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Clinical Trial Protocol

PHASE 1 TRIAL: T4 IMMUNOTHERAPY OF HEAD AND NECK CANCER

Version 2.5

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Clinical Trial Protocol Version History

Version No.	Issue Date	Reason for Update
1.0	4-8-2012	N/A
1.1	4-9-2012	Version 1 under revision following preliminary feedback from MHRA
2.0	24-11-2012	Several minor revisions following EAG/ MHRA and REC review
2.1	3-12-2012	Inclusion of tocilizumab in management of cytokine storm; add ferritin measurement
2.2	5-4-2013	Clarify the terms enrolment/ registration in Inclusion Criteria. Amend Table 3 to clarify screening period (top of table) and add 1 screening ECG that was missing. Clarify nature of AE (adverse events) in Figure 5
2.3	February 2015	Update immunophenotyping panel (p30); manufacturing process (p31); blood samples taken from inpatients (p33); management of toxicity (p34 and Appendix 2); add serological testing of blood to be used to manufacture T4 immunotherapy (p35); modify details of blood volumes/bottles taken over the 6 weeks post treatment (Chapters 6/9). Update tumour biopsy storage details (p50). Sample handling in section 9.3.3 updated (p52). References updated.
2.4	March 2015	Provide further detail on manufacturing process including amended Figure 4 to comply with IMPD version 4.1
2.5	May 2015	Correction of errors in superscripted notes on page 40 Realignment of "Xs" in Table on p40 Replacement of the inaccurate term "metronomic" with "low dose", as pertains to cyclophosphamide (no effect on treatment). Correction of typographical error (creatine kinase rather than creatinine kinase) Clarification of wording regarding prior treatments that preclude participation in the trial (p24) Clarification that manufacture of T4 immunotherapy may take 14-16 days Update drugs that may be used for local anaesthesia

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CONFIDENTIALITY STATEMENT

This Clinical Trial Protocol is a confidential document for the sole information and use of the investigating team and regulatory and other reviewing bodies. However, this document may be made available to other parties upon request to the Chief Investigator.

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List of Abbreviations

+ A chimeric cytokine receptor in which the human IL-4 receptor α ectodomain is fused

to the human IL-2 receptor β transmembrane and endomain

ACT - Adoptive Cell Therapy

AE - Adverse Event

ALT - Alanine Aminotransferase

API - Active Pharmaceutical Ingredients

AR - Adverse Reaction

ATMP - Advanced Therapeutic Medicinal Product

CAR - Chimeric Antigen Receptor
CD - Cluster of Designation
CI - Chief Investigator
CK - Creatine Kinase
CR - Complete Response
CRF - Case Report Form
CRP - C-Reactive Protein

CTCAE - Common Terminology Criteria for Adverse Events

CXR - Chest X-Ray

CT

DLT - Dose Limiting Toxicity

DSUR - Development Safety Update Report

- Computed Tomography

ECG - Electrocardiogram
ECHO - Echocardiogram

EGF(r) - Epidermal Growth Factor (receptor)

ENT - Ear, Nose and Throat EOP - End of Production

FACS - Fluorescence Activated Cell Sorting

FBC - Full Blood Count FDG - Fluorodeoxyglucose

GMP - Good Manufacturing Practice
 H&E - Haematoxylin & Eosin Staining
 HIV - Human Immunodeficiency Virus
 HLA - Human Leukocyte Antigen
 HTLV - Human T-lymphotropic virus

IFN - Interferon IL - Interleukin

IPC - Internal Process Control

KHP CTO - King's Health Partners Clinical Trials Office

LD - Lymphodepleting
LFT - Liver Function Tests

MABEL - Minimum Anticipated Biological Effect Level

MDM - Multi-disciplinary Team Meeting

MHRA - Medicines and Healthcare products Regulatory Agency

MRI - Magnetic Resonance Imaging
MTD - Maximum Tolerated Dose

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MUGA - Multi-Gated Acquisition ScanNCI - National Cancer Institute

NE - Not Evaluable

PBMC - Peripheral Blood Mononuclear Cells

PBS - Phosphate Buffered Saline

PD - Progressive Disease
PR - Partial Response
QC - Quality Control
QP - Qualified Person

(q)PCR - (Quantitative) Polymerase Chain ReactionRDPT - Recommended Dose for Phase 2 Testing

