test (test must have a sensitivity of at least 25 mIU/mL) must be available at the screening visit and urine β-HCG (pregnancy test) prior to each administration of INO-3112 and prior to tumor biopsy collection. If at any point, the β-HCG (pregnancy) test is positive, indicating that the subject is pregnant, no additional study treatment/EP will be administered, but the subject will be followed for the duration of the study and beyond to determine the outcome of the pregnancy (with the subject's consent).

6.2.4.9 Laboratory Evaluations

At screening, blood samples will be collected for serum chemistry and hematology. A urine sample will also be obtained to determine eligibility. At other visits, blood samples will be collected as specified in Table 1 - Schedule of Events. All labs for Day 0 and those associated with any treatment visit should be collected no more than 48 hours prior to treatment and reviewed/evaluated by the PI prior to treatment. Approximately 4 cups of blood will be drawn from each subject during the entire duration of the study.

Complete blood count (CBC)

White blood cell (WBC) count w/ differential
Red blood cell (RBC) count
Hemoglobin, Hematocrit
Platelet count

Serum Chemistry

Glucose
Albumin
Total protein
SGPT (serum glutamic-pyruvic transaminase)/ALT
SGOT (serum glutamic-oxaloacetic transaminase)/AST
Alkaline phosphatase
Bilirubin (total)
BUN (blood urea nitrogen)
Calcium
Creatinine
Electrolytes (Sodium, Potassium, Chloride, Carbon Dioxide or Bicarbonate)

CPK (Creatine Phosphokinase)

Serology (required only at screening if serologic test was performed ≥ 12 months of informed consent)

Antibody to HIV
Hepatitis B surface antigen
Antibody to Hepatitis C

Urinalysis

Urine samples will be tested by dipstick for glucose, protein, and hematuria. If abnormal (presence of protein, hematuria, or glucose ≥ 1+) a microscopic examination will be performed.

6.2.4.10 PET/CT Scan

Baseline PET or CT scan must be performed within 4 weeks prior to Day 0.

The follow-up scan will be performed 3-4 months after Day 0 to evaluate subject disease status. Thereafter, PET/CT scans can be performed 3- 5 months or at study discharge in accordance with local guidelines and institutional practices.

FDG-PET imaging is based on the increased glucose metabolism of tumor cells compared to normal tissue resulting in higher standard uptake volume (SUV). Increased SUV_{max} at diagnosis has been associated with persistent abnormal FDG uptake after curative chemoradiation and biopsy-proven local recurrence [Kidd 2007]. FDG-PET is already utilized as a follow-up evaluation modality in a variety of cancers, including lymphomas, head and neck cancers, and breast cancer [Schelling 2000, Smith 2000, Weber 2001, Ott 2003, Weber 2003, Brun 2002].

In a prospective study of cervical cancer patients, FDG-PET was demonstrated to be a metabolic biomarker of response and a potential prognostic marker for progression-free survival at 3 years [Schwarz 2007]. A meta-analysis of 16 studies also demonstrated statistical significance for prediction of event-free and overall survival using metabolic response derived from PET and PET/CT imaging [Zhao 2013].

Studies have previously described the abscopal effect of radiation therapy on non-irradiated tumor sites in a variety of cancers [Postow 2012, Prise 2009]. Post-treatment FDG-PET may further provide elucidation of this mechanism by highlighting sites of residual activity. Retrospective and prospective studies have demonstrated that the use of positron emission tomography (PET) with F-18 fluorodeoxyglucose (FDG) in the post-therapy evaluation of patients with cervical carcinoma is predictive of survival outcome [Grigsby 2004, Grigsby 2003].

These studies evaluated patients with similar disease stage to our current investigation and found that SUV PET response at 3 months after chemoradiation correlated with survival and patterns of failure. We propose to describe qualitatively the rates of complete metabolic response (CMR), partial metabolic response (PMR), and progressive disease (PD) in our patient population and compare these rates to patients treated per standard of care in the aforementioned studies to preliminarily explore any differential outcomes.

6.3 Study Treatment/EP with INO-3112

The timing of the first dose will be designated Day 0.

6.3.1 Management of anxiety and pain due to EP procedure

Subjects will be offered topical anesthetic (e.g. EMLA), to prevent significant discomfort from the study treatment/EP procedure. If EMLA (lidocaine 2.5% and prilocaine 2.5%) is used, an approximately 1.5 cm diameter amount will be applied with occlusion to the site of injection ~30 minutes prior to study treatment/EP.

Subjects may be offered a mild sedative (e.g. 0.5-1 mg lorazepam) for anxiety related to the EP procedure. Mild sedatives may be administered approximately 1 hour prior to EP at Weeks 0, 4, 8 and/or 12. Subjects who receive a mild sedative must not be allowed to operate a motor vehicle for 3-4 hours after receiving medication and must have arranged transportation to depart the study site.

Subjects will be offered an analgesic (e.g. ibuprofen, ketorolac) after study treatment/EP. [Note: The use of any narcotic (including Tylenol with codeine) for pain meets the definition of severe pain (Grade 3) as per the "Guidance for Industry - Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, September 2007" (Table 6.1) and therefore do not offer this to the patient unless clinically indicated.]

Subjects who are allergic to or have contraindications to ibuprofen, ketorolac or lorazepam will be offered a suitable alternative.

6.4 Assessment of Clinical Adverse Events

The injection site will be assessed by study personnel prior to and within 30-45 minutes after study treatment/EP and at next visit prior to study treatment/EP.

Subjects will also be queried regarding the occurrence of any possible adverse events, concomitant medications and new onset chronic disease during their clinic visits. Subjects will be reminded to contact study personnel and immediately report any event that may happen for the duration of the study. These events will be recorded on the subject's CRF.

At specific visits the Acute Radiation Morbidity Scoring Criteria (RTOG) (Appendix 5) will be used to assess systemic reaction/toxicity/side effects of standard (chemoradiation) therapy.

6.5 Assessment of Laboratory Abnormalities

Investigators may use clinical judgment to enroll subjects with isolated Grade 1 abnormalities in screening CBC, serum chemistry or CPK values if there is no indication of disease process in the remainder of the history and physical examination.

Blood will be drawn for serum chemistry, hematology and serology assessments as well as pregnancy testing at screening for inclusion into the study as listed in sections 6.2.4.8 and 6.2.4.9.

Urinalysis will be performed at screening to fulfill eligibility criteria. CPK will be performed at Screening and Week 16.

Complete blood count with differential and serum chemistry will be performed at each study treatment/EP and Week 16.

6.6 Assessment of Injection Site Reactions

When evaluating injection site reactions throughout the study, the investigator will be instructed to use the following grading scale:

Table 6.1: Grading Scale for Injection Site Reactions

Local Reaction to Injectable Product (Grade)	Mild(1)	Moderate(2)	Severe(3)	Potentially Life Threatening(4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness*	2.5-5 cm	5.1-10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling**	2.5-5 cm and does not interfere with activity	5.1-10 cm or interferes with activity	>10 cm or prevents daily activity	Necrosis

- September 2007 "FDA Guidance for Industry—Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials"

*in addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

**Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

6.7 Cervical Virologic and Peripheral Blood Immunogenicity Assessment

Whole blood and serum samples to be tested for antibodies to the HPV E6 and E7 proteins and/or T-lymphocytes producing IFN-γ will be obtained at baseline (Screening and Day 0 prior to dosing) and at each study treatment/ EP and follow-up visits for the duration of the trial. Other immunological testing may be performed to further define the immune responses to the INO-3112. Details of the immunology sample collection and shipment will be provided in laboratory manual.

Binding antibody responses against HPV E6 and E7 induced by INO-3112 will be measured using ELISA. Commercially available recombinant human HPV-16 and HPV-18 proteins will be used to assess induction of binding antibodies to each of the antigen components.

Using antigen-specific IFN-γ ELISpot assays, the number of antigen-specific IFN-γ–secreting T-cells in response to stimulation with overlapping peptide libraries spanning consensus antigens HPV16 E6, HPV16 E7, HPV18 E6 and HPV18 E7 will be determined. As previously described [Bagarazzi et al Sci Tran Med]. PBMCs will be incubated with HPV peptide pools at a concentration of 2 μg/ml. IFN-γ release will be detected after an overnight incubation. Spot forming units (SFU) will be adjusted to 1×10^6 PBMCs for each HPV peptide pool.

Flow cytometric assays will be employed to examine any or all of the following characteristics of Study Treatment: induction of T-cells to 1) exhibit phenotypic

markers associated with cytolytic potential after short-term stimulation by HPV antigen (i.e., CTL phenotyping); 2) remain active in the presence of long-term antigen exposure and efficiently synthesize proteins used in lytic activity (i.e., Lytic granule loading); and 3) effectively employ lytic degranulation to drive killing of target cells expressing HPV antigens (i.e., Killing Assay)

1. The CTL phenotyping assay employs short term (4-6 hours) in vitro stimulation of unfractionated PBMC using peptides spanning HPV antigens and appropriate controls. The external cellular markers employed in this assay might include CD3, CD4, CD8 (T-cell identification), CD45RO, CCR7 (memory subset identification) and CD107a (lytic degranulation). The CTL Phenotyping assay may additionally analyze the following intracellular markers: IFN-γ (Th1 biasing cytokine), Tumor Necrosis Factor-α (TNF-α), Granzyme A, Granzyme B and Perforin (involved in lytic degranulation and cytotoxic potential). This panel may vary as additional relevant markers are identified.
2. The lytic granule loading assay employs long term (115-120 hours) in vitro stimulation of unfractionated PBMC using peptides spanning HPV antigens and appropriate controls. The external cellular markers employed in this assay might include CD3, CD4, CD8 (T-cell identification) and CD137 (also known as 41BB, T-cell activation). The Lytic granule loading assay may additionally analyze the following intracellular markers: Granzyme B, Perforin and Granulysin (cytotoxic potential). This panel may vary as additional relevant markers are identified.
3. The killing assay employs long term (115-120 hours) in vitro stimulation of unfractionated PBMC using peptides spanning HPV antigens. After the initial long term incubation, stimulated whole PBMC or CD8+ T-cells (hereafter referred to as Effector Cells) are co-incubated for ~1 hr with target cells treated with a stain (Target Stain) that differentiates them from Effector Cells and have additionally been pulsed with a substrate reagent which is activated only by the activity of Granzyme B or a substrate which is activated by the activity of terminal caspases involved in the induction and perpetuation of apoptosis. Enumeration of target cells identified by the Target Stain and the presence of an active substrate reagent within the Target population represents a measure of a functional T cell response that is capable of Target cell killing.

A standardized binding ELISA will be performed to measure the anti–HPV16/HPV-18 E6 or E7 antibody response induced by INO-3112. 96-well enzyme immunoassay plates will be coated with HPV16 or HPV18 E6 or E7 proteins (1 μg/ml).

PBMC responses against a pool of known antigenic epitopes pooled from Cytomegalovirus, Epstein Barr Virus and Influenza (CEF) will be tested in order to track general cellular immune competence during the study. Assessment of the

response to these reference antigens that are not related to the study antigens will give a baseline reading of immunocompetency at study entry. Observation for variation of response against these reference antigens during the progression of study treatment may therefore give insight as to general immune competency and aid in accounting for variation in response against study antigens encoded by INO-3112 in the same manner as HPV response described above.

Cervical Virologic Assessment

Subjects must have positive HPV-16 and/or HPV-18 genotype result from ISH or PCR assays at screening or prior to screening for inclusion in the study. Subjects whose specimens also test positive for other HPV genotypes are not excluded as long as they have a positive result for HPV 16 and/or HPV 18. If a subject has documented evidence of HPV-16 and/or HPV-18 infection results from cervical specimen obtained prior to anti-cancer treatment, then those results will be eligible for inclusion in the study.

If applicable, a liquid based cytology sample (ThinPrep™) will be collected for HPV PCR at screening and at Weeks 16 and 36. Samples will be sent to a central laboratory to be analyzed for the presence of HPV infection by PCR.

Cervical Immunologic Assessment

If applicable, two Digene cervical brushes will be collected at baseline (screening and Day 0), Weeks 16 and 36 and will be banked and frozen for immunological testing.

Tissue specimens obtained as routine diagnostic and therapeutic specimens will be analyzed to characterize the presence, density, and co-localization of immune cell subsets, including macrophages, dendritic cells, T cells (CD8 and regulatory T cells), and NK cells. As tissue availability permits, the specimens will also be analyzed for cytokine expression.

At visits where multiple cervical samples are collected, the two Digene cervical brushes will be collected prior to the ThinPrep™ sample.

If adequate residual specimen is available, immunohistochemistry (IHC) studies will be performed on either tumor tissue block or unstained slides from tumor(s) from the following time points: (1) at screening; (2) at Week 16 (one month post-dose 4).

A tumor biopsy will be used to investigate the post-radiation changes at a cellular level, with particular focus on the presence and populations of immune cells to compare to pre radiation characterization.

Characterization of the various cell populations present in the primary tumor site will allow for elucidation of long-term effects of radiation-induced changes, potential cell-mediating killing in microscopic colonies of residual tumor, and mechanisms of immune cell interactions in the post-radiation setting. The maturation and clonal expansion of T cells in response to repeated immunotherapy should result in the production of a memory T cell subset in the immune cell population.

Biopsy samples can also be compared to the post-dose peripheral blood samples to study shifts in cell populations or HPV-specific proliferative response. In addition, biomarkers may be identified as predictors of early response, resistance, or recurrence, and contribute to patient outcome stratification.

6.8 Disease Status

Diseases status will be determined based on RECIST (version 1.1). Disease status should be categorized into:

1. No evidence of disease (NED)
2. Partial Response
3. Stable disease
4. Progressive disease

6.9 Concomitant Medications/Medical Care

All medications taken or medical procedures performed within 12 weeks prior to Day 0 and during the study must be recorded on the case report forms (CRFs).

6.10 Permitted Supportive Therapy

Anti-emetics, anti-diarrheals, analgesics, nutritional and fluid supplementation, and packed red blood cell transfusions are permitted as supportive therapy during the study. All medications and interventions must be recorded as concomitant medications in the CRFs.

6.11 HLA Testing

A blood sample will be collected at the Day 0 visit and sent to a central laboratory for HLA typing. If the subject has a record of previous high resolution HLA testing and access to the results, this HLA testing is not required.

6.12 Downloading of EP data from CELLECTRA®-5P device

Within 48 hours following each treatment with INO-3112, data should be downloaded from the EP device and the data file that is created should be sent to the Sponsor or designee by email to CELLECTRAdata@inovio.com. Instructions on how to download the data are provided in Appendix 7. Training will be provided.

6.13 Restrictions

Subjects should not be vaccinated (e.g. influenza vaccine) within 2 weeks of (before or after) any dose of INO-3112.

Subjects should not receive a course of systemic corticosteroids (≥2 mg/kg of prednisone or equivalent for 5 days) within 2 weeks before or after any dose of INO-3112.

7 EVALUATION OF SAFETY AND MANAGEMENT OF TOXICITY

7.1 Safety Parameters

The safety of the INO-3112 DNA plasmid vaccines will be measured and graded in accordance with the document entitled "Common Terminology Criteria for Adverse Events (CTCAE)", version 4.03 issued by the US Department of Health and Human Services on June 14, 2010 (Appendix 4).

7.1.1 Adverse Events (AEs)

An adverse event (AE) is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body, or worsening of a pre-existing condition, temporally associated with the use of a product whether or not considered related to the use of the product. In this study, such changes will be monitored, classified, and summarized, and as Clinical or Laboratory AEs, respectively. Medical condition/diseases present before starting the investigational drug will be considered adverse events only if they worsen after starting study treatment.

An unexpected AE is one not identified in the Clinical Investigator's Brochure (CIB) or otherwise not expected from the characteristics of the clinical material. AEs include the following:

- Pre- or post-treatment complications that occur as a result of protocol mandated procedure during or after the first screening visit (before the administration of study drug)
- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study drug phase of a human clinical trial, will also be considered an AE
- Complications and termination of pregnancy; see Section 7.4 for additional information
- All AEs that occur from the study screening visits onwards and throughout the duration of the study, including the follow-up off study treatment period should be recorded as an AE

AEs do not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed; the condition that leads to the procedure is an AE
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before the screening visits that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions).
- Overdose without clinical sequelae

- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF
- Uncomplicated pregnancy (documented on a pregnancy CRF)
- An induced elective abortion to terminate a pregnancy without medical reason (documented on a pregnancy CRF)

7.1.2 Serious Adverse Events (SAEs)

A serious adverse event (SAE) is any AE that meets one of the following conditions:

- Death during the period of surveillance defined by the protocol;
- Is immediately life-threatening (e.g., subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred). This does not include an AE that, had it occurred in a more serious form, might have caused death;
- An event requiring inpatient hospitalization or prolongation of existing hospitalization during the period of protocol defined surveillance (including any overnight stay in the hospital, regardless of the length of stay, even if the hospitalization is only a precautionary measure to allow continued observation. However, hospitalization (including hospitalization for an elective procedure) for a pre-existing condition that has not worsened, does not constitute an SAE;
- Results in congenital anomaly or birth defect;
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions;
- Is an important medical event that may not result in death, be life threatening, or require hospitalization, but based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse;
- Is medically significant or requires intervention to prevent one or other of the outcomes listed above. Examples of “other medically significant events” are:
    - Intensive treatment in an emergency room or at home for allergic bronchospasm
    - Blood dyscrasias or convulsions that do not result in hospitalization
    - Development of drug dependency or drug abuse

- Development of malignancies

Clarification of Serious Adverse Events

- Death is an outcome of an AE, and not an adverse event in itself
- The subject may not have been on investigational medicinal product at the occurrence of the event. Dosing may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event
- "Life-threatening" means that the subject was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity
- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE
- Inpatient hospitalization means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department

The investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms.

Serious adverse events that are ongoing should be followed until resolution. The reporting period for SAEs is described in Section 9.3.2.

7.1.3 Severity Codes for AEs

Study personnel will grade laboratory AEs and clinical AEs (based on discussions with study participants) with respect to the following levels of severity as defined in Common Terminology Criteria for adverse events (CTCAE) of the National Cancer Institute for reporting of all serious adverse events (SAE) or the Acute Radiation Morbidity Scoring Criteria (RTOG).

- Mild (Grade 1);
- Moderate (Grade 2)
- Severe (Grade 3);
- Potentially Life Threatening (Grade 4)
- Death (Grade 5)

A copy of the CTCAE version 4.03 is provided in Appendix 4 and may be downloaded from the CTEP home page (http://ctep.cancer.gov/reporting/ctc.html):
A copy of the Acute Radiation Morbidity Scoring Criteria can be downloaded from the Radiation Oncology Therapy Group home page (http://www.rtog.org/ResearchAssociates/AdverseEventReporting/AcuteRadiationMorbidityScoringCriteria.aspx).

7.2 Causal Relationship of Clinical Material to AEs

A causally related AE is one judged to have a possible, probable or definite relationship to the administration of the clinical material (INO-3112). An AE may also be assessed as not related to the investigational product. The Investigator is responsible for reporting adverse events and judging the relationship between the administration of the clinical material and a subsequent AE because the investigator is knowledgeable about the subject (e.g., medical history, concomitant medications), administers the investigational product, and monitors the subject's response to the investigational product. The Investigator is aware of the subject's clinical state and thus may be sensitive to distinctions between events due to the underlying disease process versus events that may be product related and may have observed the event. The Sponsor will assess the overall safety of the investigational product and determine whether to report expeditiously to the FDA.

The following guidance should also be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug;
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable);
- Known association of the event with the study drug or with similar treatments;
- Known association of the event with the disease under study;
- Presence of risk factors in the Study Subject or use of concomitant medications known to increase the occurrence of the event;
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

7.2.1 Abnormal Laboratory Value

Laboratory abnormalities are usually not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., serum chemistry, hematology, CPK, urinalysis) independent of the underlying medical condition that require medical or surgical intervention or lead to study treatment interruption or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., electrocardiogram, x-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Sections 7.1.1 and 7.1.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia) not the laboratory result (e.g., decreased hemoglobin).

Any laboratory abnormality that is new in onset or worsened in severity or frequency from the baseline condition and meets one of the following criteria will be recorded as an AE:

- Requires therapeutic intervention or diagnostic tests
- Leads to discontinuation of study treatment
- Has accompanying or inducing symptoms or signs

- Is judged by the investigator as clinically significant

Grade is an essential element of these criteria. Each CTCAE grading term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).

Investigators are asked to take the CTCAE grading criteria into account when assessing if a laboratory abnormality qualifies as a laboratory AE. Their clinical judgment ultimately determines whether the abnormality in question is "clinically significant (CS)" or "not clinically significant (NCS)" and the severity of the event. CTCAE grading can be used as a reference when making this determination. It is the responsibility of the Investigators to ensure all AEs are accurately reported and graded.

7.2.2 Post-Study Reporting Requirements

All AEs and SAEs including deaths, regardless of cause or relationship, must be reported for subjects on study (including any protocol-required post-treatment follow-up).

Investigators are not obligated to actively seek AEs or SAEs beyond study discharge for subjects. However, if the investigator learns of an AE or SAE that occurs after the completion or termination visit and the event is deemed by the investigator to be probably or possibly related to the Study Treatment, he/she should promptly document and report the event to Inovio Pharmaceuticals.

7.3 Methods and Timing of the Collection and Recording of Safety Data

After study treatment/EP: Study subjects will be directly observed by study personnel for 30-45 minutes after each administration of study treatment/EP for immediate reactions. Injection sites will also be assessed at the subsequent study visit.

The occurrence and severity of any AE during this period or the lack of same will be recorded on the appropriate CRF. Subjects will be given an oral thermometer and instructed to take and record their temperature daily (at the same time each day).

Days 0-3 following study treatment/EP: Subjects will also be instructed to record local and systemic events in a PRC for 3 days following treatment visit as shown in Appendix 9.

Throughout the Study: Subjects will also be queried regarding the occurrence of any possible adverse events, concomitant medications and new onset chronic disease during their clinic visits. Subjects will be reminded to contact study personnel and immediately report any event that may happen for the duration of the study. These events will be recorded on the subject's CRF.

At specified visit the Acute Radiation Morbidity Scoring Criteria (RTOG) form will be completed for each patient to assess systemic reaction/toxicity/side effects of standard (chemoradiation) therapy.

On study treatment/EP visits, the assessments will be performed prior to dosing. Study subjects will be queried at each clinic visit regarding the occurrence of any AEs, including SAEs that may have occurred since the last visit. They will be reminded to contact study personnel and immediately report any such event that happens during the course of the study. These events will be recorded on the CRFs.

7.4 Procedures for Documenting Pregnancy During Study

Subjects who are pregnant or expect to become pregnant during the course of the study will be excluded from participation in the study. Should a subject become pregnant after enrolling in the study, she will not be given any further treatments with INO-3112. The Investigator will report this event to Inovio Pharmaceuticals, Inc., or its designee, within 24 hours and to the IRB. The Investigator should counsel the participant and discuss risks of continuing with the pregnancy and the possible effects on the fetus. Sites must request the subject's permission to query pregnancy outcome and follow each subject to determine the outcome of the pregnancy. Results will be summarized in the clinical study report (CSR).

Subjects who become pregnant at any point during the study should continue to be followed for safety assessments without receiving further treatments. Procedures that are contraindicated during pregnancy, including additional vaccinations, must not be performed. Investigators should use clinical judgment regarding subsequent study-related blood collection based on the presence or absence of anemia in each subject. Subjects who are not withdrawn should continue to be followed for safety assessments through discharge per protocol.

All pregnancies that occur from the time of first screening procedure through the follow up visits must be reported. Monitoring of the subject and the outcome of the pregnancy should be followed by the investigator. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to Inovio Pharmaceuticals.

7.5 Toxicity Management

The Sponsor's Medical Monitor will be responsible for the overall safety monitoring of the study.

7.5.1 Criteria for Halting of Study Enrollment

Study enrollment (enrollment of new subjects) will be halted if there is a report of Grade 3 anaphylaxis from study treatment/EP with INO-3112. The study may resume enrollment after the safety data has been reviewed and deemed safe to continue by the Medical Monitor and Investigator.

7.5.2 Events Requiring Expedited Reporting

Events requiring expedited reporting (ERER) will be defined as treatment- or EP-related adverse events including any of the following:

- Grade 3 or greater injection site pain, tenderness, erythema, and/or induration recorded ≥ 1 hour after study treatment (see Table 6.1)
- Grade 3 or greater fever assessed by the Principal Investigator as possibly, probably or definitely related to study treatment
- Grade 3 or greater systemic symptoms assessed by the Principal Investigator as possibly, probably or definitely related to study treatment

as defined in the "Common Terminology Criteria for Adverse Events (CTCAE)", version 4.03 issued by the US Department of Health and Human Services on June 14, 2010 (Appendix 4). The worse grade for that particular event is to be documented on the CRFs.

Sites should inform the Sponsor of any ERER within 72 hours to discuss whether further dosing should continue for that participant.

7.5.3 Stopping Rules (Criteria for Pausing of Study)

7.5.3.1 If at any time during the study one third (1/3) or more subjects experience an ERER assessed as possibly, probably or definitely related to study treatment, further enrollment and study treatments will be halted immediately until a thorough investigation has been conducted by the Medical Monitor and Principal Investigator.

7.5.3.2 After any SAE, potentially life threatening AE or death assessed as possibly, probably or definitely related to study treatment, further enrollment and study treatments will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator and IRB (if applicable).

7.5.3.3 If three or more subjects in this study, experience the same grade 3 or 4 adverse event, assessed as possibly, probably or definitely related to study treatment, further enrollment and study treatments will be halted immediately until a thorough investigation has been conducted by the Medical Monitor and Principal Investigator.

7.5.3.4 In the event of any unexpected Grade 4 toxicities, assessed as possibly, probably or definitely related to study treatment, further enrollment and study treatments will be halted immediately until a thorough investigation has been conducted by the Medical Monitor, Principal Investigator and IRB (if applicable).

7.5.3.5 The study will be halted for any report of Grade 3 anaphylaxis from immunotherapy/EP with INO-3112 in two or more patients (as graded per "Common Terminology Criteria for Adverse Events (CTCAE)", version 4.03 issued by the US Department of Health and Human Services on June 14, 2010 (Appendix 4)).

8 STATISTICAL CONSIDERATIONS

8.1 Sample Size Considerations

Per Rose et al., the percentage of patients with grade 3 or 4 hematologic toxicity was 23%. With n=10 patients in this study, there is approximately a 92% chance of observing of at least one grade 3 or 4 hematologic toxicity. If 0 out of 10 adverse events are observed, the study provides 95% confidence that the true proportion of such events is <31%.

8.2 Safety Analysis

With the toxicity results, data from the Acute Radiation Morbidity Scoring Criteria and CTCAE will be recorded for each patient during each visit. For the toxicity results, and for AEs and injection site reactions, descriptive statistics will be generated tabulating the percentage of subjects with events by type and grade along with associated exact 95% Clopper-Pearson confidence intervals.

8.3 Analysis of Immune Responses

Binary responses, i.e., responders/non-responders, will be analyzed by calculating the percentage of responders along with associated exact 95% Clopper-Pearson confidence intervals. Continuous responses, e.g., immune levels, will be analyzed by calculating the mean or median responses along with associated 95% confidence intervals.

8.4 Analysis of Clinical Responses

Disease status frequencies based on RECIST criteria categories will be summarized.

8.5 Summary of Demographic and Other Baseline Characteristics

Demographic and baseline characteristics will be summarized with means, medians, standard deviations, ranges or percentages.

8.6 Missing Values

Missing data will not be imputed.

8.7 Site Effects

The data will be summarized by site and compared observationally among sites.

9 DATA COLLECTION, MONITORING, AND AE REPORTING

9.1 Records to Be Kept

CRFs will be provided for each subject. Subjects must not be identified by name on any CRFs. Subjects will be identified by their subject identification number (SID) provided by Inovio Pharmaceuticals, Inc.

9.2 Safety and Quality Monitoring and Record Availability

Monitoring

Monitoring of the clinical trial will be performed by experienced monitors, who will report to the Sponsor. Records for all clinical subjects in this trial will be monitored. The following clinical site monitoring tasks will be performed at all sites:

- Prior to trial initiation, a site visit will be conducted to review all relevant forms and documentation, to ensure compliance with all applicable requirements.
- All clinical site monitoring visits will be documented.
- Periodic site visits will be performed on a per dose group basis.
- The site monitor will be responsible for addressing and documenting the following study conduct activities and obligations and will:
  - Assure that the study is being conducted in accordance with the protocol, applicable regulatory agency regulations, and IRB policies.
  - Discuss study conduct issues and incidents of noncompliance with the Investigator and/or study personnel and document them on the resolution trip report. Report any significant unresolved problems immediately to the sponsor.
  - Remind the Investigator as necessary of the obligation to immediately report SAE and provide subsequent follow-up report of the final outcome to the IRB.
  - Review all CRF pages for completeness, logic, and internal consistency throughout the study.
  - Assure that the study facilities continue to be acceptable.
  - Compare the study CRFs with source documents to assure that the data are accurate and complete and that the protocol is being followed.
  - Assure that investigational product and device accountability and reconciliation records are complete and accurate.
  - Assure that all subject specimens are being stored and forwarded properly for testing.

Record Availability

The investigator will make study documents (e.g., ICFs, drug distribution forms, CRFs) and pertinent hospital or clinic records readily available for inspection by the local IRB, the site monitors, the FDA, Inovio or its designee or confirmation of the study data.

9.3 Adverse Experience (AE) Reporting

To assure the safety of the participants, information about all AEs (see Section 7.1 Safety Parameters for definitions), whether volunteered by the subject, discovered by investigator or study staff questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded in the subject's source documents and followed as appropriate.

9.3.1 Study Reporting Period of Adverse Events

The reporting period for AEs due to chemoradiation therapy toxicity is the period immediately following initiation of chemoradiation through the Week 4 visit of the study.

The reporting period for all other AEs is the period immediately following informed consent through the end of the study

9.3.2 Study Reporting Period of Serious Adverse Events

The reporting period for SAEs (without regard to causality) is the entire period following informed consent until the end of the study.

Each AE will be assessed to determine whether it meets seriousness criteria. If the AE is considered serious, the investigator should report this event to Inovio Pharmaceuticals as outlined below and also to the Ethics Committee according to its standard operating procedures.

Expectedness of SAEs will be determined by Inovio Pharmaceuticals using reference safety information specified in the Investigator's Brochure. An event may qualify for expedited reporting to regulatory authorities if it is a SAE, serious adverse drug reaction, or suspected unexpected serious adverse reaction (SUSAR) in line with relevant legislation. All investigators will receive a safety letter notifying them of relevant SUSAR reports. The investigator should notify the Ethics Committee as soon as is practical, of serious events in writing where this is required by local regulatory authorities, and in accordance with the local institutional policy. The investigator should send the initial report to sponsor within 24 hours of becoming aware of the event. At minimum, the initial report should include the following information:

- Event
- Study code
- Subject number, initials and date of birth
- Investigational study product
- Reporter name and contact information

In the case of a "minimum report" (one that is solely comprised of the information bulleted above), a more detailed follow-up report should be sent as soon as more information becomes available but no later than 7 calendar days after the date of the initial report. Each SAE should be followed up until resolution or stabilization and for a reported death, the

investigator should provide Inovio Pharmaceuticals and the Ethics Committee with any additional requested information (e.g., autopsy reports and terminal medical reports).

The original SAE form should be kept at the study site. Inovio Pharmaceuticals or its representative will be responsible for determining and in turn, reporting SAEs to regulatory authorities according to the applicable regulatory requirements.

SAEs must be followed by the investigator until resolution, even if this extends beyond the study-reporting period. Resolution of an SAE is defined as the return to baseline status or stabilization of the condition with the expectation that it will remain chronic.

At any time after completion of the SAE reporting period, if an investigator becomes aware of an SAE that is suspected by the investigator to be related to Study Treatment, the event should be reported to the Sponsor or its designee.

9.3.3 Notification of Serious Adverse Events

In accordance with 21 CFR 312.32, the Sponsor shall notify FDA and all participating investigators in a written IND safety report of any adverse experience associated with the use of the drug that is both serious and unexpected. Reports of serious adverse events shall be made as soon as possible and in no event later than 7 calendar days if the event is a death or is life threatening and 15 calendar days for all other reportable events after the Sponsor's initial receipt of the information. Each written notification may be submitted on FDA Form 3500A or in a narrative format and shall bear prominent identification of its contents. Each written notification to FDA shall be transmitted to the FDA new product review division that has responsibility for review of the IND. In each written IND safety report, the Sponsor shall identify all safety reports previously filed with the IND concerning a similar adverse experience, and shall analyze the significance of the adverse experience in light of the previous, similar reports. The Sponsor shall also notify FDA by telephone or by facsimile transmission of all deaths regardless of causality and any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but in no event later than 7 calendar days after the sponsor's initial receipt of the information. Each telephone call or facsimile transmission to FDA shall be transmitted to the FDA new product review division that has responsibility for review of the IND.

Follow up information to a safety report shall be submitted as soon as the relevant information is available. If the results of a Sponsor's event investigation show that an adverse drug experience not initially determined to be reportable is, in fact, reportable, the Sponsor shall report such experience in a written safety report as soon as possible, but in no event later than 15 calendar days after the determination is made. Results

of investigations of other safety information shall be submitted, as appropriate, in an information amendment or annual report.

In the event of death, if an autopsy is performed, a copy of the report should be sent to Inovio Pharmaceuticals.

SAE reporting email: safety@inovio.com

SAE FAX transmission: [redacted]

SAE Phone: [redacted]

SAE MAILING ADDRESS
Inovio Pharmaceuticals, Inc.
660 W. Germantown Pike
Suite 110
Plymouth Meeting, PA 19462

MEDICAL MONITOR:

[redacted], MD
[redacted] Mobile
[redacted]

9.4 Reporting of Device Related Complaints

Any problems experienced during the treatment procedure including potential malfunctions of the CELLECTRA®-5P device, error messages displayed on the device screen following treatment or errors that occur during the treatment procedure should be reported to the Sponsor or designee immediately for evaluation. The error reporting form provided in Appendix 7 should be completed and emailed to the Sponsor at [redacted]

9.5 Study Discontinuation

Inovio Pharmaceuticals reserves the right to discontinue the study at this site or at multiple sites for safety or administrative reasons at any time. Should the study be terminated and/or the site closed for whatever reason, all documentation and study product pertaining to the study must be returned to Inovio Pharmaceuticals or its representative.

10 PUBLICATION OF RESEARCH FINDINGS

The results of this trial will be submitted for presentation and/or publication within 1 year of study completion and data availability. All data obtained, recorded in the CRF and analyzed during the course of this study are the property of the Sponsor (Inovio). Any use of these data must be approved in writing by the Sponsor. At least 60 days before any of the data or results of this study are submitted for presentation or publication, the abstract, poster, presentation, or manuscript must be sent to the Sponsor for review and approval to determine if any confidential information, trade secret, or patentable information is present. The Sponsor must approve or deny all requests for data presentation or

publication in writing within 30 days. In the event Inovio makes such objection, the researcher(s) shall refrain from making such submission for publication or presentation for a maximum of three (3) months from the date of receipt of such objection in order for patent application(s) directed to the patentable subject matter contained in the proposed publication or presentation to be filed with the United States Patent and Trademark Office and/or foreign patent office(s).

11 LIST OF ABBREVIATIONS

AE	Adverse Event
BMI	Body Mass Index
CEF	Cytomegalovirus, Epstein Barr Virus and Influenza
CFR	Code of Federal Regulations
CIB	Clinical Investigator's Brochure
CIN	Cervical Intraepithelial Neoplasia
CMI	Cell-mediated immunity
CMR	Complete Metabolic Response
CMV	CytoMegalo Virus
CRF	Case Report Forms
CPK	Creatine Phosphokinase
CT	Computed Tomography
CTL	Cytotoxic T-cells
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DAIDS	Division of Acquired Immunodeficiency Syndrome
DNA	Deoxyribonucleic Acid
DLT	Dose Limiting Toxicity
EBRT	External Beam Radiation Therapy
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EP	Electroporation
ERER	Events Requiring Expedited Reporting
ELISA	Enzyme Linked Immunosorbent Assay
ELISpot	Enzyme Linked Immunosorbent Spot-forming Assay
FDA	Food and Drug Administration
FDG	Fluordeoxyglucose
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HPV	Human Papillomavirus
IC	Intracavitary
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IFN-γ	Interferon Gamma
IL-12	Interleukin 12
IM	Intramuscular
IND	Investigational New Drug Application
IRB	Institutional Review Board
IUD	Intrauterine Device
LEEP	Loop Electrosurgical Excision Procedure

MedDRA®	Medical Dictionary for Drug Regulatory Affairs
NED	No Evidence of Disease
NIH	National Institutes of Health
NYHA	New York Heart Association
PBMC	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PET	Positron Emission Tomography
PHI	Protected Health Information
PFS	Progression Free Survival
PMR	Partial Metabolic Response
PRC	Participant Reminder Card
RECIST	Response Evaluation Criteria in Solid Tumors
ROS	Review of Systems
RTOG	Radiation Therapy Oncology Group
SAE	Serious Adverse Event
SARS	Severe Acute Respiratory Syndrome
SID	Subject Identification
SOC	System Organ Class
SUV	Standard Uptake Volume
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
WOCBP	Women of Childbearing Potential

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13 APPENDICES

13.1 Appendix 1: Subject Identification Fax Form

SCREENING NUMBER:	
GENDER:	
Date of Birth:	
Screening Date:	
Anticipated Date of Immunotherapy Dose:	
Allocation Number (to be completed by Inovio)	Allocation Number: INO initials: _____
COMMENTS BOX:	
SITE PERSONNEL REPORTING:	DATE REPORTED/FAXED:

13.2 Appendix 2: ECOG Performance Status

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

13.3 Appendix 3: Standard Chemoradiation Guidelines

Below are standard guidelines for chemoradiation in this patient population. It is highly suggested these guidelines be followed.

I. Standard therapy

a. Concurrent chemoradiotherapy

II. Chemotherapy

a. Cisplatin

I. Source and Formulation: Cisplatin is commercially available from Bristol-Myers Oncology and from Pfizer as a dry powder supplied in 10 mg and 50 mg vials, and in aqueous solution in 50 mg and 100 mg vials with 100 mg mannitol and 90 mg sodium chloride; 10 mg/vial. The 10 mg and 50 mg vials should be reconstituted with 10 mL or 50 mL sterile water for injection USP, respectively. Each mL of the resulting solution will contain 1 mg of cisplatin. Reconstitution of powder results in a clear colorless solution when completed as recommended. NOTE: Aluminum reacts with cisplatin causing precipitation formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of cisplatin.

II. Administration: Patients will be pre-hydrated per institutional guidelines. Cisplatin will be dissolved at a concentration of 1 mL of sterile water/mg of drug, and the solution will be administered intravenously over 45-60 minutes. Supportive treatment will be given according to institutional policy.

III. Storage and Stability: Store at 15º to 20ºC. Unopened vials of dry powder are stable for the lot life indicated on the package when stored at room temperature. The aqueous solution should be stored at room temperature and protected from light. The reconstituted solution is stable for 20 hours at room temperature. Do not refrigerate. The cisplatin remaining in the amber vial following initial entry is stable for 28 days protected from light or for 7 days under fluorescent room light. NOTE: Once reconstituted, the solution should be kept at room temperature. If the reconstituted solution is refrigerated, a precipitate will form.

IV. Adverse Events: Incidence rates of adverse events associated with cisplatin are provided in the product package insert. The following events are expected with the administration of cisplatin:

a. Nephrotoxicity: Dose-related and cumulative renal insufficiency is the major dose-limiting adverse events of cisplatin. Renal adverse events have been noted in 28-36% of patients treated with a single dose of 50 mg/m2. It is first noted in the second week after a dose and is manifested as elevated BUN, creatinine, and serum uric acid, or as a decrease in creatinine clearance. Because renal adverse events become more prolonged and severe with repeated

courses of cisplatin, renal function must return to normal before another dose can be given.

b. Ototoxicity: Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin 50 mg/m2. It is manifested by tinnitus and/or hearing loss in the high frequency range. Deafness has been reported rarely.
c. Hematologic Toxicity: Myelosuppression occurs in 25-30% of patients treated with cisplatin. Nadirs in circulating platelets and leukocytes occur between Days 18 and 23 with most patients recovering by Day 39. Thrombocytopenia, anemia, neutropenia, and fever are also possible adverse events.
d. Gastrointestinal Toxicity: Marked nausea and vomiting occur in almost all patients treated with cisplatin. Diarrhea and anorexia have also been reported.
e. Neurotoxicity: Neurotoxicity usually characterized by peripheral neuropathies, has been reported. Neuropathy usually occurs after prolonged therapy (4 to 7 months); however, symptoms have been reported after a single dose. Muscle cramps, loss of taste, seizures, autonomic neuropathy, dorsal column myelopathy, and Lhermitte's sign have also been reported.
f. Ocular Toxicity: Optic neuritis, papilledema, and cerebral blindness have been reported infrequently in patients receiving standard recommended doses of cisplatin. Blurred vision and altered color perception have been reported after the use of regimens with higher doses of cisplatin or greater dose frequency than those recommended in the package insert.
g. Anaphylactic-like Reactions: Anaphylactic-like reactions have occasionally been reported in patients previously exposed to cisplatin. Symptoms include facial edema, wheezing, tachycardia, and hypotension.
h. Hepatotoxicity: Transient elevations in liver enzymes, especially SGOT (AST), and bilirubin, have been reported.
i. Other Toxicities: Other infrequent toxicities that have been reported include cardiac abnormalities, hiccups, elevated serum amylase, rash, alopecia, malaise, and asthenia. Rare cases of local soft tissue adverse events have occurred.

V. Mechanism of Action: Primarily causes inhibition of DNA synthesis and, to a lesser degree, inhibition of RNA and protein; it has not been shown to be cell cycle specific.

VI. Pharmaceutical data: Cisplatin (cis-diamminedichloroplatinum II) has the empiric formula N2CL2 PtH6. It is a planar inorganic compound with a molecular weight of 300; soluble in water at a concentration of 1 mg/mL. The (II) nomenclature denotes the active valence state of the platinum. The interatomic distance of the chlorides is 3.3A, which is different from the 5-7A interatomic distance of the classic alkylating agents. Only the cis-isomer is therapeutically active.

VII. Supply: This drug is commercially available.

VIII. Duration of administration: Cisplatin 40 mg/m^2 (80 mg max) should be administered once weekly during external beam RT (5 cycles only). It is recommended that cisplatin be started on day 1 of external beam RT but it is acceptable to give cisplatin on days 1, 2, or 3 of external beam RT. Dose modifications and indications for holding cisplatin are provided below.

IX. Dose Modification

a. Chemotherapy should be held for:

- ANC < 500 /mm^3.
- Platelets < 50,000/mm^3.
- Febrile neutropenia or bleeding.
- Persistent (>24 hours) grade 3 or 4 nausea and vomiting.
- Renal Failure (creatinine > 2.0 mg% or creatinine clearance < 50 ml/min).

b. Cisplatin can be resumed at a dose of 30 mg/m^2 (60 mg max) after the resolution of:

- Persistent (>24 hours) grade 3 or 4 nausea and vomiting.
- Renal Failure (creatinine > 2.0 mg% or creatinine clearance < 50 ml/min).

III. Radiation Therapy

Patients should receive pelvic radiation therapy in combination with cisplatin infusion given on a weekly basis for six weeks. The last dose can be given during parametrial boost.

Radiation therapy should be administered to the pelvis with external beam and intracavitary techniques. Radiation therapy may also be administered to the para-aortic nodal chain as clinically indicated when there is clinical and/or imaging evidence of nodal disease in the high common iliac or para-aortic nodal chain. Radiation therapy **must** be completed within 10 weeks of its initiation.

a. Physical Factors

External beam radiation sources will be linear accelerators which produce megavoltage energy radiation beams. SAD (source-axis distance) 100 cm is required. Low-Dose-Rate (LDR) intracavitary radiation may be delivered by Cesium-137 sources. High-Dose-Rate (HDR) may also be used using an Iridium-192 source.

b. Simulation and Localization

i. Simulation should be done in the supine position.

ii. Recommended contrast and markers are intravenous contrast unless medically contraindicated, oral contrast, bladder contrast, rectal contrast, and a radio-opaque cervical marker at the apex of the vagina. Implanted fiducials are optional.

iii. A gyne swab with CT wire at the tip should be placed into into the vagina

iv. A foley catheter should be placed for simulation with both an empty and full bladder. Full bladder is recommend to be achieved through injection 120 cc of 90cc bacteriostatic water and 30 cc of conray through foley into bladder.
v. Patient should be scanned with both full and empty bladder. Full and empty bladder CT scans should be fused.
vi. Immobilization should be achieved with custom alpha cradles.
vii. Imaging should include CT simulation using 2-5mm slice thickness from T10 to 5cm below the ischial tuberosities, or to include the maximal extent of disease.
viii. Isocenter placement is per the discretion of the treating physicians
ix. Localization films taken on the simulator and/or treatment machine are necessary in all patients. Polaroid or digital pictures of all treatment portals with the patient in the treatment position are recommended.

Treatment Plan, Dose Specification and Distribution

i. Depending on the FIGO stage and radiographic extent of disease, patients should receive radiation therapy to the pelvis, cervix, gross lymph nodes, and if indicated, the paraortic nodal chain.
ii. The volume irradiated should include the totality of the gross disease locally and regionally, as visualized by CT, PET or MRI scanning, the whole uterus, paracervical, parametrial and uterosacral ligaments as well as the areas of the obturator, hypogastric, external and internal iliac lymph nodes. A margin of 2-3 cm should be given around the gross disease and 1.5-2 cm around involved lymph nodes.
iii. Patients treated to the whole pelvis +/- paraaortic chain should receive a total dose of 4500 cGy in 25 fractions at 180 cGy/fx, using a four field technique or intensity modulated radiation therapy (IMRT) throughout the entire treatment with all fields treated each day. Gross nodal disease should be treated with either a sequential boost or simultaneous integrated boost per the treating physician and as determined by proximity of organs at risk.
iv. If overall treatment time for external pelvic RT exceeds 50 days, then reason for the delay must be documented.

c. Dose Specification

1. Fractionation: Conventional fractionation should consist of one fraction per day, total five fractions per week.
2. The pelvis and, if indicated, the para-aortic nodal chain, should be treated at a dose per fraction of 180 cGy per day.
3. Sequential or simultaneous integrated boost may be delivered to a maximum of 65Gy in 1.8-2.5Gy per fraction, while maintaining normal tissue constraints.
4. Parametrial boost should be delivered sequentially after pelvic/para-aortic radiation therapy to a maximum dose of 65Gy to the sidewall. Point B may be used as the calculation point dose site. The superior border should be reduced to include the true pelvis only as defined as 1cm above the inferior aspect of the sacroiliac joint.

d. Target Delineation

1. General

Pelvic MRI and/or PET fusion with the simulation scan is recommended to aid target delineation. Fusion should be optimized to match the MRI / PET scan to the treatment position. The Gross Tumor Volume (GTV) and Clinical Target Volume (CTV) and normal tissues will be contoured on all CT slices in which the structures exist. The definition of all volumes will be in accordance with the 1993 ICRU Report #50: Prescribing, Recording and Reporting Photon Beam Therapy (http://www.icru.org/home/reports/prescribing-recording-and-reporting-photon-beam-therapy-report-50).

2. GTV Delineation
   The GTV is defined as all known gross disease determined from radiographic studies, clinical information, physical examination, endoscopic examination, and biopsy results.

3. CTV Delineation
   The CTV is defined as the gross tumor plus areas containing potential microscopic disease, including the cervix, uterus (if present), the superior third of the vagina (or half of the vagina, if clinically involved), the parametria, and the regional lymph nodes. CTV delineation should follow reported consensus guidelines [Small W, Mell LK, Creutzberg C, et al. Consensus recommendations for intensity modulated radiation therapy planning for post-operative pelvic radiotherapy in endometrial and cervical cancer. Int J Radiat Oncol Biol Phys. 2008;71:428-34, http://www.ncbi.nlm.nih.gov/pubmed/18037584 and Lim K, Small W, Portelance L, et al. Consensus guidelines for delineation of clinical target volume for intensity-modulated pelvic radiotherapy for the definitive treatment of cervix cancer *Int J Radiat Oncol Biol Phys.* 2009, http://www.redjournal.org/article/S0360-3016(09)03587-1/abstract, accessed March 25, 2014].