REC - Research Ethics Committee

RECIST - Response Evaluation Criteria In Solid Tumours

RTK - Receptor Tyrosine Kinase

RT-PCT - Reverse Transcriptase Polymerase Chain Reaction

SAE - Serious Adverse Event

SCCHN - Squamous Cell Carcinoma of Head and Neck

SCID - Severe Combined Immunodeficiency

SD - Stable Disease

SPECT - Single Photon Emission Computed Tomography

SmPC - Summary of Product CharacteristicsSOP - Standard Operating Procedure

(S)SAR - (Suspected) Serious Adverse Reaction

SUSAR - Suspected Unexpected Serious Adverse Reaction

T2A - Thosea Asigna 2A Peptide

T1E - A chimeric peptide comprising transforming growth factor- α (upstream of cysteine 1)

fused to epidermal growth factor (downstream of cysteine 1)

T1E28z - A chimeric antigen receptor in which the T1E peptide is fused to CD28 (hinge

transmembrane and endodomain) followed by CD35

TBI - Total Body Irradiation

TIL - Tumour-Infiltrating Lymphocytes

(free) T4 - Thyroxine

T4 - The combination of 4αβ co-expressed with T1E28z

TGF- α - Transforming Growth Factor- α

TMF - Trial Master File

TNF - Tumour Necrosis Factor Treg - Regulatory T-Cells

TUNEL - Terminal Deoxynucleotidyl Transferase dUTP Nick End Labelling

UAR - Unexpected Adverse Reaction

U&E - Urea and Electrolytes

WOCB - Women of Childbearing Potential

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1. INTRODUCTION

1.1 Background Disease Information

1.1.1 The Unmet Need: Improved Loco-regional Control of Head and Neck Cancer

Squamous cell carcinoma of the head and neck (SCCHN) is the sixth most common cancer worldwide, with 600,000 cases diagnosed annually (1, 2). Despite state of the art multimodal and multidisciplinary therapy incorporating surgery, radiotherapy, chemotherapy and targeted agents, five-year survival remains at only 50%. Indeed there has been little improvement in patient survival over the past 30 years (1, 3). In patients with recurrent or metastatic disease the median survival time is a mere six months (4, 5).

In designing this clinical trial, we have identified two key areas of unmet need.

(i) Locally recurrent SCCHN

Loco-regional disease accounts for the majority of deaths in patients with SCCHN (4, 5). This contrasts with most other solid tumour types in which metastatic spread constitutes the primary cause of death. Loco-regional treatment failure occurs in 60% - 70% of patients after conventional surgery and radiation (6-8). Recurrent tumours can be painful and may invade into vital tissues, resulting in considerable morbidity and mortality. In that setting, younger and fitter patients may be suitable for treatment with (re)-irradiation (9) or salvage surgery (9). Surgery is the treatment of choice for resectable lesions, although salvage rates tend to vary, based on the site of primary tumour. Unfortunately however, comorbidity and/ or advanced disease stage commonly precludes the selection of either of these options for patients. Furthermore, re-irradiation may not be possible if tumours recur in a previously irradiated location (10). If surgery or radiation are not suitable, recurrent head and neck cancer is often managed with chemotherapy - either alone (11-13) - or together with the anti-EGF receptor antibody, cetuximab (14). In support of this approach, the combined use of cetuximab together with platinum-based chemotherapy has led to a three-month prolongation in median survival for patients with recurrent or metastatic SCCHN (15). However, the UK National Institute for Health and Clinical Excellence has that cost effective ruled this does not represent a use of NHS (http://guidance.nice.org.uk/TA172; accessed May 22nd, 2011). Furthermore, over 50% of patients with recurrent SCCHN died as a direct consequence of loco-regionally recurrent disease even though salvage treatment was performed (16). These considerations highlight a clear need for additional therapeutic options for patients with locally recurrent SCCHN.

(ii) Newly diagnosed patients with locally advanced SCCHN

About 1 in 10 patients with newly diagnosed SCCHN are not suitable for any form of active therapy whatsoever (17). In a two-year period, forty-four such patients were reviewed by the multidisciplinary team meeting (MDM) at Guy's and St Thomas' NHS Foundation Trust, which covers the South-East London Cancer Network. Patients are unsuitable for conventional therapies owing to co-morbidity, locally advanced disease, metastatic disease and patient refusal. For those patients, the 30 week mortality rate is 100% (17). Currently, management of such individuals involves counselling, symptom control and support of both airway (tracheostomy) and nutritional status (eg enteral feeding via PEG

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gastrostomy). A low-intensity therapeutic approach that may achieve some improvement in local disease control could provide meaningful additional benefit for some of these patients.

This study aims to investigate intra-tumoural administration of a novel cellular immunotherapy in patients with at least one measurable and accessible site of loco-regional progressive disease with or without concurrent distant metastases.