   For patients with distal one third vaginal involvement, the inguinal nodes should be contoured continuously from the external iliac nodes to 2 cm caudad to the saphenous/femoral junction. For contouring guidelines for patients with inguinal nodal involvement, refer to atlases used to treat anal carcinoma [Myerson RJ, Garofalo MC, et al. Elective clinical target volumes for conformal therapy in anorectal cancer: a radiation therapy oncology group consensus panel contouring atlas. *Int J Radiat Oncol Biol Phys*. 2009;74:824-30, http://www.ncbi.nlm.nih.gov/pubmed/19117696, accessed March 25, 2014].

4. PTV Delineation
   The Planning Target Volume (PTV) will add a 7-15mm margin around CTV to compensate for treatment setup and internal organ motion. The PTV should be manually or automatically trimmed up to 3 mm from the skin surface, if necessary, to spare skin, provided that the CTV is still included entirely within the PTV.

e. Normal Tissue Delineation

General

Normal tissues should be contoured on the simulation scan. The tissue within the skin surface and outside all other critical normal structures and the PTV is

designated as unspecified tissue. Critical normal tissues for IMRT optimization will consist of the bowel, bladder, rectum, and bone marrow. Femoral heads will be contoured to determine delivered dose but will not be used as a planning constraint.

Bowel

The bowel should be contoured beginning from the axial slice situated 1 cm superior to the superior-most slice containing PTV (if bowel is not present at this level, the bowel contour will start from its most superior extent), and will continue to its most inferior extent in the pelvis. Individual loops of bowel should not be contoured separately. Rectum should be contoured separately from bowel.

Rectum

The outer rectal wall should be contoured and will be defined from the level of the sigmoid flexure to the anus.

Bladder

The outer bladder wall should be contoured, treating the organ as a solid continuous structure.

Bone Marrow

The outer bone contour should be delineated and filled in, treating the bone marrow as a solid continuous structure. The regions contoured should include the os coxae, L5 vertebral body, entire sacrum, acetabulae, and proximal femora. The superior extent of the bone marrow contour should be at the level of the superior border of L5 or the iliac crest, whichever is more superior. When the para-aortic nodal chain is treated, the vertebral bodies should be contoured to T12 or the most cephalad vertebral level being treated. The caudal-most extent of the bone marrow contour should be at the level of the ischial tuberosities.

Femoral Heads

The outer contours of the femoral heads will be delineated and filled in, treating each as a solid continuous structure. Do not include the femoral neck.

f. Treatment Planning

Field Design

a. Conventional RT consists of a 4-field "box" arrangement using opposed AP/PA and lateral fields. For conventional RT, it is permissible to use bone landmarks to draw field borders or to use 3-D planning with explicit targeting as outlined above, using customized blocking to encompass the PTV. If bone landmarks are used, use the following portals:

- Superior border: L4-5
- Lateral border: 1-2 cm lateral to the border of the true pelvis
- Inferior border: Obturator foramen or 4 cm inferior to vaginal cuff, whichever is lower
- Anterior border: line from pubic symphysis to 1 cm anterior to common iliac nodes at L4-5

- Posterior border: draw border posterior to or splitting the sacrum from S1-S4
- Custom blocking to shield femoral heads. Do not block the obturator foramen or within 1 cm of the common iliac nodes

b. Intensity-modulated radiation therapy plans may include static field arrangements (e.g. 5-9 fields).

Target coverage requirements

- The 99% prescription isodose surface will encompass ≥ 90% of the PTV.
- ≥ 99% of the PTV will receive ≥ 90% of the prescription dose.
- ≥ 97% of the PTV will receive ≥ 97% of the prescription dose.
- < 1% of PTV will receive ≥ 115% of the prescription dose.
- < 10% of the PTV will receive ≥ 110% of the prescription dose.
- Dose maximum should occur within the PTV

Normal tissue planning goals for IMRT (soft constraints):

- Bowel: volume receiving >45 Gy (V_{45}) ≤ 200 cc; V_{40} < 30%; maximum dose < 50 Gy
- Rectum: V_{45} < 50%; V_{30} < 60%; maximum dose < 50 Gy
- Bone Marrow: V_{10} < 80%; V_{20} < 66%
- Bladder: V_{45} < 50%; maximum dose < 50 Gy
- Femoral Head: V_{30} < 15%; maximum dose < 50 Gy

Normal tissue requirements for IMRT (hard constraints):

- Bowel: volume receiving >45 Gy (V_{45}) ≤ 250 cc; maximum dose < 110%
- Rectum: maximum dose < 110%
- Bone Marrow: V_{10} < 90%; V_{20} < 75%
- Bladder: maximum dose < 110%
- Femoral Head: maximum dose < 110%

Heterogeneity corrections: Heterogeneity corrections should be applied

g. External Beam Treatment Modification
Treatment should be held for ANC <500/mm^3, platelets < 20,000 mm^3, febrile neutropenia, or uncontrolled bleeding. No dose reductions are allowed. Treatment will be resumed upon resolution of neutropenia (ANC ≥500/mm^3), thrombocytopenia (platelets ≥ 20,000 mm^3), and febrile neutropenia (temperature<38.0 ° C).

h. Setup Verification
Skeletal imaging (e.g., electronic portal MV or kV imaging or CBCT) should be performed at least weekly to verify setup accuracy. For patients treated with conventional techniques, MV portal verification is recommended at least weekly. Daily on-line imaging (image-guided radiotherapy (IGRT)) is allowed but not required.

i. Intracavitary Brachytherapy
The treating physician should select the dose rate to be used for brachytherapy, either HDR or LDR. Orthogonal x-rays, CT, and/or MRI may be used for brachytherapy

planning

j. Low Dose Rate (LDR) Brachytherapy
Following the completion of external beam RT, the patient will receive 3500-4000 cGy to Point A by intracavitary implant with Cesium-137. The patient may receive this in one or two applications at the discretion of the radiation oncologist. The first insertion should be performed promptly upon completion of external beam irradiation. If two implants are contemplated, the second implant should be completed within three weeks of the completion of external beam irradiation (with total radiation treatment time not to exceed 8 weeks).

Normal Tissue Constraints

Maximum allowable cumulative doses (external beam + brachytherapy) to normal tissues are (in EQD2, $\alpha/\beta=3$, $T_{1/2}$ = 1.5 hours): bladder (ICRU reference point), 85 Gy; rectum (ICRU reference point), 80 Gy; vaginal surface (reference point), 135 Gy. If CT is used for planning it is recommended to keep the maximum bowel dose < 25% of the brachytherapy prescription dose. Every attempt should be made to deliver the full prescription dose, even if the late responding tissues receive a slightly higher dose.

k. High Dose Rate (HDR) Brachytherapy -Iridium-192 as the source for HDR brachytherapy.
HDR Schema -
Dose should be prescribed to point A. Permissible dose/fractionation schemes are:

- 5.5 Gy x 6 fractions
- 5.5 Gy x 5 fractions
- 6.0 Gy x 5 fractions
- 6.0 Gy x 6 fractions
- 7.0 Gy x 3 fractions
- 7.0 Gy x 4 fractions
- 7.0 Gy x 5 fractions
- 7.5 Gy x 3 fractions

In general, insertions should be separated by a minimum of 48 hours and no more than 2 insertions should be performed per week. HDR brachytherapy should start at week four of chemoradiation. When HDR brachytherapy begins, at least one insertion should be performed per week with no external beam therapy given on the day of the insertion.

Instruments
It is recommended that tandem and ovoids or tandem and ring be used for brachytherapy. A tandem and cylinder or interstitial system is also permissible.

Determination of Normal Tissue Tolerance
Maximum allowable cumulative doses (external beam + brachytherapy) to normal tissues are (in EQD2, $\alpha/\beta=3$, $T_{1/2}$ = 1.5 hours): bladder (ICRU reference point), 80 Gy; rectum (ICRU reference point), 75 Gy. It is recommended that the rectum and bladder for each fraction receive less than or equal to 70% and 80% of the point A

dose, respectively, if feasible. If CT is used for planning it is recommended to keep the maximum bowel dose < 25% of the brachytherapy prescription dose. Every attempt should be made to deliver the full prescription dose, even if the late responding tissues receive a slightly higher dose.

Intracavitary Radiotherapy Dosimetry

The dose to points A and B, the rectal reference point dose, bladder reference point dose, and vaginal surface reference point dose, and central axis isodose curve should be calculated and documented.

Point A: Measure 2 cm along the intrauterine tandem from the cervical os or flange of the tandem and 2 cm laterally in the plane of the intracavitary system.

Point B: Measure 5 cm lateral from a point 2 cm vertically superior to the cervical os or flange of the central tandem along the patients' midline.

Bladder Dose: Calculated at the center (in the superior-inferior plane on AP view) of a contrast-filled balloon of a Foley catheter and closest to the applicator system on a lateral view, as defined by ICRU 38.

Rectal dose: In accordance with ICRU 38, mark the point 0.5 cm posterior to the vaginal surface (as demarcated by the opaque packing) at the midpoint of the applicator system or at the level of the flange if no ovoids are used.

Parametrial Boost to Involved Parametrium

All patients with initial parametrial involvement should be considered for a parametrial boost. The radiation oncologist should choose the dose and beam and beam energy to be used to the involved parametrium based on bulk of parametrial disease at presentation, as well as the contribution from intracavitary brachytherapy to the external beam, in order to deliver a minimum cumulative (external beam and brachytherapy) dose to the mid-parametrium, or Point B dose, of 5500 cGy (maximum of 6000 cGy) when using LDR intracavitary brachytherapy or a minimum of 5000 cGy (maximum of 5500 cGy) when using HDR intracavitary brachytherapy. Patients with parametrial involvement at the time of brachytherapy implant should receive a cumulative dose to Point B of no less than 6000 cGy (maximum of 7000 cGy) when using LDR brachytherapy or a minimum of 5500 cGy (maximum of 6500 cGy) with HDR implant.

Maximum parametrial boost shall be 1000 cGy at 180 cGy per fraction given AP/PA daily to mid-plane if unilateral or bilateral parametrial boost is used. The prescription point should be at the center of the unblocked portion of the field. The parametrial boost should be delivered if possible between implant 1 & 2 or immediately after implant 1 if only one implant is used.

The total elapsed time for completion of external whole pelvis, intracavitary RT, and parametrial RT shall not exceed eight to ten weeks.

I. Radiation Adverse Events

Risks and side effects related to radiation therapy include:

Likely (more than 10%)

- Redness and skin irritation in the treatment area that may result in bleeding and/or infection, which may require hospitalization

- Loss of pubic hair in the treated area, usually temporary
- Tiredness
- Nausea and/or vomiting
- Sterility (inability to bear children) in fertile women
- Sterility (inability to produce children) in men

Less Likely (3-9%)

- Diarrhea
- Sores and bleeding from the bowel (these side effects may occur well after treatment and be serious enough to require surgery)
- Narrowing and dryness of the vagina (birth canal) and genital area with painful or difficult intercourse and possibly bleeding
- Development of extra tissue (fibrosis) in the anal canal, which may result in decreased function
- Long-term dryness of the skin
- Inability to have or keep an erection (impotency)
- Hip, pelvic, or sacral fracture
- Build up of fluid in ankles, feet, and/or legs

Rare, but serious (less than 2%)

- Narrowing or blockage of the bowel (these side effects may occur well after treatment and be serious enough to require surgery)
- Blockage of the urinary tubes
- Development of an abnormal path or connection between organs (fistulae)
- Skin damage (tissue death), which may result in surgery
- Narrowing of or persistent bleeding in the vagina (birth canal), which may result in surgery

13.4 Appendix 4: Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 dated June 14, 2010

Common Terminology Criteria for Adverse Events (CTCAE)

Version 4.0

Published: May 28, 2009 (v4.03: June 14, 2010)

U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
National Cancer Institute

Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Publish Date: May 28, 2009

Quick Reference

The NCI Common Terminology Criteria for Adverse Events is a descriptive terminology which can be utilized for Adverse Event (AE) reporting. A grading (severity) scale is provided for each AE term.

Components and Organization

SOC

System Organ Class, the highest level of the MedDRA hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

CTCAE Terms

An Adverse Event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may *not* be considered related to the medical treatment or procedure. An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. Each CTCAE v4.0 term is a MedDRA LLT (Lowest Level Term).

Definitions

A brief definition is provided to clarify the meaning of each AE term.

Grades

Grade refers to the severity of the AE. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

A Semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a grade is not available.

Not all Grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for Grade selection.

Grade 5

Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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† CTCAE v4.0 incorporates certain elements of the MedDRA terminology. For further details on MedDRA refer to the MedDRA MSSO Web site (http://www.meddramsso.com).

CONTENTS

Blood and lymphatic system disorders

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability.					
Bone marrow hypocellular	Mildly hypocellular or <=25% reduction from normal cellularity for age	Moderately hypocellular or >25 - <50% reduction from normal cellularity for age	Severely hypocellular or >50 - <=75% reduction cellularity from normal for age	Aplastic persistent for longer than 2 weeks	Death
Definition: A disorder characterized by the inability of the bone marrow to produce hematopoietic elements.					
Disseminated intravascular coagulation	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by systemic pathological activation of blood clotting mechanisms which results in clot formation throughout the body. There is an increase in the risk of hemorrhage as the body is depleted of platelets and coagulation factors.					
Febrile neutropenia	-	-	ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an ANC <1000/mm3 and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour.					
Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test; DAT; Coombs'; schistocytes; decreased haptoglobin)	Evidence of hemolysis and >=2 gm decrease in hemoglobin.	Transfusion or medical intervention indicated (e.g., steroids)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate widespread erythrocyte cell membrane destruction.					
Hemolytic uremic syndrome	Evidence of RBC destruction (schistocytosis) without clinical consequences	-	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death
Definition: A disorder characterized by a form of thrombotic microangiopathy with renal failure, hemolytic anemia, and severe thrombocytopenia.					
Leukocytosis	-	-	>100,000/mm3	Clinical manifestations of leucostasis; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate an increased number of white blood cells in the blood.					
Lymph node pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in a lymph node.					
Spleen disorder	Incidental findings (e.g., Howell-Jolly bodies); mild degree of thrombocytosis and leukocytosis	Prophylactic antibiotics indicated	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder of the spleen.					
Thrombotic thrombocytopenic purpura	Evidence of RBC destruction (schistocytosis) without clinical consequences	-	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death
Definition: A disorder characterized by the presence of microangiopathic hemolytic anemia, thrombocytopenic purpura, fever, renal abnormalities and neurological abnormalities such as seizures, hemiplegia, and visual disturbances. It is an acute or subacute condition.					
Blood and lymphatic system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Cardiac disorders

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Acute coronary syndrome	-	Symptomatic, progressive angina; cardiac enzymes normal; hemodynamically stable	Symptomatic, unstable angina and/or acute myocardial infarction, cardiac enzymes abnormal, hemodynamically stable	Symptomatic, unstable angina and/or acute myocardial infarction, cardiac enzymes abnormal, hemodynamically unstable	Death
Definition: A disorder characterized by signs and symptoms related to acute ischemia of the myocardium secondary to coronary artery disease. The clinical presentation covers a spectrum of heart diseases from unstable angina to myocardial infarction.					
Aortic valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characterized by a defect in aortic valve function or structure.					
Asystole	Periods of asystole; non-urgent medical management indicated	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia without cardiac electrical activity. Typically, this is accompanied by cessation of the pumping function of the heart.					
Atrial fibrillation	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker), or ablation	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia without discernible P waves and an irregular ventricular response due to multiple reentry circuits. The rhythm disturbance originates above the ventricles.					
Atrial flutter	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker), or ablation	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with organized rhythmic atrial contractions with a rate of 200-300 beats per minute. The rhythm disturbance originates in the atria.					
Atrioventricular block complete	-	Non-urgent intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with complete failure of atrial electrical impulse conduction through the AV node to the ventricles.					
Atrioventricular block first degree	Asymptomatic, intervention not indicated	Non-urgent intervention indicated	-	-	-
Definition: A disorder characterized by a dysrhythmia with a delay in the time required for the conduction of an electrical impulse through the atrioventricular (AV) node beyond 0.2 seconds; prolongation of the PR interval greater than 200 milliseconds.					
Cardiac arrest	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by cessation of the pumping function of the heart.					
Chest pain - cardiac	Mild pain	Moderate pain; limiting instrumental ADL	Pain at rest; limiting self care ADL	-	-
Definition: A disorder characterized by substernal discomfort due to insufficient myocardial oxygenation.					
Conduction disorder	Mild symptoms; intervention not indicated	Moderate symptoms	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by pathological irregularities in the cardiac conduction system.					
Constrictive pericarditis	-	-	Symptomatic heart failure or other cardiac symptoms, responsive to intervention	Refractory heart failure or other poorly controlled cardiac symptoms	Death
Definition: A disorder characterized by a thickened and fibrotic pericardial sac; these fibrotic changes impede normal myocardial function by restricting myocardial muscle action.					
Heart failure	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death
Definition: A disorder characterized by the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements, or, the ability to do so only at an elevation in the filling pressure.					

Cardiac disorders

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Left ventricular systolic dysfunction	-	-	Symptomatic due to drop in ejection fraction responsive to intervention	Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated	Death
Definition: A disorder characterized by failure of the left ventricle to produce adequate output despite an increase in distending pressure and in end-diastolic volume. Clinical manifestations mayinclude dyspnea, orthopnea, and other signs and symptoms of pulmonary congestion and edema.					
Mitral valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characterized by a defect in mitral valve function or structure.					
Mobitz (type) II atrioventricular block	Asymptomatic, intervention not indicated	Symptomatic; medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with relatively constant PR interval prior to the block of an atrial impulse. This is the result of intermittent failure of atrial electrical impulse conduction through the atrioventricular (AV) node to the ventricles.					
Mobitz type I	Asymptomatic, intervention not indicated	Symptomatic; medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a progressively lengthening PR interval prior to the blocking of an atrial impulse. This is the result of intermittent failure of atrial electrical impulse conduction through the atrioventricular (AV) node to the ventricles.					
Myocardial infarction	-	Asymptomatic and cardiac enzymes minimally abnormal and no evidence of ischemic ECG changes	Severe symptoms; cardiac enzymes abnormal; hemodynamically stable; ECG changes consistent with infarction	Life-threatening consequences; hemodynamically unstable	Death
Definition: A disorder characterized by gross necrosis of the myocardium; this is due to an interruption of blood supply to the area.					
Myocarditis	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death
Definition: A disorder characterized by inflammation of the muscle tissue of the heart.					
Palpitations	Mild symptoms; intervention not indicated	Intervention indicated	-	-	-
Definition: A disorder characterized by an unpleasant sensation of irregular and/or forceful beating of the heart.					
Paroxysmal atrial tachycardia	Asymptomatic, intervention not indicated	Symptomatic; medical management indicated	IV medication indicated	Life-threatening consequences; incompletely controlled medically; cardioversion indicated	Death
Definition: A disorder characterized by a dysrhythmia with abrupt onset and sudden termination of atrial contractions with a rate of 150-250 beats per minute. The rhythm disturbance originates in the atria.					
Pericardial effusion	-	Asymptomatic effusion size small to moderate	Effusion with physiologic consequences	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by fluid collection within the pericardial sac, usually due to inflammation.					
Pericardial tamponade	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in intrapericardial pressure due to the collection of blood or fluid in the pericardium.					
Pericarditis	Asymptomatic, ECG or physical findings (e.g., rub) consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by irritation to the layers of the pericardium (the protective sac around the heart).					

Cardiac disorders

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Pulmonary valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characterized by a defect in pulmonary valve function or structure.					
Restrictive cardiomyopathy	-	-	Symptomatic heart failure or other cardiac symptoms, responsive to intervention	Refractory heart failure or other poorly controlled cardiac symptoms	Death
Definition: A disorder characterized by an inability of the ventricles to fill with blood because the myocardium (heart muscle) stiffens and loses its flexibility.					
Right ventricular dysfunction	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with mild to moderate activity or exertion	Severe symptoms, associated with hypoxemia, right heart failure; oxygen indicated	Life-threatening consequences; urgent intervention indicated (e.g., ventricular assist device); heart transplant indicated	Death
Definition: A disorder characterized by impairment of right ventricular function associated with low ejection fraction and a decrease in motility of the right ventricular wall.					
Sick sinus syndrome	Asymptomatic, intervention not indicated	Non-urgent intervention indicated	Severe, medically significant; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with alternating periods of bradycardia and atrial tachycardia accompanied by syncope, fatigue and dizziness.					
Sinus bradycardia	Asymptomatic, intervention not indicated	Symptomatic, medical intervention indicated	Severe, medically significant, medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate less than 60 beats per minute that originates in the sinus node.					
Sinus tachycardia	Asymptomatic, intervention not indicated	Symptomatic; non-urgent medical intervention indicated	Urgent medical intervention indicated	-	-
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates in the sinus node.					
Supraventricular tachycardia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates above the ventricles.					
Tricuspid valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characterized by a defect in tricuspid valve function or structure.					
Ventricular arrhythmia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia that originates in the ventricles.					
Ventricular fibrillation	-	-	-	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia without discernible QRS complexes due to rapid repetitive excitation of myocardial fibers without coordinated contraction of the ventricles.					
Ventricular tachycardia	-	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates distal to the bundle of His.					
Wolff-Parkinson-White syndrome	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with procedure	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the presence of an accessory conductive pathway between the atria and the ventricles that causes premature ventricular activation.					
Cardiac disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Congenital, familial and genetic disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Congenital, familial and genetic disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Ear and labyrinth disorders

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Ear pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the ear.					
External ear inflammation	External otitis with erythema or dry desquamation	External otitis with moist desquamation, edema, enhanced cerumen or discharge; tympanic membrane perforation; tympanostomy	External otitis with mastoiditis; stenosis or osteomyelitis; necrosis of soft tissue or bone	Urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation, swelling and redness to the outer ear and ear canal.					
External ear pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the external ear region.					
Hearing impaired	Adults enrolled on a Monitoring Program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift of 15 - 25 dB averaged at 2 contiguous test frequencies in at least one ear. Adults not enrolled in Monitoring Program: subjective change in hearing in the absence of documented hearing loss. Pediatric (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift >20 dB at 8 kHz in at least one ear.	Adults enrolled in Monitoring Program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift of >25 dB averaged at 2 contiguous test frequencies in at least one ear. Adults not enrolled in Monitoring Program: hearing loss but hearing aid or intervention not indicated; limiting instrumental ADL. Pediatric (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift >20 dB at 4 kHz and above in at least one ear.	Adults enrolled in Monitoring Program (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): Threshold shift of >25 dB averaged at 3 contiguous test frequencies in at least one ear; therapeutic intervention indicated. Adults not enrolled in Monitoring Program: hearing loss with hearing aid or intervention indicated; limiting self care ADL. Pediatric (on a 1, 2, 3, 4, 6 and 8 kHz audiogram): hearing loss sufficient to indicate therapeutic intervention, including hearing aids; threshold shift >20 dB at 3 kHz and above in at least one ear; additional speech-language related services indicated.	Adults: Decrease in hearing to profound bilateral loss (absolute threshold >80 dB HL at 2 kHz and above); non-servicable hearing. Pediatric: Audiologic indication for cochlear implant and additional speech-language related services indicated.	-
Definition: A disorder characterized by partial or complete loss of the ability to detect or understand sounds resulting from damage to ear structures.					
Middle ear inflammation	Serous otitis	Serous otitis, medical intervention indicated	Mastoiditis; necrosis of canal soft tissue or bone	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation (physiologic response to irritation), swelling and redness to the middle ear.					
Tinnitus	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by noise in the ears, such as ringing, buzzing, roaring or clicking.					
Vertigo	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation as if the external world were revolving around the patient (objective vertigo) or as if he himself were revolving in space (subjective vertigo).					
Vestibular disorder	-	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dizziness, imbalance, nausea, and vision problems.					
Ear and labyrinth disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Endocrine disorders

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Adrenal insufficiency	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder that occurs when the adrenal cortex does not produce enough of the hormone cortisol and in some cases, the hormone aldosterone. It may be due to a disorder of the adrenal cortex as in Addison's disease or primary adrenal insufficiency.					
Cushingoid	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms, medical intervention or hospitalization indicated	-	-
Definition: A disorder characterized by signs and symptoms that resemble Cushing's disease or syndrome: buffalo hump obesity, striations, adiposity, hypertension, diabetes, and osteoporosis, usually due to exogenous corticosteroids.					
Delayed puberty	-	No breast development by age 13 yrs for females; testes volume of <3 cc or no Tanner Stage 2 development by age 14.5 yrs for males	No breast development by age 14 yrs for females; no increase in testes volume or no Tanner Stage 2 by age 16 yrs for males; hormone replacement indicated	-	-
Definition: A disorder characterized by unusually late sexual maturity.					
Growth accelerated	-	>= +2 SD (standard deviation) above mid parental height or target height	-	-	-
Definition: A disorder characterized by greater growth than expected for age.					
Hyperparathyroidism	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by an increase in production of parathyroid hormone by the parathyroid glands. This results in hypercalcemia (abnormally high levels of calcium in the blood).					
Hyperthyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by excessive levels of thyroid hormone in the body. Common causes include an overactive thyroid gland or thyroid hormone overdose.					
Hypoparathyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; medical intervention or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a decrease in production of parathyroid hormone by the parathyroid glands.					
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a decrease in production of thyroid hormone by the thyroid gland.					
Precocious puberty	Physical signs of puberty with no biochemical markers for females <8 years and males <9 years	Physical signs and biochemical markers of puberty for females <8 years and males <9 years	-	-	-
Definition: A disorder characterized by unusually early development of secondary sexual features; the onset of sexual maturation begins usually before age 8 for girls and before age 9 for boys.					
Virilization	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by inappropriate masculinization occurring in a female or prepubertal male.					
Endocrine disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Eye disorders					
	Grade				
Adverse Event	1	2	3	4	5
Blurred vision	Intervention not indicated	Symptomatic; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by visual perception of unclear or fuzzy images.					
Cataract	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; moderate decrease in visual acuity (20/40 or better)	Symptomatic with marked decrease in visual acuity (worse than 20/40 but better than 20/200); operative intervention indicated (e.g., cataract surgery)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by partial or complete opacity of the crystalline lens of one or both eyes. This results in a decrease in visual acuity and eventual blindness if untreated.					
Conjunctivitis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; topical intervention indicated (e.g., antibiotics); limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by inflammation, swelling and redness to the conjunctiva of the eye.					
Corneal ulcer	-	Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL	Limiting self care ADL; declining vision (worse than 20/40 but better than 20/200)	Perforation or blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by an area of epithelial tissue loss on the surface of the cornea. It is associated with inflammatory cells in the cornea and anterior chamber.					
Dry eye	Asymptomatic; clinical or diagnostic observations only; mild symptoms relieved by lubricants	Symptomatic; multiple agents indicated; limiting instrumental ADL	Decrease in visual acuity (<20/40); limiting self care ADL	-	-
Definition: A disorder characterized by dryness of the cornea and conjunctiva.					
Extraocular muscle paresis	Asymptomatic; clinical or diagnostic observations only	Symptomatic; limiting instrumental ADL	Limiting self care ADL; disabling	-	-
Definition: A disorder characterized by incomplete paralysis of an extraocular muscle.					
Eye pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the eye.					
Eyelid function disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; nonoperative intervention indicated; limiting instrumental ADL	Limiting self care ADL; operative intervention indicated	-	-
Definition: A disorder characterized by impaired eyelid function.					
Flashing lights	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by a sudden or brief burst of light.					
Floaters	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by an individual seeing spots before their eyes. The spots are shadows of opaque cell fragments in the vitreous humor or lens.					
Glaucoma	Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual field deficit	EIOP causing early visual field deficits; multiple topical or oral agents indicated; limiting instrumental ADL	EIOP causing marked visual field deficits (e.g., involving both superior and inferior visual fields); operative intervention indicated; limiting self care ADL	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by an increase in pressure in the eyeball due to obstruction of the aqueous humor outflow.					
Keratitis	-	Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL	Decline in vision (worse than 20/40 but better than 20/200); limiting self care ADL	Perforation or blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by inflammation to the cornea of the eye.					
Night blindness	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by an inability to see clearly in dim light.					

Eye disorders

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Optic nerve disorder	Asymptomatic; clinical or diagnostic observations only	Limiting vision of the affected eye (20/40 or better)	Limiting vision in the affected eye (worse than 20/40 but better than 20/200)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by involvement of the optic nerve (second cranial nerve).					
Papilledema	Asymptomatic; no visual field defects	Symptomatic decline in vision; visual field defect present sparing the central 20 degrees	Marked visual field defect (worse than 20/40 but better than 20/200)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by swelling around the optic disc.					
Photophobia	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by fear and avoidance of light.					
Retinal detachment	Asymptomatic	Exudative and visual acuity 20/40 or better	Rhegmatogenous or exudative detachment; operative intervention indicated; decline in vision (worse than 20/40 but better than 20/200)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by the separation of the inner retina layers from the underlying pigment epithelium.					
Retinal tear	-	Laser therapy or pneumopexy indicated	Vitroretinal surgical repair indicated	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by a small laceration of the retina, this occurs when the vitreous separates from the retina. Symptoms include flashes and floaters.					
Retinal vascular disorder	-	Topical medication indicated	Intravitreal medication; operative intervention indicated	-	-
Definition: A disorder characterized by pathological retinal blood vessels that adversely affects vision.					
Retinopathy	Asymptomatic; clinical or diagnostic observations only	Symptomatic with moderate decrease in visual acuity (20/40 or better); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (worse than 20/40); disabling; limiting self care ADL	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder involving the retina.					
Scleral disorder	Asymptomatic; clinical or diagnostic observations only	Symptomatic, limiting instrumental ADL; moderate decrease in visual acuity (20/40 or better)	Symptomatic, limiting self care ADL; marked decrease in visual acuity (worse than 20/40)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by involvement of the sclera of the eye.					
Uveitis	Asymptomatic; clinical or diagnostic observations only	Anterior uveitis; medical intervention indicated	Posterior or pan-uveitis	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by inflammation to the uvea of the eye.					
Vitreous hemorrhage	Asymptomatic or mild symptoms; clinical or diagnostic observations only	Symptomatic; limiting instrumental ADL	Limiting self care ADL; vitrectomy indicated	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized by blood extravasation into the vitreous humor.					
Watering eyes	Intervention not indicated	Intervention indicated	Operative intervention indicated	-	-
Definition: A disorder of excessive tearing in the eyes; it can be caused by overproduction of tears or impaired drainage of the tear duct.					
Eye disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately sight-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Sight-threatening consequences; urgent intervention indicated; blindness (20/200 or worse) in the affected eye	-

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Abdominal distension	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe discomfort; limiting self care ADL	-	-
Definition: A disorder characterized by swelling of the abdomen.					
Abdominal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the abdominal region.					
Anal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the opening in the anal canal to the perianal skin.					
Anal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the anal region.					
Anal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the mucous membrane of the anus.					
Anal necrosis	-	-	TPN or hospitalization indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the anal region.					
Anal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the anal region.					
Anal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Symptomatic and severely altered GI function; non-emergent operative intervention indicated; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the anal canal.					
Anal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the anal canal.					
Ascites	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by accumulation of serous or hemorrhagic fluid in the peritoneal cavity.					
Bloating	No change in bowel function or oral intake	Symptomatic, decreased oral intake; change in bowel function	-	-	-
Definition: A disorder characterized by subject-reported feeling of uncomfortable fullness of the abdomen.					
Cecal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the cecum.					
Cheilitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; intervention indicated	-	-
Definition: A disorder characterized by inflammation of the lip.					

Gastrointestinal disorders

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the colon.					
Colonic fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; bowel rest, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the large intestine and another organ or anatomic site.					
Colonic hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the colon.					
Colonic obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Hospitalization indicated; elective operative intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the colon.					
Colonic perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the colonic wall.					
Colonic stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the colon.					
Colonic ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the colon.					
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by irregular and infrequent or difficult evacuation of the bowels.					
Dental caries	One or more dental caries, not involving the root	Dental caries involving the root	Dental caries resulting in pulpitis or periapical abscess or resulting in tooth loss	-	-
Definition: A disorder characterized by the decay of a tooth, in which it becomes softened, discolored and/or porous.					
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by frequent and watery bowel movements.					
Dry mouth	Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1 ml/min	-	-
Definition: A disorder characterized by reduced salivary flow in the oral cavity.					

Gastrointestinal disorders

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Duodenal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the duodenum and another organ or anatomic site.					
Duodenal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the duodenum.					
Duodenal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Hospitalization or elective operative intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of stomach contents through the duodenum.					
Duodenal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the duodenal wall.					
Duodenal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the duodenum.					
Duodenal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the duodenal wall.					
Dyspepsia	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	-
Definition: A disorder characterized by an uncomfortable, often painful feeling in the stomach, resulting from impaired digestion. Symptoms include burning stomach, bloating, heartburn, nausea and vomiting.					
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by difficulty in swallowing.					
Enterocolitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe or persistent abdominal pain; fever; ileus; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the small and large intestines.					
Enterovesical fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; noninvasive intervention indicated	Severe, medically significant; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the urinary bladder and the intestine.					
Esophageal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the esophagus and another organ or anatomic site.					
Esophageal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the esophagus.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Esophageal necrosis	-	-	Inability to aliment adequately by GI tract; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the esophageal wall.					
Esophageal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the contents in the esophagus.					
Esophageal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the esophageal region.					
Esophageal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the wall of the esophagus.					
Esophageal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the esophagus.					
Esophageal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the esophageal wall.					
Esophageal varices hemorrhage	-	Self-limited; intervention not indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from esophageal varices.					
Esophagitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered eating/swallowing; oral supplements indicated	Severely altered eating/swallowing; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the esophageal wall.					
Fecal incontinence	Occasional use of pads required	Daily use of pads required	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by inability to control the escape of stool from the rectum.					
Flatulence	Mild symptoms; intervention not indicated	Moderate; persistent; psychosocial sequelae	-	-	-
Definition: A disorder characterized by a state of excessive gas in the alimentary canal.					
Gastric fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; bowel rest; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the stomach and another organ or anatomic site.					
Gastric hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the gastric wall.					
Gastric necrosis	-	-	Inability to aliment adequately by GI tract; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the gastric wall.					

Gastrointestinal disorders

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Gastric perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the stomach wall.					
Gastric stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the stomach.					
Gastric ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the stomach.					
Gastritis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated	Severely altered eating or gastric function; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the stomach.					
Gastroesophageal reflux disease	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	-
Definition: A disorder characterized by reflux of the gastric and/or duodenal contents into the distal esophagus. It is chronic in nature and usually caused by incompetence of the lower esophageal sphincter, and may result in injury to the esophageal mucosal. Symptoms include heartburn and acid indigestion.					
Gastrointestinal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between any part of the gastrointestinal system and another organ or anatomic site.					
Gastrointestinal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the gastrointestinal region.					
Gastroparesis	Mild nausea, early satiety and bloating, able to maintain caloric intake on regular diet	Moderate symptoms; able to maintain nutrition with dietary and lifestyle modifications; may need pharmacologic intervention	Weight loss; refractory to medical intervention; unable to maintain nutrition orally	-	-
Definition: A disorder characterized by an incomplete paralysis of the muscles of the stomach wall resulting in delayed emptying of the gastric contents into the small intestine.					
Gingival pain	Mild pain	Moderate pain interfering with oral intake	Severe pain; inability to aliment orally	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the gingival region.					
Hemorrhoidal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the hemorrhoids.					
Hemorrhoids	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; banding or medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	-	-
Definition: A disorder characterized by the presence of dilated veins in the rectum and surrounding area.					
Ileal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the ileum and another organ or anatomic site.					
Ileal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the ileal wall.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Ileal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the ileum.					
Ileal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the ileal wall.					
Ileal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the ileum.					
Ileal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the ileum.					
Ileus	-	Symptomatic; altered GI function; bowel rest indicated	Severely altered GI function; TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by failure of the ileum to transport intestinal contents.					
Intra-abdominal hemorrhage	-	Medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding in the abdominal cavity.					
Jejunal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the jejunum and another organ or anatomic site.					
Jejunal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the jejunal wall.					
Jejunal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the jejunum.					
Jejunal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the jejunal wall.					
Jejunal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the jejunum.					
Jejunal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the jejunum.					
Lip pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort of the lip.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Lower gastrointestinal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the lower gastrointestinal tract (small intestine, large intestine, and anus).					
Malabsorption	-	Altered diet; oral intervention indicated	Inability to aliment adequately; TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inadequate absorption of nutrients in the small intestine. Symptoms include abdominal marked discomfort, bloating and diarrhea.					
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the oral mucosal.					
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Definition: A disorder characterized by a queasy sensation and/or the urge to vomit.					
Obstruction gastric	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the contents in the stomach.					
Oral cavity fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the oral cavity and another organ or anatomic site.					
Oral dysesthesia	Mild discomfort; not interfering with oral intake	Moderate pain; interfering with oral intake	Disabling pain; tube feeding or TPN indicated	-	-
Definition: A disorder characterized by a burning or tingling sensation on the lips, tongue or entire mouth.					
Oral hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the mouth.					
Oral pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the mouth, tongue or lips.					
Pancreatic duct stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the pancreatic duct.					
Pancreatic fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the pancreas and another organ or anatomic site.					
Pancreatic hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the pancreas.					
Pancreatic necrosis	-	-	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the pancreas.					
Pancreatitis	-	Enzyme elevation or radiologic findings only	Severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated	Death

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by inflammation of the pancreas.					
Periodontal disease	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	-	-
Definition: A disorder in the gingival tissue around the teeth.					
Peritoneal necrosis	-	-	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the peritoneum.					
Proctitis	Rectal discomfort, intervention not indicated	Symptoms (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL	Severe symptoms; fecal urgency or stool incontinence; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the rectum.					
Rectal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the rectum and another organ or anatomic site.					
Rectal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the rectal wall and discharged from the anus.					
Rectal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the mucous membrane of the rectum.					
Rectal necrosis	-	-	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the rectal wall.					
Rectal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the rectum.					
Rectal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the rectal region.					
Rectal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the rectal wall.					
Rectal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the rectum.					
Rectal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function (e.g. altered dietary habits, vomiting, diarrhea)	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the rectum.					

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Retroperitoneal hemorrhage	-	Self-limited; intervention indicated	Transfusion, medical, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the retroperitoneal area.					
Salivary duct inflammation	Slightly thickened saliva; slightly altered taste (e.g., metallic)	Thick, ropy, sticky saliva; markedly altered taste; alteration in diet indicated; secretion-induced symptoms; limiting instrumental ADL	Acute salivary gland necrosis; severe secretion-induced symptoms (e.g., thick saliva/oral secretions or gagging); tube feeding or TPN indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the salivary duct.					
Salivary gland fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; tube feeding indicated	Severely altered GI function; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between a salivary gland and another organ or anatomic site.					
Small intestinal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe pain; interfering with oral intake; tube feeding, TPN or hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the mucous membrane of the small intestine.					
Small intestinal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; elective operative intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents.					
Small intestinal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the small intestine wall.					
Small intestinal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Symptomatic and severely altered GI function; tube feeding, TPN or hospitalization indicated; non-emergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the small intestine.					
Small intestine ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self care ADL; disabling	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the small intestine.					
Stomach pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the stomach.					
Tooth development disorder	Asymptomatic; hypoplasia of tooth or enamel	Impairment correctable with oral surgery	Maldevelopment with impairment not surgically correctable; disabling	-	-
Definition: A disorder characterized by a pathological process of the teeth occurring during tooth development.					
Tooth discoloration	Surface stains	-	-	-	-
Definition: A disorder characterized by a change in tooth hue or tint.					
Toothache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the tooth.					

Gastrointestinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Typhlitis	-	-	Symptomatic (e.g., abdominal pain, fever, change in bowel habits with ileus); peritoneal signs	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the cecum.					
Upper gastrointestinal hemorrhage	Mild; intervention not indicated	Moderate symptoms; medical intervention or minor cauterization indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the upper gastrointestinal tract (oral cavity, pharynx, esophagus, and stomach).					
Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.					
Gastrointestinal disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

General disorders and administration site conditions					
	Grade				
Adverse Event	1	2	3	4	5
Chills	Mild sensation of cold; shivering; chattering of teeth	Moderate tremor of the entire body; narcotics indicated	Severe or prolonged, not responsive to narcotics	-	-
Definition: A disorder characterized by a sensation of cold that often marks a physiologic response to sweating after a fever.					
Death neonatal	-	-	-	-	Death
Definition: A disorder characterized by cessation of life occurring during the first 28 days of life.					
Death NOS	-	-	-	-	Death
Definition: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.					
Edema face	Localized facial edema	Moderate localized facial edema; limiting instrumental ADL	Severe swelling; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation in facial tissues.					
Edema limbs	5 - 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection	>10 - 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	>30% inter-limb discrepancy in volume; gross deviation from normal anatomic contour; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation in the upper or lower extremities.					
Edema trunk	Swelling or obscuration of anatomic architecture on close inspection	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	Gross deviation from normal anatomic contour; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation in the trunk area.					
Facial pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the face.					
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	-	-
Definition: A disorder characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities.					
Fever	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)	>39.0 - 40.0 degrees C (102.3 - 104.0 degrees F)	>40.0 degrees C (>104.0 degrees F) for <=24 hrs	>40.0 degrees C (>104.0 degrees F) for >24 hrs	Death
Definition: A disorder characterized by elevation of the body's temperature above the upper limit of normal.					
Flu like symptoms	Mild flu-like symptoms present	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a group of symptoms similar to those observed in patients with the flu. It includes fever, chills, body aches, malaise, loss of appetite and dry cough.					
Gait disturbance	Mild change in gait (e.g., wide-based, limping or hobbling)	Moderate change in gait (e.g., wide-based, limping or hobbling); assistive device indicated; limiting instrumental ADL	Disabling; limiting self care ADL	-	-
Definition: A disorder characterized by walking difficulties.					
Hypothermia	-	35 - >32 degrees C; 95 - >89.6 degrees F	32 - >28 degrees C; 89.6 - >82.4 degrees F	<=28 degrees C; 82.4 degrees F; life-threatening consequences (e.g., coma, hypotension, pulmonary edema, acidemia, ventricular fibrillation)	Death
Definition: A disorder characterized by an abnormally low body temperature. Treatment is required when the body temperature is 35C (95F) or below.					

General disorders and administration site conditions					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Infusion related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.					
Infusion site extravasation	-	Erythema with associated symptoms (e.g., edema, pain, induration, phlebitis)	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by leakage of a pharmacologic or a biologic substance from the infusion site into the surrounding tissue. Signs and symptoms include induration, erythema, swelling, burning sensation and marked discomfort at the infusion site.					
Injection site reaction	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection.					
Irritability	Mild; easily consolable	Moderate; limiting instrumental ADL; increased attention indicated	Severe abnormal or excessive response; limiting self care ADL; inconsolable	-	-
Definition: A disorder characterized by an abnormal responsiveness to stimuli or physiological arousal; may be in response to pain, fright, a drug, an emotional situation or a medical condition.					
Localized edema	Localized to dependent areas, no disability or functional impairment	Moderate localized edema and intervention indicated; limiting instrumental ADL	Severe localized edema and intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation at a specific anatomic site.					
Malaise	Uneasiness or lack of well being	Uneasiness or lack of well being; limiting instrumental ADL	-	-	-
Definition: A disorder characterized by a feeling of general discomfort or uneasiness, an out-of-sorts feeling.					
Multi-organ failure	-	-	Shock with azotemia and acid-base disturbances; significant coagulation abnormalities	Life-threatening consequences (e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic acidosis)	Death
Definition: A disorder characterized by progressive deterioration of the lungs, liver, kidney and clotting mechanisms.					
Neck edema	Asymptomatic localized neck edema	Moderate neck edema; slight obliteration of anatomic landmarks; limiting instrumental ADL	Generalized neck edema (e.g., difficulty in turning neck); limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to an accumulation of excessive fluid in the neck.					
Non-cardiac chest pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by discomfort in the chest unrelated to a heart disorder.					
Pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by the sensation of marked discomfort, distress or agony.					
Sudden death NOS	-	-	-	-	Death
Definition: An unexpected cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.					
General disorders and administration site conditions - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Hepatobiliary disorders					
	Grade				
Adverse Event	1	2	3	4	5
Bile duct stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; IV fluids indicated <24 hrs	Severely altered GI function; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the bile duct.					
Biliary fistula	-	Symptomatic and intervention not indicated	Severely altered GI function; TPN indicated; endoscopic intervention indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the bile ducts and another organ or anatomic site.					
Cholecystitis	-	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation involving the gallbladder. It may be associated with the presence of gallstones.					
Gallbladder fistula	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Symptomatic or severely altered GI function; TPN indicated; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the gallbladder and another organ or anatomic site.					
Gallbladder necrosis	-	-	-	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the gallbladder.					
Gallbladder obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; tube feeding, TPN or hospitalization indicated; non-emergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the contents of the gallbladder.					
Gallbladder pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the gallbladder region.					
Gallbladder perforation	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the gallbladder wall.					
Hepatic failure	-	-	Asterixis; mild encephalopathy; limiting self care ADL	Moderate to severe encephalopathy; coma; life-threatening consequences	Death
Definition: A disorder characterized by the inability of the liver to metabolize chemicals in the body. Laboratory test results reveal abnormal plasma levels of ammonia, bilirubin, lactic dehydrogenase, and alkaline phosphatase.					
Hepatic hemorrhage	Mild; intervention not indicated	Symptomatic; medical intervention indicated	Transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the liver.					
Hepatic necrosis	-	-	-	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the hepatic parenchyma.					
Hepatic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the liver region.					
Perforation bile duct	-	-	Radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the wall of the extrahepatic or intrahepatic bile duct.					

Hepatobiliary disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Portal hypertension	-	Decreased portal vein flow	Reversal/retrograde portal vein flow; associated with varices and/or ascites	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in blood pressure in the portal venous system.					
Portal vein thrombosis	-	Intervention not indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the formation of a thrombus (blood clot) in the portal vein.					
Hepatobiliary disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Immune system disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Allergic reaction	Transient flushing or rash, drug fever <38 degrees C (<100.4 degrees F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.					
Autoimmune disorder	Asymptomatic; serologic or other evidence of autoimmune reaction, with normal organ function; intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Autoimmune reactions involving major organ (e.g., colitis, anemia, myocarditis, kidney)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder resulting from loss of function or tissue destruction of an organ or multiple organs, arising from humoral or cellular immune responses of the individual to his own tissue constituents.					
Cytokine release syndrome	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)	Life-threatening consequences; pressor or ventilatory support indicated	Death
Definition: A disorder characterized by nausea, headache, tachycardia, hypotension, rash, and shortness of breath; it is caused by the release of cytokines from the cells.					
Serum sickness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate arthralgia; fever, rash, urticaria, antihistamines indicated	Severe arthralgia or arthritis; extensive rash; steroids or IV fluids indicated	Life-threatening consequences; pressor or ventilatory support indicated	Death
Definition: A disorder characterized by a delayed-type hypersensitivity reaction to foreign proteins derived from an animal serum. It occurs approximately six to twenty-one days following the administration of the foreign antigen. Symptoms include fever, arthralgias, myalgias, skin eruptions, lymphadenopathy, chest marked discomfort and dyspnea.					
Immune system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Infections and infestations					
	Grade				
Adverse Event	1	2	3	4	5
Abdominal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the abdominal cavity.					
Anorectal infection	Localized; local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the anal area and the rectum.					
Appendicitis	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation to the vermiform appendix caused by a pathogenic agent.					
Appendicitis perforated	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation to the vermiform appendix caused by a pathogenic agent with gangrenous changes resulting in the rupture of the appendiceal wall. The appendiceal wall rupture causes the release of inflammatory and bacterial contents from the appendiceal lumen into the abdominal cavity.					
Arteritis infective	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving an artery.					
Biliary tract infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the biliary tract.					
Bladder infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the bladder.					
Bone infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the bones.					
Breast infection	-	Local infection with moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	Severe infection; axillary adenitis; IV antibacterial, antifungal, or antiviral intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the breast.					
Bronchial infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the bronchi.					
Catheter related infection	-	Localized; local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process that arises secondary to catheter use.					
Cecal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

Infections and infestations					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by an infectious process involving the cecum.					
Cervicitis infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the uterine cervix.					
Conjunctivitis infective	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the conjunctiva. Clinical manifestations include pink or red color in the eyes.					
Corneal infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the cornea.					
Cranial nerve infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a cranial nerve.					
Device related infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the use of a medical device.					
Duodenal infection	-	Moderate symptoms; medical intervention indicated (e.g., oral antibiotics)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the duodenum.					
Encephalitis infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; severe changes in mental status; self-limited seizure activity; focal neurologic abnormalities	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the brain tissue.					
Encephalomyelitis infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the brain and spinal cord tissues.					
Endocarditis infective	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the endocardial layer of the heart.					
Endophthalmitis	-	Local intervention indicated	Systemic intervention or hospitalization indicated	Blindness (20/200 or worse)	-
Definition: A disorder characterized by an infectious process involving the internal structures of the eye.					