1.1.2 Target and Rationale

In SCCHN, the ErbB family of receptor tyrosine kinases (RTK) represents a highly attractive target for novel therapies. The ErbB family comprises four members, namely epidermal growth factor receptor (EGFr or ErbB-1), ErbB-2 (HER2/neu), ErbB-3 and ErbB-4 (18-20). These molecules provide a molecular network that plays a fundamental role in many biological systems. Individual ErbB molecules bind 2-8 distinct ligands with the exception of the orphan receptor, ErbB2. Signal complexity is diversified by the ability of ErbB RTK to undergo ligand-driven homo- or hetero-dimerization. Although all possible binary ErbB combinations have been detected, ErbB2 is the preferred dimerization partner for all other family members, owing to its constitutively "open" ectodomain (21). In the adult, ErbB receptors are expressed at low levels in several non-haemopoietic tissues. However, increased synthesis of ErbB family members correlates strongly with the development of several solid tumors, particularly squamous cell carcinomas.

Overwhelming evidence implicates dysregulated ErbB signalling in the pathogenesis of SCCHN (22-29). This tumour represents a classical model of EGF-driven oncogenesis since it strongly overexpresses ErbB1 in >90% of cases. Over-expression of ErbB1 is implicated in resistance to radiotherapy and is a strong prognostic marker for poor survival and metastasis (27-29). Furthermore, since the level of ErbB1 expression increases with tumour progression, this molecule represents an increasingly appropriate target with disease evolution (30, 31). Disappointingly however, clinical data indicate that only a minority of patients with SCCHN benefit from ErbB1 targeted therapies (32). In part, this may result from the frequency with which other ErbB family members are co-expressed, conferring worsened prognosis (22, 23, 25). In many tumours, therapeutic resistance to ErbB-directed therapies is mediated by upregulated activity of non-targeted family members (33-37). In agreement with this, resistance of SCCHN cell lines to ErbB1-targeted antibody or small molecule agents has been associated with increased ErbB2/ErbB3 signalling (32, 38).

1.2 Background Therapeutic Information

1.2.1 Chimeric Antigen Receptor-Engrafted T-cells in the Treatment of Relapsed Head and Neck Cancer

The above considerations provide a strong rationale for targeting of the extended ErbB network in SCCHN. This study aims to achieve this goal using a novel immunotherapeutic strategy based upon chimeric antigen receptor (CAR) technology. Chimeric antigen receptors are fusion molecules in which a targeting moiety (eg an antibody fragment or ligand) is coupled in series to hinge, transmembrane and

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T-cell activating domains (39, 40). When expressed in T-lymphocytes, CARs engage native target on the tumour cell surface, obviating the need for either HLA expression or antigen processing. Use of this technology is particularly suited to SCCHN in light of the frequent down regulation by tumour cells of HLA antigens, co-stimulatory ligands or other elements of the antigen processing machinery (41-44). The development of CAR-based immunotherapy has attracted increasing interest in recent years, largely owing to the development of efficient systems for genetic modification of primary human T-cells. Consequently, it is now feasible to engineer large numbers of patient-derived T-cells with specificity for a chosen tumour-associated target molecule.

A number of investigators have examined the efficacy and safety of adoptively transferred T-cells to treat SCCHN (45). Occasional striking and durable clinical responses have been described in patients with advanced disease, both following loco-regional and systemic delivery (46, 47). However, logistic difficulties involved in the generation and expansion of tumour-specific T-cells has compromised further study. With the advent of efficient genetic targeting and *ex-vivo* T-cell culture systems, we now wish to re-investigate this therapeutic modality for patients with SCCHN.

1.2.2 T4 Immunotherapy

The ErbB family of receptor tyrosine kinases will be targeted with a second generation CAR named T1E28z. In this fusion receptor, targeting is achieved with a novel chimeric peptide named T1E. To create the T1E peptide, the five most N-terminal amino acids (amino acids 971-975 of pro-epidermal growth factor precursor (NP_001954.2)) were replaced by sequences encoding the seven most N-terminal amino acids of the mature human TGF- α protein (amino acids 40-46 of pro-transforming growth factor α isoform 1 (NP_003227.1)). The T1E peptide retains the ability of its parent ligands to bind ErbB1 but can also bind with high affinity to the ErbB2/ErbB3 heterodimer combination (48-50).

To engineer the T1E28z fusion receptor (51), cDNA encoding for T1E (amino acids 1-55) was placed downstream of a colony-stimulating factor-1 leader (bases 1-75) and upstream of a human CD28-derived hinge, transmembrane and endodomain (amino acids 114-220), followed by the cytoplasmic domain of the T-cell receptor CD3ζ chain (amino acids 52-164). The structure of the T1E28z CAR is shown in cartoon form in **Figure 1A**. Expression of T1E28z in transduced human T-cells has been demonstrated by flow cytometry and western blotting.