Infections and infestations

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Enterocolitis infectious	-	Passage of >3 unformed stools per 24 hrs or duration of illness >48 hrs; moderate abdominal pain	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated; profuse watery diarrhea with signs of hypovolemia; bloody diarrhea; fever; severe abdominal pain; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the small and large intestines.					
Esophageal infection	-	Local intervention indicated (e.g., oral antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the esophagus.					
Eye infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated; enucleation	Death
Definition: A disorder characterized by an infectious process involving the eye.					
Gallbladder infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the gallbladder.					
Gum infection	Local therapy indicated (swish and swallow)	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the gums.					
Hepatic infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the liver.					
Hepatitis viral	Asymptomatic, treatment not indicated	-	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis; reactivation of chronic hepatitis	Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma)	Death
Definition: A disorder characterized by a viral pathologic process involving the liver parenchyma.					
Infective myositis	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the skeletal muscles.					
Joint infection	-	Localized; local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); needle aspiration indicated (single or multiple)	Arthroscopic intervention indicated (e.g., drainage) or arthrotomy (e.g., open surgical drainage)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a joint.					
Kidney infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the kidney.					

Infections and infestations

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Laryngitis	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an inflammatory process involving the larynx.					
Lip infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	-	-
Definition: A disorder characterized by an infectious process involving the lips.					
Lung infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the lungs.					
Lymph gland infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the lymph nodes.					
Mediastinal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the mediastinum.					
Meningitis	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated; focal neurologic deficit	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation of the meninges of the brain and/or spinal cord.					
Mucosal infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a mucosal surface.					
Nail infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	-	-
Definition: A disorder characterized by an infectious process involving the nail.					
Otitis externa	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the outer ear and ear canal. Contributory factors include excessive water exposure (swimmer's ear infection) and cuts in the ear canal. Symptoms include fullness, itching, swelling and marked discomfort in the ear and ear drainage.					
Otitis media	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the middle ear.					
Ovarian infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the ovary.					

Infections and infestations					
	Grade				
Adverse Event	1	2	3	4	5
Pancreas infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the pancreas.					
Papulopustular rash	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	Death
Definition: A disorder characterized by an eruption consisting of papules (a small, raised pimple) and pustules (a small pus filled blister), typically appearing in face, scalp, and upper chest and back Unlike acne, this rash does not present with whiteheads or blackheads, and can be symptomatic, with itchy or tender lesions.					
Paronychia	Nail fold edema or erythema; disruption of the cuticle	Localized intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Surgical intervention or IV antibiotics indicated; limiting self care ADL	-	-
Definition: A disorder characterized by an infectious process involving the soft tissues around the nail.					
Pelvic infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the pelvic cavity.					
Penile infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the penis.					
Periorbital infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the orbit of the eye.					
Peripheral nerve infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the peripheral nerves.					
Peritoneal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the peritoneum.					
Pharyngitis	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the throat.					
Phlebitis infective	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

Infections and infestations					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by an infectious process involving the vein. Clinical manifestations include erythema, marked discomfort, swelling, and induration along the course of the infected vein.					
Pleural infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the pleura.					
Prostate infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the prostate gland.					
Rash pustular	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	-	-
Definition: A disorder characterized by a circumscribed and elevated skin lesion filled with pus.					
Rhinitis infective	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	-	-	-
Definition: A disorder characterized by an infectious process involving the nasal mucosal.					
Salivary gland infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the salivary gland.					
Scrotal infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the scrotum.					
Sepsis	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the presence of pathogenic microorganisms in the blood stream that cause a rapidly progressing systemic reaction that may lead to shock.					
Sinusitis	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the mucous membranes of the paranasal sinuses.					
Skin infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the skin.					
Small intestine infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the small intestine.					
Soft tissue infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving soft tissues.					
Splenic infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

Infections and infestations					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by an infectious process involving the spleen.					
Stoma site infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a stoma (surgically created opening on the surface of the body).					
Tooth infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a tooth.					
Tracheitis	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the trachea.					
Upper respiratory infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the upper respiratory tract (nose, paranasal sinuses, pharynx, larynx, or trachea).					
Urethral infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the urethra.					
Urinary tract infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the urinary tract, most commonly the bladder and the urethra.					
Uterine infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the endometrium. It may extend to the myometrium and parametrial tissues.					
Vaginal infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the vagina.					
Vulval infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the vulva.					
Wound infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the wound.					
Infections and infestations - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Injury, poisoning and procedural complications

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Ankle fracture	Mild; non-surgical intervention indicated	Limiting instrumental ADL; operative intervention indicated	Limiting self care ADL; elective surgery indicated	-	-
Definition: A finding of damage to the ankle joint characterized by a break in the continuity of the ankle bone. Symptoms include marked discomfort, swelling and difficulty moving the affected leg and foot.					
Aortic injury	-	-	Severe symptoms; limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to the aorta.					
Arterial injury	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); repair or revision not indicated	Severe symptoms; limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to an artery.					
Biliary anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of bile due to breakdown of a biliary anastomosis (surgical connection of two separate anatomic structures).					
Bladder anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of urine due to breakdown of a bladder anastomosis (surgical connection of two separate anatomic structures).					
Bruising	Localized or in a dependent area	Generalized	-	-	-
Definition: A finding of injury of the soft tissues or bone characterized by leakage of blood into surrounding tissues.					
Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
Definition: A finding of impaired integrity to the anatomic site of an adverse thermal reaction. Burns can be caused by exposure to chemicals, direct heat, electricity, flames and radiation. The extent of damage depends on the length and intensity of exposure and time until provision of treatment.					
Dermatitis radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death
Definition: A finding of cutaneous inflammatory reaction occurring as a result of exposure to biologically effective levels of ionizing radiation.					
Esophageal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of an esophageal anastomosis (surgical connection of two separate anatomic structures).					
Fall	Minor with no resultant injuries; intervention not indicated	Symptomatic; noninvasive intervention indicated	Hospitalization indicated	-	-
Definition: A finding of sudden movement downward, usually resulting in injury.					
Fallopian tube anastomotic leak	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a fallopian tube anastomosis (surgical connection of two separate anatomic structures).					
Fallopian tube perforation	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated (e.g., organ resection)	Death
Definition: A finding of rupture of the fallopian tube wall.					
Fracture	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic but non-displaced; immobilization indicated	Severe symptoms; displaced or open wound with bone exposure; disabling; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of traumatic injury to the bone in which the continuity of the bone is broken.					

Injury, poisoning and procedural complications					
	Grade				
Adverse Event	1	2	3	4	5
Gastric anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a gastric anastomosis (surgical connection of two separate anatomic structures).					
Gastrointestinal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a gastrointestinal anastomosis (surgical connection of two separate anatomic structures).					
Gastrointestinal stoma necrosis	-	Superficial necrosis; intervention not indicated	Severe symptoms; hospitalization or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of a necrotic process occurring in the gastrointestinal tract stoma.					
Hip fracture	-	Hairline fracture; mild pain; limiting instrumental ADL; non-surgical intervention indicated	Severe pain; hospitalization or intervention indicated for pain control (e.g., traction); operative intervention indicated	Life-threatening consequences; symptoms associated with neurovascular compromise	-
Definition: A finding of traumatic injury to the hip in which the continuity of either the femoral head, femoral neck, intertrochanteric or subtrochanteric regions is broken.					
Injury to carotid artery	-	-	Severe symptoms; limiting self care ADL (e.g., transient cerebral ischemia); repair or revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the carotid artery.					
Injury to inferior vena cava	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the inferior vena cava.					
Injury to jugular vein	-	-	Symptomatic limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the jugular vein.					
Injury to superior vena cava	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; repair or revision not indicated	Severe symptoms; limiting self care ADL; disabling; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to the superior vena cava.					
Intestinal stoma leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of contents from an intestinal stoma (surgically created opening on the surface of the body).					
Intestinal stoma obstruction	-	Self-limited; intervention not indicated	Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of blockage of the normal flow of the contents of the intestinal stoma.					
Intestinal stoma site bleeding	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of blood leakage from the intestinal stoma.					
Intraoperative arterial injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to an artery during a surgical procedure.					
Intraoperative breast injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death

Injury, poisoning and procedural complications					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A finding of damage to the breast parenchyma during a surgical procedure.					
Intraoperative cardiac injury	-	-	Primary repair of injured organ/structure indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the heart during a surgical procedure.					
Intraoperative ear injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection of injured organ/structure indicated; disabling (e.g., impaired hearing; impaired balance)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the ear during a surgical procedure.					
Intraoperative endocrine injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the endocrine gland during a surgical procedure.					
Intraoperative gastrointestinal injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the gastrointestinal system during a surgical procedure.					
Intraoperative head and neck injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the head and neck during a surgical procedure.					
Intraoperative hemorrhage	-	-	Postoperative radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of uncontrolled bleeding during a surgical procedure.					
Intraoperative hepatobiliary injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the hepatic parenchyma and/or biliary tract during a surgical procedure.					
Intraoperative musculoskeletal injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the musculoskeletal system during a surgical procedure.					
Intraoperative neurological injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the nervous system during a surgical procedure.					
Intraoperative ocular injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the eye during a surgical procedure.					
Intraoperative renal injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the kidney during a surgical procedure.					
Intraoperative reproductive tract injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death

Injury, poisoning and procedural complications					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A finding of damage to the reproductive organs during a surgical procedure.					
Intraoperative respiratory injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the respiratory system during a surgical procedure.					
Intraoperative skin injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the skin during a surgical procedure.					
Intraoperative splenic injury	-	Primary repair of injured organ/structure indicated	Resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the spleen during a surgical procedure.					
Intraoperative urinary injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the urinary system during a surgical procedure.					
Intraoperative venous injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to a vein during a surgical procedure.					
Kidney anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of urine due to breakdown of a kidney anastomosis (surgical connection of two separate anatomic structures).					
Large intestinal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of an anastomosis (surgical connection of two separate anatomic structures) in the large intestine.					
Pancreatic anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a pancreatic anastomosis (surgical connection of two separate anatomic structures).					
Pharyngeal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a pharyngeal anastomosis (surgical connection of two separate anatomic structures).					
Postoperative hemorrhage	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; radiologic, endoscopic, or operative intervention indicated	Transfusion indicated of >=2 units (10 cc/kg for pediatrics) pRBCs beyond protocol specification; urgent radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of bleeding occurring after a surgical procedure.					
Postoperative thoracic procedure complication	-	Extubated within 24 - 72 hrs postoperatively	Extubated >72 hrs postoperatively, but before tracheostomy indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A finding of a previously undocumented problem that occurs after a thoracic procedure.					
Prolapse of intestinal stoma	Asymptomatic; reducible	Recurrent after manual reduction; local irritation or stool leakage; difficulty to fit appliance; limiting instrumental ADL	Severe symptoms; elective operative intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death

Injury, poisoning and procedural complications

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A finding of protrusion of the intestinal stoma (surgically created opening on the surface of the body) above the abdominal surface.					
Prolapse of urostomy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Local care or maintenance; minor revision indicated	Dysfunctional stoma; elective operative intervention or major stomal revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of displacement of the urostomy.					
Radiation recall reaction (dermatologic)	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death
Definition: A finding of acute skin inflammatory reaction caused by drugs, especially chemotherapeutic agents, for weeks or months following radiotherapy. The inflammatory reaction is confined to the previously irradiated skin and the symptoms disappear after the removal of the pharmaceutical agent.					
Rectal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a rectal anastomosis (surgical connection of two separate anatomic structures).					
Seroma	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; simple aspiration indicated	Symptomatic, elective radiologic or operative intervention indicated	-	-
Definition: A finding of tumor-like collection of serum in the tissues.					
Small intestinal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of an anastomosis (surgical connection of two separate anatomic structures) in the small bowel.					
Spermatic cord anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a spermatic cord anastomosis (surgical connection of two separate anatomic structures).					
Spinal fracture	Mild back pain; nonprescription analgesics indicated	Moderate back pain; prescription analgesics indicated; limiting instrumental ADL	Severe back pain; hospitalization or intervention indicated for pain control (e.g., vertebroplasty); limiting self care ADL; disability	Life-threatening consequences; symptoms associated with neurovascular compromise	Death
Definition: A finding of traumatic injury to the spine in which the continuity of a vertebral bone is broken.					
Stenosis of gastrointestinal stoma	-	Symptomatic; IV fluids indicated <24 hrs; manual dilation at bedside	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of narrowing of the gastrointestinal stoma (surgically created opening on the surface of the body).					
Stomal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the jejunal mucosal surface close to the anastomosis site following a gastroenterostomy procedure.					
Tracheal hemorrhage	Minimal bleeding identified on clinical or diagnostic exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of bleeding from the trachea.					
Tracheal obstruction	Partial asymptomatic obstruction on examination (e.g., visual, radiologic or endoscopic)	Symptomatic (e.g., noisy airway breathing), no respiratory distress; medical intervention indicated (e.g., steroids); limiting instrumental ADL	Stridor; radiologic or endoscopic intervention indicated (e.g., stent, laser); limiting self care ADL	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A finding of blockage of the lumen of the trachea.					

Injury, poisoning and procedural complications

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Tracheostomy site bleeding	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of blood leakage from the tracheostomy site.					
Ureteric anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a ureteral anastomosis (surgical connection of two separate anatomic structures).					
Urethral anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a urethral anastomosis (surgical connection of two separate anatomic structures).					
Urostomy leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of contents from a urostomy.					
Urostomy obstruction	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; dilation or endoscopic repair or stent placement indicated	Altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); elective operative intervention indicated	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Definition: A finding of blockage of the urostomy.					
Urostomy site bleeding	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of bleeding from the urostomy site.					
Urostomy stenosis	-	Symptomatic but no hydronephrosis, no sepsis or no renal dysfunction; dilation or endoscopic repair or stent placement indicated	Symptomatic (e.g., hydronephrosis, or renal dysfunction); elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of narrowing of the opening of a urostomy.					
Uterine anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a uterine anastomosis (surgical connection of two separate anatomic structures).					
Uterine perforation	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the uterine wall.					
Vaginal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a vaginal anastomosis (surgical connection of two separate anatomic structures).					
Vas deferens anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a vas deferens anastomosis (surgical connection of two separate anatomic structures).					
Vascular access complication	-	Device dislodgement, blockage, leak, or malposition; device replacement indicated	Deep vein or cardiac thrombosis; intervention indicated (e.g., anticoagulation, lysis, filter, invasive procedure)	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Definition: A finding of a previously undocumented problem related to the vascular access site.					

Injury, poisoning and procedural complications					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Venous injury	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); repair or revision not indicated	Severe symptoms; limiting self care ADL; repair or revision indicated; disabling	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to a vein.					
Wound complication	Incisional separation of <=25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound; local care indicated	Hernia without evidence of strangulation; fascial disruption/dehiscence; primary wound closure or revision by operative intervention indicated	Hernia with evidence of strangulation; major reconstruction flap, grafting, resection, or amputation indicated	Death
Definition: A finding of development of a new problem at the site of an existing wound.					
Wound dehiscence	Incisional separation of <=25% of wound, no deeper than superficial fascia	Incisional separation >25% of wound with local care; asymptomatic hernia or symptomatic hernia without evidence of strangulation	Fascial disruption or dehiscence without evisceration; primary wound closure or revision by operative intervention indicated	Life-threatening consequences; symptomatic hernia with evidence of strangulation; fascial disruption with evisceration; major reconstruction flap, grafting, resection, or amputation indicated	Death
Definition: A finding of separation of the approximated margins of a surgical wound.					
Wrist fracture	Mild; non-surgical intervention indicated	Limiting instrumental ADL; operative intervention indicated	Limiting self care ADL; elective surgery indicated	-	-
Definition: A finding of traumatic injury to the wrist joint in which the continuity of a wrist bone is broken.					
Injury, poisoning and procedural complications - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Investigations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage	-	-
Definition: An abnormal laboratory test result in which the partial thromboplastin time is found to be greater than the control value. As a possible indicator of coagulopathy, a prolonged partial thromboplastin time (PTT) may occur in a variety of diseases and disorders, both primary and related to treatment.					
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen.					
Alkaline phosphatase increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alkaline phosphatase in a blood specimen.					
Aspartate aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen.					
Blood antidiuretic hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of antidiuretic hormone in the blood specimen.					
Blood bilirubin increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice.					
Blood corticotrophin decreased	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of corticotrophin in a blood specimen.					
Blood gonadotrophin abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of gonadotrophin hormone in a blood specimen.					
Blood prolactin abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	-	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of prolactin hormone in a blood specimen.					
Carbon monoxide diffusing capacity decreased	3 - 5 units below LLN; for follow-up, a decrease of 3 - 5 units (ml/min/mm Hg) below the baseline value	6 - 8 units below LLN; for follow-up, an asymptomatic decrease of >5 - 8 units (ml/min/mm Hg) below the baseline value	Asymptomatic decrease of >8 units drop; >5 units drop along with the presence of pulmonary symptoms (e.g. , >Grade 2 hypoxia or >Grade 2 or higher dyspnea)	-	-
Definition: A finding based on lung function test results that indicate a decrease in the lung capacity to absorb carbon monoxide.					
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer	-	-
Definition: A laboratory test result which indicates increased levels of cardiac troponin I in a biological specimen.					
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer	-	-
Definition: A laboratory test result which indicates increased levels of cardiac troponin T in a biological specimen.					
CD4 lymphocytes decreased	<LLN - 500/mm3; <LLN - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200 - 50/mm3; <0.2 x 0.05 - 10e9 /L	<50/mm3; <0.05 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of CD4 lymphocytes in a blood specimen.					
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	-
Definition: A finding based on laboratory test results that indicate higher than normal levels of cholesterol in a blood specimen.					
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in levels of creatine phosphokinase in a blood specimen.					

Investigations

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-
Definition: A finding based on laboratory test results that indicate increased levels of creatinine in a biological specimen.					
Ejection fraction decreased	-	Resting ejection fraction (EF) 50 - 40%; 10 - 19% drop from baseline	Resting ejection fraction (EF) 39 - 20%; >20% drop from baseline	Resting ejection fraction (EF) <20%	-
Definition: The percentage computed when the amount of blood ejected during a ventricular contraction of the heart is compared to the amount that was present prior to the contraction.					
Electrocardiogram QT corrected interval prolonged	QTc 450 - 480 ms	QTc 481 - 500 ms	QTc >= 501 ms on at least two separate ECGs	QTc >= 501 or >60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia	-
Definition: A finding of a cardiac dysrhythmia characterized by an abnormally long corrected QT interval.					
Fibrinogen decreased	<1.0 - 0.75 x LLN or <25% decrease from baseline	<0.75 - 0.5 x LLN or 25 - <50% decrease from baseline	<0.5 - 0.25 x LLN or 50 - <75% decrease from baseline	<0.25 x LLN or 75% decrease from baseline or absolute value <50 mg/dL	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of fibrinogen in a blood specimen.					
Forced expiratory volume decreased	FEV1% (percentages of observed FEV1 and FVC related to their respective predicted values) 99 - 70% predicted	FEV1 60 - 69%	50 - 59%	<= 49%	-
Definition: A finding based on test results that indicate a relative decrease in the fraction of the forced vital capacity that is exhaled in a specific number of seconds.					
GGT increased	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-
Definition: A finding based on laboratory test results that indicate higher than normal levels of the enzyme gamma-glutamyltransferase in the blood specimen. GGT (gamma-glutamyltransferase) catalyzes the transfer of a gamma glutamyl group from a gamma glutamyl peptide to another peptide, amino acids or water.					
Growth hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	-	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of growth hormone in a biological specimen.					
Haptoglobin decreased	<LLN	-	-	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of haptoglobin in a blood specimen.					
Hemoglobin increased	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	-	-
Definition: A finding based on laboratory test results that indicate increased levels of hemoglobin in a biological specimen.					
INR increased	>1 - 1.5 x ULN; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5 x ULN; >1.5 - 2.5 times above baseline if on anticoagulation	>2.5 x ULN; >2.5 times above baseline if on anticoagulation	-	-
Definition: A finding based on laboratory test results that indicate an increase in the ratio of the patient's prothrombin time to a control sample in the blood.					
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the level of lipase in a biological specimen.					
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9 /L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of lymphocytes in a blood specimen.					
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-
Definition: A finding based on laboratory test results that indicate an abnormal increase in the number of lymphocytes in the blood, effusions or bone marrow.					
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.					
Pancreatic enzymes decreased	<LLN and asymptomatic	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of pancreatic enzymes in a biological specimen.					

Investigations					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.					
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN	>2.0 - 5.0 x ULN	>5.0 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in the levels of amylase in a serum specimen.					
Urine output decreased	-	-	Oliguria (<80 ml in 8 hr)	Anuria (<240 ml in 24 hr)	-
Definition: A finding based on test results that indicate urine production is less relative to previous output.					
Vital capacity abnormal	90 - 75% of predicted value	<75 - 50% of predicted value; limiting instrumental ADL	<50% of predicted value; limiting self care ADL	-	-
Definition: A finding based on pulmonary function test results that indicate an abnormal vital capacity (amount of exhaled after a maximum inhalation) when compared to the predicted value.					
Weight gain	5 - <10% from baseline	10 - <20% from baseline	>=20% from baseline	-	-
Definition: A finding characterized by an increase in overall body weight; for pediatrics, greater than the baseline growth curve.					
Weight loss	5 to <10% from baseline; intervention not indicated	10 - <20% from baseline; nutritional support indicated	>=20% from baseline; tube feeding or TPN indicated	-	-
Definition: A finding characterized by a decrease in overall body weight; for pediatrics, less than the baseline growth curve.					
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate an decrease in number of white blood cells in a blood specimen.					
Investigations - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Metabolism and nutrition disorders

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Acidosis	pH <normal, but >=7.3	-	pH <7.3	Life-threatening consequences	Death
Definition: A disorder characterized by abnormally high acidity (high hydrogen-ion concentration) of the blood and other body tissues.					
Alcohol intolerance	-	Present	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in sensitivity to the adverse effects of alcohol, which can include nasal congestion, skin flushes, heart dysrhythmias, nausea, vomiting, indigestion and headaches.					
Alkalosis	pH >normal, but <=7.5	-	pH >7.5	Life-threatening consequences	Death
Definition: A disorder characterized by abnormally high alkalinity (low hydrogen-ion concentration) of the blood and other body tissues.					
Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a loss of appetite.					
Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated <24 hrs	IV fluids or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by excessive loss of water from the body. It is usually caused by severe diarrhea, vomiting or diaphoresis.					
Glucose intolerance	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; dietary modification or oral agent indicated	Severe symptoms; insulin indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an inability to properly metabolize glucose.					
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of calcium (corrected for albumin) in blood.					
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of blood sugar. It is usually an indication of diabetes mellitus or glucose intolerance.					
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of potassium in the blood; associated with kidney failure or sometimes with the use of diuretic drugs.					
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of magnesium in the blood.					
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of sodium in the blood.					
Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of triglyceride concentration in the blood.					
Hyperuricemia	>ULN - 10 mg/dL (0.59 mmol/L) without physiologic consequences	-	>ULN - 10 mg/dL (0.59 mmol/L) with physiologic consequences	>10 mg/dL; >0.59 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of uric acid.					
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of albumin in the blood.					

Metabolism and nutrition disorders					
	Grade				
Adverse Event	1	2	3	4	5
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of calcium (corrected for albumin) in the blood.					
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of glucose in the blood.					
Hypokalemia	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of potassium in the blood.					
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of magnesium in the blood.					
Hyponatremia	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of sodium in the blood.					
Hypophosphatemia	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of phosphates in the blood.					
Iron overload	-	Moderate symptoms; intervention not indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by accumulation of iron in the tissues.					
Obesity	-	BMI 25 - 29.9 kg/m2	BMI 30 - 39.9 kg/m2	BMI >=40 kg/m2	-
Definition: A disorder characterized by having a high amount of body fat.					
Tumor lysis syndrome	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by metabolic abnormalities that result from a spontaneous or therapy-related cytolysis of tumor cells.					
Metabolism and nutrition disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Musculoskeletal and connective tissue disorders

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Abdominal soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g. tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the abdominal wall.					
Arthralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in a joint.					
Arthritis	Mild pain with inflammation, erythema, or joint swelling	Moderate pain associated with signs of inflammation, erythema, or joint swelling; limiting instrumental ADL	Severe pain associated with signs of inflammation, erythema, or joint swelling; irreversible joint damage; disabling; limiting self care ADL	-	-
Definition: A disorder characterized by inflammation involving a joint.					
Avascular necrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by necrotic changes in the bone tissue due to interruption of blood supply. Most often affecting the epiphysis of the long bones, the necrotic changes result in the collapse and the destruction of the bone structure.					
Back pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the back region.					
Bone pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the bones.					
Buttock pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the buttocks.					
Chest wall pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the chest wall region.					
Exostosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	-	-
Definition: A disorder characterized by non-neoplastic overgrowth of bone.					
Fibrosis deep connective tissue	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g. mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death
Definition: A disorder characterized by fibrotic degeneration of the deep connective tissues.					
Flank pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation on the lateral side of the body in the region below the ribs and above the hip.					
Generalized muscle weakness	Symptomatic; weakness perceived by patient but not evident on physical exam	Symptomatic; weakness evident on physical exam; weakness limiting instrumental ADL	Weakness limiting self care ADL; disabling	-	-
Definition: A disorder characterized by a reduction in the strength of muscles in multiple anatomic sites.					
Growth suppression	Reduction in growth velocity by 10 - 29% ideally measured over the period of a year	Reduction in growth velocity by 30 - 49% ideally measured over the period of a year or 0 - 49% reduction in growth from the baseline growth curve	Reduction in growth velocity of >=50% ideally measured over the period of a year	-	-
Definition: A disorder characterized by of stature that is smaller than normal as expected for age.					

Musculoskeletal and connective tissue disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Head soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the head.					
Joint effusion	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated; disabling	-	-
Definition: A disorder characterized by excessive fluid in a joint, usually as a result of joint inflammation.					
Joint range of motion decreased	<=25% loss of ROM (range of motion); decreased ROM limiting athletic activity	>25 - 50% decrease in ROM; limiting instrumental ADL	>50% decrease in ROM; limiting self care ADL; disabling	-	-
Definition: A disorder characterized by a decrease in joint flexibility of any joint.					
Joint range of motion decreased cervical spine	Mild restriction of rotation or flexion between 60 - 70 degrees	Rotation <60 degrees to right or left; <60 degrees of flexion	Ankylosed/fused over multiple segments with no C-spine rotation	-	-
Definition: A disorder characterized by a decrease in flexibility of a cervical spine joint.					
Joint range of motion decreased lumbar spine	Stiffness; difficulty bending to the floor to pick up a very light object but able to do athletic activity	Pain with range of motion (ROM) in lumbar spine; requires a reaching aid to pick up a very light object from the floor	<50% lumbar spine flexion; associated with symptoms of ankylosis or fused over multiple segments with no L-spine flexion (e.g., unable to reach to floor to pick up a very light object)	-	-
Definition: A disorder characterized by a decrease in flexibility of a lumbar spine joint.					
Kyphosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate accentuation; limiting instrumental ADL	Severe accentuation; operative intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by an abnormal increase in the curvature of the thoracic portion of the spine.					
Lordosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate accentuation; limiting instrumental ADL	Severe accentuation; operative intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by an abnormal increase in the curvature of the lumbar portion of the spine.					
Muscle weakness left-sided	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL; disabling	-	-
Definition: A disorder characterized by a reduction in the strength of the muscles on the left side of the body.					
Muscle weakness lower limb	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL; disabling	-	-
Definition: A disorder characterized by a reduction in the strength of the lower limb muscles.					
Muscle weakness right-sided	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL; disabling	-	-
Definition: A disorder characterized by a reduction in the strength of the muscles on the right side of the body.					
Muscle weakness trunk	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL; disabling	-	-
Definition: A disorder characterized by a reduction in the strength of the trunk muscles.					
Muscle weakness upper limb	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL; disabling	-	-
Definition: A disorder characterized by a reduction in the strength of the upper limb muscles.					

Musculoskeletal and connective tissue disorders

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Musculoskeletal deformity	Cosmetically and functionally insignificant hypoplasia	Deformity, hypoplasia, or asymmetry able to be remediated by prosthesis (e.g., shoe insert) or covered by clothing	Significant deformity, hypoplasia, or asymmetry, unable to be remediated by prosthesis or covered by clothing; disabling	-	-
Definition: A disorder characterized by of a malformation of the musculoskeletal system.					
Myalgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation originating from a muscle or group of muscles.					
Myositis	Mild pain	Moderate pain associated with weakness; pain limiting instrumental ADL	Pain associated with severe weakness; limiting self care ADL	-	-
Definition: A disorder characterized by inflammation involving the skeletal muscles.					
Neck pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the neck area.					
Neck soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the neck.					
Osteonecrosis of jaw	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the bone of the mandible.					
Osteoporosis	Radiologic evidence of osteoporosis or Bone Mineral Density (BMD) t-score -1 to -2.5 (osteopenia); no loss of height or intervention indicated	BMD t-score <-2.5; loss of height <2 cm; anti-osteoporotic therapy indicated; limiting instrumental ADL	Loss of height >=2 cm; hospitalization indicated; limiting self care ADL	-	-
Definition: A disorder characterized by reduced bone mass, with a decrease in cortical thickness and in the number and size of the trabeculae of cancellous bone (but normal chemical composition), resulting in increased fracture incidence.					
Pain in extremity	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the upper or lower extremities.					
Pelvic soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the pelvis.					
Scoliosis	<20 degrees; clinically undetectable	>20 - 45 degrees; visible by forward flexion; limiting instrumental ADL	>45 degrees; scapular prominence in forward flexion; operative intervention indicated; limiting self care ADL; disabling	-	-
Definition: A disorder characterized by a malformed, lateral curvature of the spine.					
Soft tissue necrosis lower limb	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the lower extremity.					
Soft tissue necrosis upper limb	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the upper extremity.					

Musculoskeletal and connective tissue disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Superficial soft tissue fibrosis	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death
Definition: A disorder characterized by fibrotic degeneration of the superficial soft tissues.					
Trismus	Decreased ROM (range of motion) without impaired eating	Decreased ROM requiring small bites, soft foods or purees	Decreased ROM with inability to adequately aliment or hydrate orally	-	-
Definition: A disorder characterized by lack of ability to open the mouth fully due to a decrease in the range of motion of the muscles of mastication.					
Unequal limb length	Mild length discrepancy <2 cm	Moderate length discrepancy 2 - 5 cm; shoe lift indicated; limiting instrumental ADL	Severe length discrepancy >5 cm; limiting self care ADL; disabling; operative intervention indicated	-	-
Definition: A disorder characterized by of a discrepancy between the lengths of the lower or upper extremities.					
Musculoskeletal and connective tissue disorder - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Leukemia secondary to oncology chemotherapy	-	-	-	Present	Death
Definition: A disorder characterized by leukemia arising as a result of the mutagenic effect of chemotherapy agents.					
Myelodysplastic syndrome	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by insufficiently healthy hematapoietic cell production by the bone marrow.					
Treatment related secondary malignancy	-	-	Non life-threatening secondary malignancy	Acute life-threatening secondary malignancy; blast crisis in leukemia	Death
Definition: A disorder characterized by development of a malignancy most probably as a result of treatment for a previously existing malignancy.					
Tumor pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort from a neoplasm that may be pressing on a nerve, blocking blood vessels, inflamed or fractured from metastasis.					
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Nervous system disorders					
	Grade				
Adverse Event	1	2	3	4	5
Abducens nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the abducens nerve (sixth cranial nerve).					
Accessory nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the accessory nerve (eleventh cranial nerve).					
Acoustic nerve disorder NOS	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the acoustic nerve (eighth cranial nerve).					
Akathisia	Mild restlessness or increased motor activity	Moderate restlessness or increased motor activity; limiting instrumental ADL	Severe restlessness or increased motor activity; limiting self care ADL	-	-
Definition: A disorder characterized by an uncomfortable feeling of inner restlessness and inability to stay still; this is a side effect of some psychotropic drugs.					
Amnesia	Mild; transient memory loss	Moderate; short term memory loss; limiting instrumental ADL	Severe; long term memory loss; limiting self care ADL	-	-
Definition: A disorder characterized by systematic and extensive loss of memory.					
Aphonia	-	-	Voicelessness; unable to speak	-	-
Definition: A disorder characterized by the inability to speak. It may result from injuries to the vocal cords or may be functional (psychogenic).					
Arachnoiditis	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the arachnoid membrane and adjacent subarachnoid space.					
Ataxia	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; mechanical assistance indicated	-	-
Definition: A disorder characterized by lack of coordination of muscle movements resulting in the impairment or inability to perform voluntary activities.					
Brachial plexopathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by regional paresthesia of the brachial plexus, marked discomfort and muscle weakness, and limited movement in the arm or hand.					
Central nervous system necrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; corticosteroids indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the brain and/or spinal cord.					
Cerebrospinal fluid leakage	Post-craniotomy: asymptomatic; Post-lumbar puncture: transient headache; postural care indicated	Post-craniotomy: moderate symptoms; medical intervention indicated; Post-lumbar puncture: persistent moderate symptoms; blood patch indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by loss of cerebrospinal fluid into the surrounding tissues.					
Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	-	-
Definition: A disorder characterized by a conspicuous change in cognitive function.					
Concentration impairment	Mild inattention or decreased level of concentration	Moderate impairment in attention or decreased level of concentration; limiting instrumental ADL	Severe impairment in attention or decreased level of concentration; limiting self care ADL	-	-
Definition: A disorder characterized by a deterioration in the ability to concentrate.					

Nervous system disorders					
	Grade				
Adverse Event	1	2	3	4	5
Depressed level of consciousness	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences	Death
Definition: A disorder characterized by a decrease in ability to perceive and respond.					
Dizziness	Mild unsteadiness or sensation of movement	Moderate unsteadiness or sensation of movement; limiting instrumental ADL	Severe unsteadiness or sensation of movement; limiting self care ADL	-	-
Definition: A disorder characterized by a disturbing sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking.					
Dysarthria	Mild slurred speech	Moderate impairment of articulation or slurred speech	Severe impairment of articulation or slurred speech	-	-
Definition: A disorder characterized by slow and slurred speech resulting from an inability to coordinate the muscles used in speech.					
Dysesthesia	Mild sensory alteration	Moderate sensory alteration; limiting instrumental ADL	Severe sensory alteration; limiting self care ADL	-	-
Definition: A disorder characterized by distortion of sensory perception, resulting in an abnormal and unpleasant sensation.					
Dysgeusia	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	-	-	-
Definition: A disorder characterized by abnormal sensual experience with the taste of foodstuffs; it can be related to a decrease in the sense of smell.					
Dysphasia	Awareness of receptive or expressive characteristics; not impairing ability to communicate	Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously	Severe receptive or expressive characteristics; impairing ability to read, write or communicate intelligibly	-	-
Definition: A disorder characterized by impairment of verbal communication skills, often resulting from brain damage.					
Edema cerebral	-	-	-	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the brain.					
Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a pathologic process involving the brain.					
Extrapyramidal disorder	Mild involuntary movements	Moderate involuntary movements; limiting instrumental ADL	Severe involuntary movements or torticollis; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by abnormal, repetitive, involuntary muscle movements, frenzied speech and extreme restlessness.					
Facial muscle weakness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a reduction in the strength of the facial muscles.					
Facial nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the facial nerve (seventh cranial nerve).					
Glossopharyngeal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by involvement of the glossopharyngeal nerve (ninth cranial nerve).					
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution of any nerve.					
Hydrocephalus	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; intervention not indicated	Severe symptoms or neurological deficit; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal increase of cerebrospinal fluid in the ventricles of the brain.					
Hypersomnia	Mild increased need for sleep	Moderate increased need for sleep	Severe increased need for sleep	-	-
Definition: A disorder characterized by characterized by excessive sleepiness during the daytime.					

Nervous system disorders					
	Grade				
Adverse Event	1	2	3	4	5
Hypoglossal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the hypoglossal nerve (twelfth cranial nerve).					
Intracranial hemorrhage	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the cranium.					
Ischemia cerebrovascular	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	-	-	-
Definition: A disorder characterized by a decrease or absence of blood supply to the brain caused by obstruction (thrombosis or embolism) of an artery resulting in neurological damage.					
IVth nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the trochlear nerve (fourth cranial nerve).					
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	-	-	-
Definition: A disorder characterized by a decrease in consciousness characterized by mental and physical inertness.					
Leukoencephalopathy	Asymptomatic; small focal T2/FLAIR hyperintensities; involving periventricular white matter or <1/3 of susceptible areas of cerebrum +/- mild increase in subarachnoid space (SAS) and/or mild ventriculomegaly	Moderate symptoms; focal T2/FLAIR hyperintensities, involving periventricular white matter extending into centrum semiovale or involving 1/3 to 2/3 of susceptible areas of cerebrum +/- moderate increase in SAS and/or moderate ventriculomegaly	Severe symptoms; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving 2/3 or more of susceptible areas of cerebrum +/- moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Life-threatening consequences; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving most of susceptible areas of cerebrum +/- moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Death
Definition: A disorder characterized by diffuse reactive astrocytosis with multiple areas of necrotic foci without inflammation.					
Memory impairment	Mild memory impairment	Moderate memory impairment; limiting instrumental ADL	Severe memory impairment; limiting self care ADL	-	-
Definition: A disorder characterized by a deterioration in memory function.					
Meningismus	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by neck stiffness, headache, and photophobia resulting from irritation of the cerebral meninges.					
Movements involuntary	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by uncontrolled and purposeless movements.					
Myelitis	Asymptomatic; mild signs (e.g., Babinski's reflex or Lhermitte's sign)	Moderate weakness or sensory loss; limiting instrumental ADL	Severe weakness or sensory loss; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation involving the spinal cord. Symptoms include weakness, paresthesia, sensory loss, marked discomfort and incontinence.					
Neuralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by intense painful sensation along a nerve or group of nerves.					
Nystagmus	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involuntary movements of the eyeballs.					
Oculomotor nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the oculomotor nerve (third cranial nerve).					
Olfactory nerve disorder	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the olfactory nerve (first cranial nerve).					

Nervous system disorders					
	Grade				
Adverse Event	1	2	3	4	5
Paresthesia	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and warmth that are experienced in the absence of a stimulus.					
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; assistive device indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation or degeneration of the peripheral motor nerves.					
Peripheral sensory neuropathy	Asymptomatic; loss of deep tendon reflexes or paresthesia	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation or degeneration of the peripheral sensory nerves.					
Phantom pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort related to a limb or an organ that is removed from or is not physically part of the body.					
Presyncope	-	Present (e.g., near fainting)	-	-	-
Definition: A disorder characterized by an episode of lightheadedness and dizziness which may precede an episode of syncope.					
Pyramidal tract syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by dysfunction of the corticospinal (pyramidal) tracts of the spinal cord. Symptoms include an increase in the muscle tone in the lower extremities, hyperreflexia, positive Babinski and a decrease in fine motor coordination.					
Radiculitis	Mild symptoms	Moderate symptoms; limiting instrumental ADL; medical intervention indicated	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation involving a nerve root. Patients experience marked discomfort radiating along a nerve path because of spinal pressure on the connecting nerve root.					
Recurrent laryngeal nerve palsy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	Severe symptoms; medical intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by paralysis of the recurrent laryngeal nerve.					
Reversible posterior leukoencephalopathy syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; abnormal imaging studies; limiting instrumental ADL	Severe symptoms; very abnormal imaging studies; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by headaches, mental status changes, visual disturbances, and seizures associated with imaging findings of posterior leukoencephalopathy. It has been observed in association with hypertensive encephalopathy, eclampsia, and immunosuppressive and cytotoxic drug treatment. It is an acute or subacute reversible condition.					
Seizure	Brief partial seizure; no loss of consciousness	Brief generalized seizure	Multiple seizures despite medical intervention	Life-threatening; prolonged repetitive seizures	Death
Definition: A disorder characterized by a sudden, involuntary skeletal muscular contractions of cerebral or brain stem origin.					
Sinus pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort in the face, between the eyes, or upper teeth originating from the sinuses.					
Somnolence	Mild but more than usual drowsiness or sleepiness	Moderate sedation; limiting instrumental ADL	Obtundation or stupor	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by characterized by excessive sleepiness and drowsiness.					
Spasticity	Mild or slight increase in muscle tone	Moderate increase in muscle tone and increase in resistance through range of motion	Severe increase in muscle tone and increase in resistance through range of motion	Life-threatening; unable to move active or passive range of motion	Death
Definition: A disorder characterized by increased involuntary muscle tone that affects the regions interfering with voluntary movement. It results in gait, movement, and speech disturbances.					
Stroke	Asymptomatic or mild neurologic deficit; radiographic findings only	Moderate neurologic deficit	Severe neurologic deficit	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a sudden loss of sensory function due to an intracranial vascular event.					
Syncope	-	-	Fainting; orthostatic collapse	-	-
Definition: A disorder characterized by spontaneous loss of consciousness caused by insufficient blood supply to the brain.					

Nervous system disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Transient ischemic attacks	Mild neurologic deficit with or without imaging confirmation	Moderate neurologic deficit with or without imaging confirmation	-	-	-
Definition: A disorder characterized by a brief attack (less than 24 hours) of cerebral dysfunction of vascular origin, with no persistent neurological deficit.					
Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by the uncontrolled shaking movement of the whole body or individual parts.					
Trigeminal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involvement of the trigeminal nerve (fifth cranial nerve).					
Vagus nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by involvement of the vagus nerve (tenth cranial nerve).					
Vasovagal reaction	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a sudden drop of the blood pressure, bradycardia, and peripheral vasodilation that may lead to loss of consciousness. It results from an increase in the stimulation of the vagus nerve.					
Nervous system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Pregnancy, puerperium and perinatal conditions					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Fetal death	-	-	-	-	Fetal loss at any gestational age
Definition: A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation.					
Fetal growth retardation	-	<10% percentile of weight for gestational age	<5% percentile of weight for gestational age	<1% percentile of weight for gestational age	-
Definition: A disorder characterized by inhibition of fetal growth resulting in the inability of the fetus to achieve its potential weight.					
Premature delivery	Delivery of a liveborn infant at >34 to 37 weeks gestation	Delivery of a liveborn infant at >28 to 34 weeks gestation	Delivery of a liveborn infant at 24 to 28 weeks gestation	Delivery of a liveborn infant at 24 weeks of gestation or less	-
Definition: A disorder characterized by delivery of a viable infant before the normal end of gestation. Typically, viability is achievable between the twentieth and thirty-seventh week of gestation.					
Unintended pregnancy	-	-	Unintended pregnancy	-	-
Definition: A disorder characterized by an unexpected pregnancy at the time of conception.					
Pregnancy, puerperium and perinatal conditions - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate, local or noninvasive intervention indicated; limiting instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Psychiatric disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Agitation	Mild mood alteration	Moderate mood alteration	Severe agitation; hospitalization not indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a state of restlessness associated with unpleasant feelings of irritability and tension.					
Anorgasmia	Inability to achieve orgasm not adversely affecting relationship	Inability to achieve orgasm adversely affecting relationship	-	-	-
Definition: A disorder characterized by an inability to achieve orgasm.					
Anxiety	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization not indicated	Life-threatening; hospitalization indicated	Death
Definition: A disorder characterized by apprehension of danger and dread accompanied by restlessness, tension, tachycardia, and dyspnea unattached to a clearly identifiable stimulus.					
Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a lack of clear and orderly thought and behavior.					
Delayed orgasm	Delay in achieving orgasm not adversely affecting relationship	Delay in achieving orgasm adversely affecting relationship	-	-	-
Definition: A disorder characterized by sexual dysfunction characterized by a delay in climax.					
Delirium	Mild acute confusional state	Moderate and acute confusional state; limiting instrumental ADL	Severe and acute confusional state; limiting self care ADL; hospitalization indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by the acute and sudden development of confusion, illusions, movement changes, inattentiveness, agitation, and hallucinations. Usually, it is a reversible condition.					
Delusions	-	Moderate delusional symptoms	Severe delusional symptoms; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by false personal beliefs held contrary to reality, despite contradictory evidence and common sense.					
Depression	Mild depressive symptoms	Moderate depressive symptoms; limiting instrumental ADL	Severe depressive symptoms; limiting self care ADL; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by melancholic feelings of grief or unhappiness.					
Euphoria	Mild mood elevation	Moderate mood elevation	Severe mood elevation (e.g., hypomania)	-	-
Definition: A disorder characterized by an exaggerated feeling of well-being which is disproportionate to events and stimuli.					
Hallucinations	Mild hallucinations (e.g., perceptual distortions)	Moderate hallucinations	Severe hallucinations; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by a false sensory perception in the absence of an external stimulus.					
Insomnia	Mild difficulty falling asleep, staying asleep or waking up early	Moderate difficulty falling asleep, staying asleep or waking up early	Severe difficulty in falling asleep, staying asleep or waking up early	-	-
Definition: A disorder characterized by difficulty in falling asleep and/or remaining asleep.					
Libido decreased	Decrease in sexual interest not adversely affecting relationship	Decrease in sexual interest adversely affecting relationship	-	-	-
Definition: A disorder characterized by a decrease in sexual desire.					
Libido increased	Mild increase in sexual interest not adversely affecting relationship	Moderate increase in sexual interest adversely affecting relationship	Severe increase in sexual interest leading to dangerous behavior	-	-
Definition: A disorder characterized by an increase in sexual desire.					
Mania	Mild manic symptoms (e.g., elevated mood, rapid thoughts, rapid speech, decreased need for sleep)	Moderate manic symptoms (e.g., relationship and work difficulties; poor hygiene)	Severe manic symptoms (e.g., hypomania; major sexual or financial indiscretions); hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by excitement of psychotic proportions manifested by mental and physical hyperactivity, disorganization of behavior and elevation of mood.					
Personality change	Mild personality change	Moderate personality change	Severe personality change; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death

Psychiatric disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by a conspicuous change in a person's behavior and thinking.					
Psychosis	Mild psychotic symptoms	Moderate psychotic symptoms (e.g., disorganized speech; impaired reality testing)	Severe psychotic symptoms (e.g., paranoid; extreme disorganization); hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by personality change, impaired functioning, and loss of touch with reality. It may be a manifestation of schizophrenia, bipolar disorder or brain tumor.					
Restlessness	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by an inability to rest, relax or be still.					
Suicidal ideation	Increased thoughts of death but no wish to kill oneself	Suicidal ideation with no specific plan or intent	Specific plan to commit suicide without serious intent to die which may not require hospitalization	Specific plan to commit suicide with serious intent to die which requires hospitalization	-
Definition: A disorder characterized by thoughts of taking one's own life.					
Suicide attempt	-	-	Suicide attempt or gesture without intent to die which may not require hospitalization	Suicide attempt with intent to die which requires hospitalization	Death
Definition: A disorder characterized by self-inflicted harm in an attempt to end one's own life.					
Psychiatric disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; disabling; limiting self care ADL	Life-threatening consequences; hospitalization or urgent intervention indicated	Death

Renal and urinary disorders

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Acute kidney injury	Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0 x above baseline	Creatinine 2 - 3 x above baseline	Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	Life-threatening consequences; dialysis indicated	Death
Definition: A disorder characterized by the acute loss of renal function and is traditionally classified as pre-renal (low blood flow into kidney), renal (kidney damage) and post-renal causes (ureteral or bladder outflow obstruction).					
Bladder perforation	-	Extraperitoneal perforation, indwelling catheter indicated	Intraperitoneal perforation; elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the bladder wall.					
Bladder spasm	Intervention not indicated	Antispasmodics indicated	Hospitalization indicated	-	-
Definition: A disorder characterized by a sudden and involuntary contraction of the bladder wall.					
Chronic kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN - 60 ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5	eGFR or CrCl 59 - 30 ml/min/1.73 m2	eGFR or CrCl 29 - 15 ml/min/1.73 m2	eGFR or CrCl <15 ml/min/1.73 m2; dialysis or renal transplant indicated	Death
Definition: A disorder characterized by gradual and usually permanent loss of kidney function resulting in renal failure.					
Cystitis noninfective	Microscopic hematuria; minimal increase in frequency, urgency, dysuria, or nocturia; new onset of incontinence	Moderate hematuria; moderate increase in frequency, urgency, dysuria, nocturia or incontinence; urinary catheter placement or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the bladder which is not caused by an infection of the urinary tract.					
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated; limiting instrumental ADL	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective endoscopic, radiologic or operative intervention indicated; limiting self care ADL	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate blood in the urine.					
Hemoglobinuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by laboratory test results that indicate the presence of free hemoglobin in the urine.					
Proteinuria	1+ proteinuria; urinary protein <1.0 g/24 hrs	Adults: 2+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Pediatric: urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Adults: urinary protein >=3.5 g/24 hrs; Pediatric: urine P/C >1.9	-	-
Definition: A disorder characterized by laboratory test results that indicate the presence of excessive protein in the urine. It is predominantly albumin, but also globulin.					
Renal calculi	Asymptomatic or mild symptoms; occasional use of nonprescription analgesics indicated	Symptomatic; oral antiemetics indicated; around the clock nonprescription analgesics or any oral narcotic analgesics indicated	Hospitalization indicated; IV intervention (e.g., analgesics, antiemetics); elective endoscopic or radiologic intervention indicated	Life-threatening consequences; urgent radiologic, endoscopic or operative intervention indicated	Death
Definition: A disorder characterized by the formation of crystals in the pelvis of the kidney.					
Renal colic	Mild pain not interfering with activity; nonprescription medication indicated	Moderate pain; limiting instrumental ADL; prescription medication indicated	Hospitalization indicated; limiting self care ADL	-	-
Definition: A disorder characterized by paroxysmal and severe flank marked discomfort radiating to the inguinal area. Often, the cause is the passage of kidney stones.					

Renal and urinary disorders					
	Grade				
Adverse Event	1	2	3	4	5
Renal hemorrhage	Mild symptoms; intervention not indicated	Analgesics and hematocrit monitoring indicated	Transfusion, radiation, or hospitalization indicated; elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by bleeding from the kidney.					
Urinary fistula	-	Noninvasive intervention indicated; urinary or suprapubic catheter placement indicated	Limiting self care ADL; elective radiologic, endoscopic or operative intervention indicated; permanent urinary diversion indicated	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between any part of the urinary system and another organ or anatomic site.					
Urinary frequency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Definition: A disorder characterized by urination at short intervals.					
Urinary incontinence	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous; pads indicated; limiting instrumental ADL	Intervention indicated (e.g., clamp, collagen injections); operative intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by inability to control the flow of urine from the bladder.					
Urinary retention	Urinary, suprapubic or intermittent catheter placement not indicated; able to void with some residual	Placement of urinary, suprapubic or intermittent catheter placement indicated; medication indicated	Elective operative or radiologic intervention indicated; substantial loss of affected kidney function or mass	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Definition: A disorder characterized by accumulation of urine within the bladder because of the inability to urinate.					
Urinary tract obstruction	Asymptomatic; clinical or diagnostic observations only	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; urethral dilation, urinary or suprapubic catheter indicated	Symptomatic and altered organ function (e.g., hydronephrosis, or renal dysfunction); elective radiologic, endoscopic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of contents of the urinary tract.					
Urinary tract pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the urinary tract.					
Urinary urgency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Definition: A disorder characterized by a sudden compelling urge to urinate.					
Urine discoloration	Present	-	-	-	-
Definition: A disorder characterized by a change in the color of the urine.					
Renal and urinary disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate, local or noninvasive intervention indicated; limiting instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Reproductive system and breast disorders					
	Grade				
Adverse Event	1	2	3	4	5
Azoospermia	-	-	Absence of sperm in ejaculate	-	-
Definition: A disorder characterized by laboratory test results that indicate complete absence of spermatozoa in the semen.					
Breast atrophy	Minimal asymmetry; minimal atrophy	Moderate asymmetry; moderate atrophy	Asymmetry >1/3 of breast volume; severe atrophy	-	-
Definition: A disorder characterized by underdevelopment of the breast.					
Breast pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the breast region.					
Dysmenorrhea	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by abnormally painful abdominal cramps during menses.					
Dyspareunia	Mild discomfort or pain associated with vaginal penetration; discomfort relieved with use of vaginal lubricants or estrogen	Moderate discomfort or pain associated with vaginal penetration; discomfort or pain partially relieved with use of vaginal lubricants or estrogen	Severe discomfort or pain associated with vaginal penetration; discomfort or pain unrelieved by vaginal lubricants or estrogen	-	-
Definition: A disorder characterized by painful or difficult coitus.					
Ejaculation disorder	Diminished ejaculation	Anejaculation or retrograde ejaculation	-	-	-
Definition: A disorder characterized by problems related to ejaculation. This category includes premature, delayed, retrograde and painful ejaculation.					
Erectile dysfunction	Decrease in erectile function (frequency or rigidity of erections) but intervention not indicated (e.g., medication or use of mechanical device, penile pump)	Decrease in erectile function (frequency/rigidity of erections), erectile intervention indicated, (e.g., medication or mechanical devices such as penile pump)	Decrease in erectile function (frequency/rigidity of erections) but erectile intervention not helpful (e.g., medication or mechanical devices such as penile pump); placement of a permanent penile prosthesis indicated (not previously present)	-	-
Definition: A disorder characterized by the persistent or recurrent inability to achieve or to maintain an erection during sexual activity.					
Fallopian tube obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by blockage of the normal flow of the contents in the fallopian tube.					
Fallopian tube stenosis	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated (e.g., organ resection)	Death
Definition: A disorder characterized by a narrowing of the fallopian tube lumen.					
Female genital tract fistula	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between a female reproductive system organ and another organ or anatomic site.					
Feminization acquired	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by the development of secondary female sex characteristics in males due to extrinsic factors.					
Genital edema	Mild swelling or obscuration of anatomic architecture on close inspection	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	Lymphorrhea; gross deviation from normal anatomic contour; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the genitals.					
Gynecomastia	Asymptomatic breast enlargement	Symptomatic (e.g., pain or psychosocial impact)	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by excessive development of the breasts in males.					
Hematosalpinx	Minimal bleeding identified on imaging study or laparoscopy; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death

Reproductive system and breast disorders					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by the presence of blood in a fallopian tube.					
Irregular menstruation	Intermittent menses with skipped menses for no more than 1 to 3 months	Intermittent menses with skipped menses for more than 4 to 6 months	Persistent amenorrhea for more than 6 months	-	-
Definition: A disorder characterized by irregular cycle or duration of menses.					
Lactation disorder	Mild changes in lactation, not significantly affecting production or expression of breast milk	Changes in lactation, significantly affecting breast production or expression of breast milk	-	-	-
Definition: A disorder characterized by disturbances of milk secretion. It is not necessarily related to pregnancy that is observed in females and can be observed in males.					
Menorrhagia	Mild; iron supplements indicated	Moderate symptoms; medical intervention indicated (e.g., hormones)	Severe; transfusion indicated; surgical intervention indicated (e.g., hysterectomy)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by abnormally heavy vaginal bleeding during menses.					
Nipple deformity	Asymptomatic; asymmetry with slight retraction and/or thickening of the nipple areolar complex	Symptomatic; asymmetry of nipple areolar complex with moderate retraction and/or thickening of the nipple areolar complex	-	-	-
Definition: A disorder characterized by a malformation of the nipple.					
Oligospermia	Sperm concentration >48 million/mL or motility >68%	Sperm concentration 13 - 48 million/mL or motility 32 - 68%	Sperm concentration <13 million/mL or motility <32%	-	-
Definition: A disorder characterized by a decrease in the number of spermatozoa in the semen.					
Ovarian hemorrhage	Minimal bleeding identified on imaging study or laproscopy; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by bleeding from the ovary.					
Ovarian rupture	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by tearing or disruption of the ovarian tissue.					
Ovulation pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in one side of the abdomen between menstrual cycles, around the time of the discharge of the ovum from the ovarian follicle.					
Pelvic floor muscle weakness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic, not interfering with bladder, bowel, or vaginal function; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a reduction in the strength of the muscles of the pelvic floor.					
Pelvic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the pelvis.					
Penile pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the penis.					
Perineal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the area between the genital organs and the anus.					
Premature menopause	-	-	Present	-	-
Definition: A disorder characterized by ovarian failure before the age of 40. Symptoms include hot flashes, night sweats, mood swings and a decrease in sex drive.					
Prostatic hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death

Reproductive system and breast disorders					
	Grade				
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by bleeding from the prostate gland.					
Prostatic obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by compression of the urethra secondary to enlargement of the prostate gland. This results in voiding difficulties (straining to void, slow urine stream, and incomplete emptying of the bladder).					
Prostatic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the prostate gland.					
Scrotal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the scrotal area.					
Spermatic cord hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by bleeding from the spermatic cord.					
Spermatic cord obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by blockage of the normal flow of the contents of the spermatic cord.					
Testicular disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic but not interfering with urination or sexual activities; intervention not indicated; limiting instrumental ADL	Severe symptoms; interfering with urination or sexual function; limiting self care ADL; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by involvement of the testis.					
Testicular hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by bleeding from the testis.					
Testicular pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the testis.					
Uterine fistula	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the uterus and another organ or anatomic site.					
Uterine hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by bleeding from the uterus.					
Uterine obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by blockage of the uterine outlet.					
Uterine pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the uterus.					
Vaginal discharge	Mild vaginal discharge (greater than baseline for patient)	Moderate to heavy vaginal discharge; use of perineal pad or tampon indicated	-	-	-
Definition: A disorder characterized by vaginal secretions. Mucus produced by the cervical glands is discharged from the vagina naturally, especially during the childbearing years.					
Vaginal dryness	Mild vaginal dryness not interfering with sexual function	Moderate vaginal dryness interfering with sexual function or causing frequent discomfort	Severe vaginal dryness resulting in dyspareunia or severe discomfort	-	-
Definition: A disorder characterized by an uncomfortable feeling of itching and burning in the vagina.					

Reproductive system and breast disorders					
	Grade				
Adverse Event	1	2	3	4	5
Vaginal fistula	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the vagina and another organ or anatomic site.					
Vaginal hemorrhage	Minimal bleeding identified on clinical exam or imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by bleeding from the vagina.					
Vaginal inflammation	Mild discomfort or pain, edema, or redness	Moderate discomfort or pain, edema, or redness; limiting instrumental ADL	Severe discomfort or pain, edema, or redness; limiting self care ADL; small areas of mucosal ulceration	Widespread areas of mucosal ulceration; life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation involving the vagina. Symptoms may include redness, edema, marked discomfort and an increase in vaginal discharge.					
Vaginal obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by blockage of vaginal canal.					
Vaginal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the vagina.					
Vaginal perforation	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the vaginal wall.					
Vaginal stricture	Asymptomatic; mild vaginal shortening or narrowing	Vaginal narrowing and/or shortening not interfering with physical examination	Vaginal narrowing and/or shortening interfering with the use of tampons, sexual activity or physical examination	-	Death
Definition: A disorder characterized by a narrowing of the vaginal canal.					
Vaginismus	Mild discomfort or pain associated with vaginal spasm/tightening; no impact upon sexual function or physical examination	Moderate discomfort or pain associated with vaginal spasm/tightening; disruption in sexual function and physical examination	Severe discomfort or pain associated with vaginal spasm/tightening; unable to tolerate vaginal penetration or physical examination	-	-
Definition: A disorder characterized by involuntary spasms of the pelvic floor muscles, resulting in pathologic tightness of the vaginal wall during penetration such as during sexual intercourse.					
Reproductive system and breast disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Respiratory, thoracic and mediastinal disorders

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Adult respiratory distress syndrome	-	-	Present with radiologic findings; intubation not indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by progressive and life-threatening pulmonary distress in the absence of an underlying pulmonary condition, usually following major trauma or surgery.					
Allergic rhinitis	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by an inflammation of the nasal mucous membranes caused by an IgE-mediated response to external allergens. The inflammation may also involve the mucous membranes of the sinuses, eyes, middle ear, and pharynx. Symptoms include sneezing, nasal congestion, rhinorrhea and itching.					
Apnea	-	-	Present; medical intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by cessation of breathing.					
Aspiration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Altered eating habits; coughing or choking episodes after eating or swallowing; medical intervention indicated (e.g., suction or oxygen)	Dyspnea and pneumonia symptoms (e.g., aspiration pneumonia); hospitalization indicated; unable to aliment orally	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by inhalation of solids or liquids into the lungs.					
Atelectasis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., dyspnea, cough); medical intervention indicated (e.g., chest physiotherapy, suctioning); bronchoscopic suctioning	Oxygen indicated; hospitalization or elective operative intervention indicated (e.g., stent, laser)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by the collapse of part or the entire lung.					
Bronchial fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical management indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death
Definition: A disorder characterized by an abnormal communication between the bronchus and another organ or anatomic site.					
Bronchial obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., mild wheezing); endoscopic evaluation indicated; radiographic evidence of atelectasis/lobar collapse; medical management indicated (e.g., steroids, bronchodilators)	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by blockage of a bronchus passage, most often by bronchial secretions and exudates.					
Bronchial stricture	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., rhonchi or wheezing) but without respiratory distress; medical intervention indicated (e.g., steroids, bronchodilators)	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by a narrowing of the bronchial tube.					
Bronchopleural fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention with thoracoplasty, chronic open drainage or multiple thoracotomies indicated	Death
Definition: A disorder characterized by an abnormal communication between a bronchus and the pleural cavity.					
Bronchopulmonary hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the bronchial wall and/or lung parenchyma.					

Respiratory, thoracic and mediastinal disorders

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Bronchospasm	Mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Limiting self care ADL; oxygen saturation decreased	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by a sudden contraction of the smooth muscles of the bronchial wall.					
Chylothorax	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thoracentesis or tube drainage indicated	Severe symptoms; elective operative intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by milky pleural effusion (abnormal collection of fluid) resulting from accumulation of lymph fluid in the pleural cavity.					
Cough	Mild symptoms; nonprescription intervention indicated	Moderate symptoms, medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by sudden, often repetitive, spasmodic contraction of the thoracic cavity, resulting in violent release of air from the lungs and usually accompanied by a distinctive sound.					
Dyspnea	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an uncomfortable sensation of difficulty breathing.					
Epistaxis	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated (e.g., nasal packing, cauterization; topical vasoconstrictors)	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the nose.					
Hiccups	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe symptoms; interfering with sleep; limiting self care ADL	-	-
Definition: A disorder characterized by repeated gulp sounds that result from an involuntary opening and closing of the glottis. This is attributed to a spasm of the diaphragm.					
Hoarseness	Mild or intermittent voice change; fully understandable; self-resolves	Moderate or persistent voice changes; may require occasional repetition but understandable on telephone; medical evaluation indicated	Severe voice changes including predominantly whispered speech	-	-
Definition: A disorder characterized by harsh and raspy voice arising from or spreading to the larynx.					
Hypoxia	-	Decreased oxygen saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen	Decreased oxygen saturation at rest (e.g., pulse oximeter <88% or PaO2 <=55 mm Hg)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a decrease in the level of oxygen in the body.					
Laryngeal edema	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., dexamethasone, epinephrine, antihistamines)	Stridor; respiratory distress; hospitalization indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the larynx.					
Laryngeal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical management indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention indicated (e.g., thoracoplasty, chronic open drainage or multiple thoracotomies)	Death
Definition: A disorder characterized by an abnormal communication between the larynx and another organ or anatomic site.					
Laryngeal hemorrhage	Mild cough or trace hemoptysis; laryngoscopic findings	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by bleeding from the larynx.					
Laryngeal inflammation	Mild sore throat; raspy voice	Moderate sore throat; analgesics indicated	Severe throat pain; endoscopic intervention indicated	-	-
Definition: A disorder characterized by an inflammation involving the larynx.					

Respiratory, thoracic and mediastinal disorders

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Laryngeal mucositis	Endoscopic findings only; mild discomfort with normal intake	Moderate discomfort; altered oral intake	Severe pain; severely altered eating/swallowing; medical intervention indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by an inflammation involving the mucous membrane of the larynx.					
Laryngeal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids); limiting instrumental ADL	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by blockage of the laryngeal airway.					
Laryngeal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a narrowing of the laryngeal airway.					
Laryngopharyngeal dysesthesia	Mild symptoms; no anxiety; intervention not indicated	Moderate symptoms; mild anxiety, but no dyspnea; short duration of observation and or anxiolytic indicated; limiting instrumental ADL	Severe symptoms; dyspnea and swallowing difficulty; limiting self care ADL	Life-threatening consequences	Death
Definition: A disorder characterized by an uncomfortable persistent sensation in the area of the laryngopharynx.					
Laryngospasm	-	Transient episode; intervention not indicated	Recurrent episodes; noninvasive intervention indicated (e.g., breathing technique, pressure point massage)	Persistent or severe episodes associated with syncope; urgent intervention indicated (e.g., fiberoptic laryngoscopy, intubation, botox injection)	Death
Definition: A disorder characterized by paroxysmal spasmodic muscular contraction of the vocal cords.					
Mediastinal hemorrhage	Radiologic evidence only; minimal symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the mediastinum.					
Nasal congestion	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Associated with bloody nasal discharge or epistaxis	-	-
Definition: A disorder characterized by obstruction of the nasal passage due to mucosal edema.					
Pharyngeal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the pharynx and another organ or anatomic site.					
Pharyngeal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Transfusion, radiologic, endoscopic, or operative intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the pharynx.					
Pharyngeal mucositis	Endoscopic findings only; minimal symptoms with normal oral intake; mild pain but analgesics not indicated	Moderate pain and analgesics indicated; altered oral intake; limiting instrumental ADL	Severe pain; unable to adequately aliment or hydrate orally; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an inflammation involving the mucous membrane of the pharynx.					
Pharyngeal necrosis	-	-	Inability to aliment adequately by GI tract; tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by a necrotic process occurring in the pharynx.					
Pharyngeal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids); limiting instrumental ADL	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a narrowing of the pharyngeal airway.					
Pharyngolaryngeal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the pharyngolaryngeal region.					
Pleural effusion	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated (e.g., diuretics or limited therapeutic thoracentesis)	Symptomatic with respiratory distress and hypoxia; surgical intervention including chest tube or pleurodesis indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by an increase in amounts of fluid within the pleural cavity. Symptoms include shortness of breath, cough and marked chest discomfort.					
Pleural hemorrhage	Asymptomatic; mild hemorrhage confirmed by thoracentesis	Symptomatic or associated with pneumothorax; chest tube drainage indicated	>1000 ml of blood evacuated; persistent bleeding (150-200 ml/hr for 2 - 4 hr); persistent transfusion indicated; elective operative intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the pleural cavity.					
Pleuritic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the pleura.					
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma.					
Pneumothorax	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated (e.g., tube placement without sclerosis)	Sclerosis and/or operative intervention indicated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by abnormal presence of air in the pleural cavity resulting in the collapse of the lung.					
Postnasal drip	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by excessive mucous secretion in the back of the nasal cavity or throat, causing sore throat and/or coughing.					
Productive cough	Occasional/minimal production of sputum with cough	Moderate sputum production; limiting instrumental ADL	Persistent or copious production of sputum; limiting self care ADL	-	-
Definition: A disorder characterized by expectorated secretions upon coughing.					
Pulmonary edema	Radiologic findings only; minimal dyspnea on exertion	Moderate dyspnea on exertion; medical intervention indicated; limiting instrumental ADL	Severe dyspnea or dyspnea at rest; oxygen indicated; limiting self care ADL	Life-threatening respiratory compromise; urgent intervention or intubation with ventilatory support indicated	Death
Definition: A disorder characterized by accumulation of fluid in the lung tissues that causes a disturbance of the gas exchange that may lead to respiratory failure.					
Pulmonary fibrosis	Mild hypoxemia; radiologic pulmonary fibrosis <25% of lung volume	Moderate hypoxemia; evidence of pulmonary hypertension; radiographic pulmonary fibrosis 25 - 50%	Severe hypoxemia; evidence of right-sided heart failure; radiographic pulmonary fibrosis >50 - 75%	Life-threatening consequences (e.g., hemodynamic/pulmonary complications); intubation with ventilatory support indicated; radiographic pulmonary fibrosis >75% with severe honeycombing	Death
Definition: A disorder characterized by the replacement of the lung tissue by connective tissue, leading to progressive dyspnea, respiratory failure or right heart failure.					
Pulmonary fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical management indicated; limiting instrumental ADL	Limiting self care ADL; endoscopic stenting or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death

Respiratory, thoracic and mediastinal disorders

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Definition: A disorder characterized by an abnormal communication between the lung and another organ or anatomic site.					
Pulmonary hypertension	Minimal dyspnea; findings on physical exam or other evaluation	Moderate dyspnea, cough; requiring evaluation by cardiac catheterization and medical intervention	Severe symptoms, associated with hypoxemia, right heart failure; oxygen indicated	Life-threatening airway consequences; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by an increase in pressure within the pulmonary circulation due to lung or heart disorder.					
Respiratory failure	-	-	-	Life-threatening consequences; urgent intervention, intubation, or ventilatory support indicated	Death
Definition: A disorder characterized by impaired gas exchange by the respiratory system resulting in hypoxemia and a decrease in oxygenation of the tissues that may be associated with an increase in arterial levels of carbon dioxide.					
Retinoic acid syndrome	Fluid retention; <3 kg of weight gain; intervention with fluid restriction and/or diuretics indicated	Moderate signs or symptoms; steroids indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; ventilatory support indicated	Death
Definition: A disorder characterized by weight gain, dyspnea, pleural and pericardial effusions, leukocytosis and/or renal failure originally described in patients treated with all-trans retinoic acid.					
Sinus disorder	Asymptomatic mucosal crusting; blood-tinged secretions	Symptomatic stenosis or edema/narrowing interfering with airflow; limiting instrumental ADL	Stenosis with significant nasal obstruction; limiting self care ADL	Necrosis of soft tissue or bone; urgent operative intervention indicated	Death
Definition: A disorder characterized by involvement of the paranasal sinuses.					
Sleep apnea	Snoring and nocturnal sleep arousal without apneic periods	Moderate apnea and oxygen desaturation; excessive daytime sleepiness; medical evaluation indicated; limiting instrumental ADL	Oxygen desaturation; associated with hypertension; medical intervention indicated; limiting self care ADL	Cardiovascular or neuropsychiatric symptoms; urgent operative intervention indicated	Death
Definition: A disorder characterized by cessation of breathing for short periods during sleep.					
Sneezing	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by the involuntary expulsion of air from the nose.					
Sore throat	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL; limiting ability to swallow	-	-
Definition: A disorder characterized by of marked discomfort in the throat					
Stridor	-	-	Respiratory distress limiting self care ADL; medical intervention indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a high pitched breathing sound due to laryngeal or upper airway obstruction.					
Tracheal fistula	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; tube thoracostomy or medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., stent or primary closure)	Life-threatening consequences; urgent operative intervention indicated (e.g., thoracoplasty, chronic open drainage or multiple thoracotomies)	Death
Definition: A disorder characterized by an abnormal communication between the trachea and another organ or anatomic site.					
Tracheal mucositis	Endoscopic findings only; minimal hemoptysis, pain, or respiratory symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an inflammation involving the mucous membrane of the trachea.					
Tracheal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., steroids)	Stridor or respiratory distress limiting self care ADL; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a narrowing of the trachea.					

Respiratory, thoracic and mediastinal disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Voice alteration	Mild or intermittent change from normal voice	Moderate or persistent change from normal voice; still understandable	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; may require assistive technology	-	-
Definition: A disorder characterized by a change in the sound and/or speed of the voice.					
Wheezing	Detectable airway noise with minimal symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe respiratory symptoms limiting self care ADL; oxygen therapy or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a high-pitched, whistling sound during breathing. It results from the narrowing or obstruction of the respiratory airways.					
Respiratory, thoracic and mediastinal disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Skin and subcutaneous tissue disorders					
	Grade				
Adverse Event	1	2	3	4	5
Alopecia	Hair loss of <50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss but it does not require a wig or hair piece to camouflage	Hair loss of >=50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by a decrease in density of hair compared to normal for a given individual at a given age and body location.					
Body odor	Mild odor; physician intervention not indicated; self care interventions	Pronounced odor; psychosocial impact; patient seeks medical intervention	-	-	-
Definition: A disorder characterized by an abnormal body smell resulting from the growth of bacteria on the body.					
Bullous dermatitis	Asymptomatic; blisters covering <10% BSA	Blisters covering 10 - 30% BSA; painful blisters; limiting instrumental ADL	Blisters covering >30% BSA; limiting self care ADL	Blisters covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Definition: A disorder characterized by inflammation of the skin characterized by the presence of bullae which are filled with fluid.					
Dry skin	Covering <10% BSA and no associated erythema or pruritus	Covering 10 - 30% BSA and associated with erythema or pruritus; limiting instrumental ADL	Covering >30% BSA and associated with pruritus; limiting self care ADL	-	-
Definition: A disorder characterized by flaky and dull skin; the pores are generally fine, the texture is a papery thin texture.					
Erythema multiforme	Target lesions covering <10% BSA and not associated with skin tenderness	Target lesions covering 10 - 30% BSA and associated with skin tenderness	Target lesions covering >30% BSA and associated with oral or genital erosions	Target lesions covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Definition: A disorder characterized by target lesions (a pink-red ring around a pale center).					
Erythroderma	-	Erythema covering >90% BSA without associated symptoms; limiting instrumental ADL	Erythema covering >90% BSA with associated symptoms (e.g., pruritus or tenderness); limiting self care ADL	Erythema covering >90% BSA with associated fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Definition: A disorder characterized by generalized inflammatory erythema and exfoliation. The inflammatory process involves > 90% of the body surface area.					
Fat atrophy	Covering <10% BSA and asymptomatic	Covering 10 - 30% BSA and associated with erythema or tenderness; limiting instrumental ADL	Covering >30% BSA; associated with erythema or tenderness; limiting self-care ADL	-	-
Definition: A disorder characterized by shrinking of adipose tissue.					
Hirsutism	In women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair	In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by the presence of excess hair growth in women in anatomic sites where growth is considered to be a secondary male characteristic and under androgen control (beard, moustache, chest, abdomen)					
Hyperhidrosis	Limited to one site (palms, soles, or axillae); self care interventions	Involving >1 site; patient seeks medical intervention; associated with psychosocial impact	Generalized involving sites other than palms, soles, or axillae; associated with electrolyte/hemodynamic imbalance	-	-
Definition: A disorder characterized by excessive perspiration.					

Skin and subcutaneous tissue disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Hypertrichosis	Increase in length, thickness or density of hair that the patient is either able to camouflage by periodic shaving or removal of hairs or is not concerned enough about the overgrowth to use any form of hair removal	Increase in length, thickness or density of hair at least on the usual exposed areas of the body [face (not limited to beard/moustache area) plus/minus arms] that requires frequent shaving or use of destructive means of hair removal to camouflage; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by hair density or length beyond the accepted limits of normal in a particular body region, for a particular age or race.					
Hypohidrosis	-	Symptomatic; limiting instrumental ADL	Increase in body temperature; limiting self care ADL	Heat stroke	Death
Definition: A disorder characterized by reduced sweating.					
Lipohypertrophy	Asymptomatic and covering <10% BSA	Covering 10 - 30% BSA and associated tenderness; limiting instrumental ADL	Covering >30% BSA and associated tenderness and narcotics or NSAIDs indicated; lipohypertrophy; limiting self care ADL	-	-
Definition: A disorder characterized by hypertrophy of the subcutaneous adipose tissue at the site of multiple subcutaneous injections of insulin.					
Nail discoloration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by a change in the color of the nail plate.					
Nail loss	Asymptomatic separation of the nail bed from the nail plate or nail loss	Symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental ADL	-	-	-
Definition: A disorder characterized by loss of all or a portion of the nail.					
Nail ridging	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by vertical or horizontal ridges on the nails.					
Pain of skin	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the skin.					
Palmar-plantar erythrodysesthesia syndrome	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self care ADL	-	-
Definition: A disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet.					
Periorbital edema	Soft or non-pitting	Indurated or pitting edema; topical intervention indicated	Edema associated with visual disturbance; increased intraocular pressure, glaucoma or retinal hemorrhage; optic neuritis; diuretics indicated; operative intervention indicated	-	-
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid around the orbits of the face.					
Photosensitivity	Painless erythema and erythema covering <10% BSA	Tender erythema covering 10 - 30% BSA	Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in sensitivity of the skin to light.					

Skin and subcutaneous tissue disorders

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Pruritus	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	-	-
Definition: A disorder characterized by an intense itching sensation.					
Purpura	Combined area of lesions covering <10% BSA	Combined area of lesions covering 10 - 30% BSA; bleeding with trauma	Combined area of lesions covering >30% BSA; spontaneous bleeding	-	-
Definition: A disorder characterized by hemorrhagic areas of the skin and mucous membrane. Newer lesions appear reddish in color. Older lesions are usually a darker purple color and eventually become a brownish-yellow color.					
Rash acneiform	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences	Death
Definition: A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back.					
Rash maculo-papular	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbillform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritus.					
Scalp pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation in the skin covering the top and the back of the head.					
Skin atrophy	Covering <10% BSA; associated with telangiectasias or changes in skin color	Covering 10 - 30% BSA; associated with striae or adnexal structure loss	Covering >30% BSA; associated with ulceration	-	-
Definition: A disorder characterized by the degeneration and thinning of the epidermis and dermis.					
Skin hyperpigmentation	Hyperpigmentation covering <10% BSA; no psychosocial impact	Hyperpigmentation covering >10% BSA; associated psychosocial impact	-	-	-
Definition: A disorder characterized by darkening of the skin due to excessive melanin deposition.					
Skin hypopigmentation	Hypopigmentation or depigmentation covering <10% BSA; no psychosocial impact	Hypopigmentation or depigmentation covering >10% BSA; associated psychosocial impact	-	-	-
Definition: A disorder characterized by loss of skin pigment.					
Skin induration	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration, unable to slide or pinch skin; limiting joint movement or orifice (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death
Definition: A disorder characterized by an area of hardness in the skin.					
Skin ulceration	Combined area of ulcers <1 cm; nonblanchable erythema of intact skin with associated warmth or edema	Combined area of ulcers 1 - 2 cm; partial thickness skin loss involving skin or subcutaneous fat	Combined area of ulcers >2 cm; full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia	Any size ulcer with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures with or without full thickness skin loss	Death
Definition: A disorder characterized by circumscribed, inflammatory and necrotic erosive lesion on the skin.					

Skin and subcutaneous tissue disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Stevens-Johnson syndrome	-	-	Skin sloughing covering <10% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Skin sloughing covering 10 - 30% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Death
Definition: A disorder characterized by less than 10% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.					
Telangiectasia	Telangiectasias covering <10% BSA	Telangiectasias covering >10% BSA; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by local dilatation of small vessels resulting in red discoloration of the skin or mucous membranes.					
Toxic epidermal necrolysis	-	-	-	Skin sloughing covering >=30% BSA with associated symptoms (e.g., erythema, purpura, or epidermal detachment)	Death
Definition: A disorder characterized by greater than 30% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.					
Urticaria	Urticarial lesions covering <10% BSA; topical intervention indicated	Urticarial lesions covering 10 - 30% BSA; oral intervention indicated	Urticarial lesions covering >30% BSA; IV intervention indicated	-	-
Definition: A disorder characterized by an itchy skin eruption characterized by wheals with pale interiors and well-defined red margins.					
Skin and subcutaneous tissue disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Social circumstances					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Menopause	Menopause occurring at age 46 - 53 years of age	Menopause occurring at age 40 - 45 years of age	Menopause occurring before age 40 years of age	-	-
Definition: A disorder characterized by the permanent cessation of menses, usually defined by 12 consecutive months of amenorrhea in a woman over 45 years of age.					
Social circumstances - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Surgical and medical procedures					
	Grade				
Adverse Event	1	2	3	4	5
Surgical and medical procedures - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

Vascular disorders

	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Capillary leak syndrome	-	Symptomatic; medical intervention indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by leakage of intravascular fluids into the extravascular space. This syndrome is observed in patients who demonstrate a state of generalized leaky capillaries following shock syndromes, low-flow states, ischemia-reperfusion injuries, toxemias, medications, or poisoning. It can lead to generalized edema and multiple organ failure.					
Flushing	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Symptomatic, associated with hypotension and/or tachycardia; limiting self care ADL	-	-
Definition: A disorder characterized by episodic reddening of the face.					
Hematoma	Mild symptoms; intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a localized collection of blood, usually clotted, in an organ, space, or tissue, due to a break in the wall of a blood vessel.					
Hot flashes	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by an uncomfortable and temporary sensation of intense body warmth, flushing, sometimes accompanied by sweating upon cooling.					
Hypertension	Prehypertension (systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg)	Stage 1 hypertension (systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg); medical intervention indicated; recurrent or persistent (>=24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg if previously WNL; monotherapy indicated Pediatric: recurrent or persistent (>=24 hrs) BP >ULN; monotherapy indicated	Stage 2 hypertension (systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg); medical intervention indicated; more than one drug or more intensive therapy than previously used indicated Pediatric: Same as adult	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated Pediatric: Same as adult	Death
Definition: A disorder characterized by a pathological increase in blood pressure; a repeatedly elevation in the blood pressure exceeding 140 over 90 mm Hg.					
Hypotension	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention or hospitalization indicated	Life-threatening and urgent intervention indicated	Death
Definition: A disorder characterized by a blood pressure that is below the normal expected for an individual in a given environment.					
Lymph leakage	-	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the loss of lymph fluid into the surrounding tissue or body cavity.					
Lymphedema	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by excessive fluid collection in tissues that causes swelling.					
Lymphocele	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	-	-
Definition: A disorder characterized by a cystic lesion containing lymph.					
Peripheral ischemia	-	Brief (<24 hrs) episode of ischemia managed non-surgically and without permanent deficit	Recurring or prolonged (>=24 hrs) and/or invasive intervention indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A disorder characterized by impaired circulation to an extremity.					
Phlebitis	-	Present	-	-	-
Definition: A disorder characterized by inflammation of the wall of a vein.					
Superficial thrombophlebitis	-	Present	-	-	-
Definition: A disorder characterized by a blood clot and inflammation involving a superficial vein of the extremities.					

Vascular disorders					
	Grade				
Adverse Event	**1**	**2**	**3**	**4**	**5**
Superior vena cava syndrome	Asymptomatic; incidental finding of SVC thrombosis	Symptomatic; medical intervention indicated (e.g., anticoagulation, radiation or chemotherapy)	Severe symptoms; multi-modality intervention indicated (e.g., anticoagulation, chemotherapy, radiation, stenting)	Life-threatening consequences; urgent multi-modality intervention indicated (e.g., lysis, thrombectomy, surgery)	Death
Definition: A disorder characterized by obstruction of the blood flow in the superior vena cava. Signs and symptoms include swelling and cyanosis of the face, neck, and upper arms, cough, orthopnea and headache.					
Thromboembolic event	Venous thrombosis (e.g., superficial thrombosis)	Venous thrombosis (e.g., uncomplicated deep vein thrombosis), medical intervention indicated	Thrombosis (e.g., uncomplicated pulmonary embolism [venous], non-embolic cardiac mural [arterial] thrombus), medical intervention indicated	Life-threatening (e.g., pulmonary embolism, cerebrovascular event, arterial insufficiency); hemodynamic or neurologic instability; urgent intervention indicated	Death
Definition: A disorder characterized by occlusion of a vessel by a thrombus that has migrated from a distal site via the blood stream.					
Vasculitis	Asymptomatic, intervention not indicated	Moderate symptoms, medical intervention indicated	Severe symptoms, medical intervention indicated (e.g., steroids)	Life-threatening; evidence of peripheral or visceral ischemia; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation involving the wall of a vessel.					
Visceral arterial ischemia	-	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (>=24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A disorder characterized by a decrease in blood supply due to narrowing or blockage of a visceral (mesenteric) artery.					
Vascular disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; disabling; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death

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13.5 Appendix 5: Acute Radiation Morbidity Scoring Criteria (RTOG)

	[0]	[1]	[2]	[3]	[4]
SKIN	No change over baseline	Follicular, faint or dull erythema/ epilation/dry desquamation/ decreased sweating	Tender or bright erythema, patchy moist desquamation/ moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
UPPER G.I.	No change	Anorexia with <=5% weight loss from pretreatment baseline/ nausea not requiring antiemetics/ abdominal discomfort not requiring parasympatholytic drugs or analgesics	Anorexia with <=15% weight loss from pretreatment baseline/nausea &/ or vomiting requiring antiemetics/ abdominal pain requiring analgesics	Anorexia with >15% weight loss from pretreatment baseline or requiring N-G tube or parenteral support. Nausea &/or vomiting requiring tube or parenteral support/abdominal pain, severe despite medication/hematemesis or melena/ abdominal distention (flat plate radiograph demonstrates distended bowel loops	Ileus, subacute or acute obstruction, perforation, GI bleeding requiring transfusion/abdominal pain requiring tube decompression or bowel diversion
LOWER G.I. INCLUDING PELVIS	No change	Increased frequency or change in quality of bowel habits not requiring medication/ rectal discomfort not requiring analgesics	Diarrhea requiring parasympatholytic drugs (e.g., Lomotil)/ mucous discharge not necessitating sanitary pads/ rectal or abdominal pain requiring analgesics	Diarrhea requiring parenteral support/ severe mucous or blood discharge necessitating sanitary pads/abdominal distention (flat plate radiograph demonstrates distended bowel loops)	Acute or subacute obstruction, fistula or perforation; GI bleeding requiring transfusion; abdominal pain or tenesmus requiring tube decompression or bowel diversion

	[0]	[1]	[2]	[3]	[4]
GENITOURINARY	No change	Frequency of urination or nocturia twice pretreatment habit/ dysuria, urgency not requiring medication	Frequency of urination or nocturia which is less frequent than every hour. Dysuria, urgency, bladder spasm requiring local anesthetic (e.g., Pyridium)	Frequency with urgency and nocturia hourly or more frequently/ dysuria, pelvis pain or bladder spasm requiring regular, frequent narcotic/gross hematuria with/ without clot passage	Hematuria requiring transfusion/ acute bladder obstruction not secondary to clot passage, ulceration or necrosis
HEMATOLOGIC WBC (X 1000)	>=4.0	3.0 - <4.0	2.0 - <3.0	1.0 - <2.0	<1.0
PLATELETS (X 1000)	>=100	75 - <100	50 - <75	25 - <50	<25 or spontaneous bleeding
NEUTROPHILS	>=1.9	1.5 - <1.9	1.0 - <1.5	0.5 - <1.0	<0.5 or sepsis
HEMOGLOBIN (GM %)	>11	11-9.5	<9.5 - 7.5	<7.5 - 5.0	-------
HEMATOCRIT (%)	>=32	28 - <32	<28	Packed RBC transfusion required	-------

GUIDELINES: The acute morbidity criteria are used to score/grade toxicity from radiation therapy. The criteria are relevant from day 1, the commencement of therapy, through day 90.

The evaluator must attempt to discriminate between disease- and treatment-related signs and symptoms.

An accurate baseline evaluation prior to commencement of therapy is necessary.

All toxicities Grade 3, 4 or 5* must be verified by the Principal Investigator.

*ANY TOXICITY WHICH CAUSED DEATH IS GRADED 5.

13.6 Appendix 6: Preparation of Investigational Products

VGX-3100 and INO-9012 will be combined by the site pharmacist into a single syringe for subjects using the following procedure:

0. Using aseptic technique, withdraw 1.2 mL from the vial SynCon™ VGX-3100 with a 3 mL syringe and inject into an empty sterile vial. Set this "mixing" vial which now contains 1.2 mL of VGX-3100 aside.
1. Using a new 1 mL syringe, withdraw 0.12 mL from the vial SynCon™ INO-9012 and add the 0.12 mL to the "mixing" vial containing 1.2 mL of VGX-3100. The final volume of this vial should now be 1.32 mL of INO-3112(VGX-3100 / INO-9012).
2. Using a 3 mL syringe, withdraw 1.1 mL of INO-3112 from the "mixing" vial. This syringe will be used for dosing of subjects.

13.7 Appendix 7: CELLECTRA®-5P Error Reporting Form

Please complete the form and fax to [redacted] **or scan the form to** [redacted]

Protocol#_____ **Site#** _____ **Subject ID** _____ **Week#**_____ **Visit Date**_____

DEVICE INFORMATION

CELLECTRA®-5P Serial No: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
Located on label on the front cover

CELLECTRA®-5P Applicator Serial No: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
Located on label on the handle

CELLECTRA®-5P Array Lot No: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
Located on label on the package

Time of Electroporation: _____ **Location of Treatment/EP:** ☐ Deltoid **R**ight/**L**eft _____

☐ Other Location, specify:_____ **IM-5P, was the EP Guide used?** ☐ YES ☐ NO

If EP Guide was used, please provide reason and include subject's BMI.

Was injection successful? ☐ YES ☐ NO

If NO, please provide reason and include needle gauge and syringe volume used.

Did the display on the device read EP successful? ☐ YES ☐ NO

If NO, please check all complications that led to failure and describe complication below

☐ Impedance Test Error message displayed, fill out Impedance Test Error section below

☐ Electroporation Error message displayed, fill out Electroporation Error section below

☐ EP aborted by trigger or keypad error message displayed

☐ Battery level too low for electroporation message displayed

☐ Difficulty inserting array into muscle or skin

☐ Other, please specify below

Describe device complication below (continue on back if necessary):

Total # of arrays used: _____

Impedance Test Error

Was the array inserted in subject's arm? ☐ YES ☐ NO Total # of attempts: _____

Were all attempts performed on the same day? ☐ YES ☐ NO
(provide other date(s):_____

Was a different location used for each attempt? ☐ YES ☐ NO

Was a new array used for each attempt? ☐ YES ☐ NO

Please provide any additional information below (continue on back if necessary):

Electroporation Error

Were there 3 (IM) or 4 (ID) involuntary muscle contractions? ☐ YES ☐ NO (how many_____

Was the array fully inserted in the subject's arm? ☐ YES ☐ NO

Was the array inserted perpendicular to the subject's skin? ☐ YES ☐ NO

Did the needles of the array appear damaged in any way? ☐ YES ☐ NO

If you were provided a sharps shuttle, please eject the array into a shuttle and ship to Inovio.

Please provide any additional information below (continue on back if necessary):

13.8 Appendix 8: New York Heart Association (NYHA) Functional Classification

The NYHA classifies heart failure into classes based on functional limitations and severity.

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

*The Criteria Committee of the New York Heart Association. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256.

13.9 Appendix 9: Participant Reminder Card

Appendix 10. Participant Reminder Card

Participant ID: _____ Date of Study Treatment_____

Site of Injection: ☐ Right Arm ☐ Left Arm ☐ Right Leg ☐ Left Leg

Instructions: Please complete this reminder card in the evening after and for three days following your study treatment. The "Evening of study treatment" column should include any side effects from the time you received the study treatment until 11:59pm of that day. Days 1, 2 and 3 should include any side effects from midnight (12:00 am) to 11:59 pm of that day (1 day, 2 days or 3 days after receiving the study treatment).

Take this card with you to your next study visit for review with the study team. If you have any questions, or if you have any concerns or side effects that you'd like to discuss, please contact your study team.

To describe the size of any area that is red or swollen, please use the measuring tool provided with this reminder card to indicate the approximate size of a circle that could fully cover the area of redness or swelling.

Possible side effects	Evening of study treatment	1 day after study treatment	2 days after study treatment	3 days after study treatment	Date Resolved
Redness or bruising at treatment site	□ None □ Diameter (in cm) from measuring tool: _____ □ Greater than 7cm	□ None □ Diameter (in cm) from measuring tool: _____ □ Greater than 7cm	□ None □ Diameter (in cm) from measuring tool: _____ □ Greater than 7cm	□ None □ Diameter (in cm) from measuring tool: _____ □ Greater than 7cm	_____ If date unknown: □ 1 week** □ 2 weeks** □ 3 weeks**
Pain at treatment site	□ None □ A little, controlled with OTC* meds □ A lot, OTC meds didn't work, prevented normal activity	□ None □ A little, controlled with OTC* meds □ A lot, OTC meds didn't work, prevented normal activity	□ None □ A little, controlled with OTC* meds □ A lot, OTC meds didn't work, prevented normal activity	□ None □ A little, controlled with OTC* meds □ A lot, OTC meds didn't work, prevented normal activity	_____ If date unknown: □ 1 week** □ 2 weeks** □ 3 weeks**
Swelling/ Edema at treatment site	□ None □ Diameter (in cm) from measuring tool: _____ □ Greater than 7cm	□ None □ Diameter (in cm) from measuring tool: _____ □ Greater than 7cm	□ None □ Diameter (in cm) from measuring tool: _____ □ Greater than 7cm	□ None □ Diameter (in cm) from measuring tool: _____ □ Greater than 7cm	_____ If date unknown: □ 1 week** □ 2 weeks** □ 3 weeks**
Oral Temperature	Please record below: □ °F _____ □ °C	Please record below: □ °F _____ □ °C	Please record below: □ °F _____ □ °C	Please record below: □ °F _____ □ °C	

* OTC – Over the counter analgesics or painkillers such as paracetamol, acetaminophen (e.g. Tylenol®) or ibuprofen (e.g. Advil® or Motrin®).
** After study treatment

Did you have any other side effects?

Other side effects (insert below)	Evening of study treatment	1 day after study treatment	2 days after study treatment	3 days after study treatment	Date Resolved
	□ Mild, barely noticeable □ Moderate, slowed me down □ Severe	□ Mild, barely noticeable □ Moderate, slowed me down □ Severe	□ Mild, barely noticeable □ Moderate, slowed me down □ Severe	□ Mild, barely noticeable □ Moderate, slowed me down □ Severe	_____ If date unknown: □ 1 week** □ 2 weeks** □ 3 weeks**
	□ Mild, barely noticeable □ Moderate, slowed me down □ Severe	□ Mild, barely noticeable □ Moderate, slowed me down □ Severe	□ Mild, barely noticeable □ Moderate, slowed me down □ Severe	□ Mild, barely noticeable □ Moderate, slowed me down □ Severe	_____ If date unknown: □ 1 week** □ 2 weeks** □ 3 weeks**

** After study treatment

Did you contact the study team for any symptoms that were not listed here or the severity was worse than the available choices? ☐ Yes ☐ No

About Injection Site Reaction

The most common reactions to the study treatment are reactions at the injection site such as an area of redness, a little bruising, possible swelling, and temporary pain. For most people, it is not bothersome at all and disappears in a day or two. However, it may last a week or more.

If you have any concerns about your symptoms, have any ongoing injection site reactions or side effects that are still present more than 3 days after the study treatment, please contact your study team.

Coordinator Name: _____
Coordinator Telephone Number: _____

Did you take any medications for your injection site reactions or other symptoms?
☐ Yes (record below) ☐ No

Is there anything else that you would like to discuss with the study team?
☐ Yes (record below) ☐ No

13.10 Appendix 10: RECIST

A. Response will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1). 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:

i. 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.

ii. 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).

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.

iii. Response Criteria

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.

iv. 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).

v. 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.

vi. 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 target and non-target disease.

Time point response: patients with target (+/- non-target disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-CR/Non-PD/not evaluated	No	PR
SD	Non-CR/Non-PD/not evaluated	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Time point response: patients with non-target disease only

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		

vii. Confirmation/Duration of Response

Confirmation: Confirmation of PR and CR is required to ensure responses identified are not the results of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation.

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 on study)

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 recurrent disease is objectively documented.

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 sum on study (if baseline sum is the smallest, this is the reference for calculation of PD).

B. **Progression Free Survival**- any progression of disease as defined below will be recorded and summarized for subjects in the individual cohorts and overall

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