In this clinical trial, the T1E28z CAR will be co-expressed in human T-cells together with a chimeric cytokine receptor named $4\alpha\beta$. The $4\alpha\beta$ chimeric cytokine receptor consists of a fusion in which the human IL-4 receptor (IL-4R) α ectodomain (amino acids 1-233) is fused to the transmembrane and endodomain of the common β receptor subunit (β_c ; amino acids 241-551) used by IL-2 and IL-15 (52). The structure of $4\alpha\beta$ is shown in cartoon form in **Figure 1A**. Binding of IL-4 leads to approximation of the $4\alpha\beta$ chimeric cytokine receptor with the common γ chimeric cytokine receptor. By this means, a potent IL-2-like growth signal is delivered selectively to the transduced T-cells by IL-4, a cytokine that is normally a much weaker growth factor for T-cells. Use of the $4\alpha\beta$ fusion receptor enables rapid, robust and selective expansion of T-cells *ex-vivo* in response to the cytokine interleukin-4 (IL-4) (52).

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Expression of T1E28z and $4\alpha\beta$ will be achieved in patient T-cells using the SFG onco-retroviral expression vector (Figure 1B) (53). Stoichiometric coexpression of both transgenes will be obtained obtained by insertion of an intervening optimized Furin cleavage site (RRKR; (54)) followed by a linker (SGSG) and finally a *Thosea Asigna* 2A (T2A) peptide sequence (EGRGSLLTCGDVEENPGP; Figure 1B) (55). Such peptide sequences cause ribosomal skipping during protein translation, meaning that two polypeptides are produced from a single open reading frame (ie sequences encoded on either side of the "skip" motif). Since the upstream protein will contain T2A-derived peptide on its C-terminus (EGRGSLLTCGDVEENPG), the incorporation of an upstream Furin cleavage site is a useful device to remove this unwanted sequence.

The combination of T1E28z and $4\alpha\beta$ is referred to as "T4". Consequently, we use the term immunotherapy" describe the therapeutic to application of autologous T-cells derived from patients that have been engineered to co-express $4\alpha\beta$ and T1E28z. This study will determine the safety and maximum tolerated dose of intra-tumoural T4

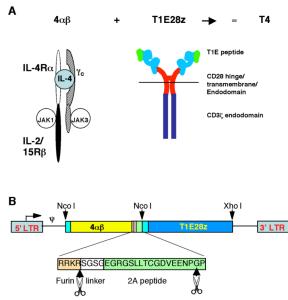


FIGURE 1. Transgene products. **A.** Cartoon structure of the transgenes to be co-expressed in patient T-cells. **B.** The SFG T4 retroviral vector. Stoichiometric co-expression of $4\alpha\beta$ and T1E28z is achieved using a *Thosea Asigna* (T2A) peptide. Since this leaves a short peptide overhang on the C-terminus of the N-terminal protein $(4\alpha\beta)$, a Furin cleavage site is placed upstream as indicated.

immunotherapy (alone, or combined with metronomic cyclophosphamide) in patients with relapsed SCCHN. We will not administer exogenous IL-4 to patients enrolled in this study.

1.2.3 Pre-Clinical Efficacy

Pre-clinical efficacy data are presented in greater detail in the **Investigator Brochure** and the **Investigational Medical Product Dossier.** Findings are summarized briefly below.

First, we set out to characterize precisely which ErbB homo- and heterodimer combinations can be targeted using the T1E28z fusion receptor. To achieve this, T1E28z T-cells were co-cultivated with a panel of (ErbB ^{neg}) 32D haemopoietic cells (56) that had been engineered to express ErbB receptors in all possible single or dual combinations. T-cell activation was indicated by production of the proinflammatory cytokines, interferon-γ (IFN-γ) and IL-2. Comparison was made with a variety of control CARs. T1E28z but not control T-cells were activated by targets that express ErbB1 or ErbB2/3 heterodimers. Weaker activation was also observed in response to ErbB4 homo- and heterodimers. To assess anti-tumour activity, T1E28z T-cells were co-cultivated with a panel of SCCHN cell lines, representing a broad diversity of ErbB receptor expression. T1E28z, but not control T-cells, underwent activation when cultured with several SCCHN cell lines. This was accompanied by the selective destruction of tumour cell monolayers by T1E28z, but not control T-cells. Together, these findings confirm that human T1E28z-engrafted T-cells can recognize a broad range of human SCCHN cell types as a consequence of engagement of ErbB receptors on target cells.

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To examine anti-tumour activity of T1E28z and T4-cells *in-vivo*, a model was established in SCID Beige (immunodeficient) mice engrafted with a firefly luciferase-expressing SCCHN xenograft. When compared to control animals, both populations of ErbB re-targeted T-cells achieved significant anti-tumour activity, without clinical evidence of toxicity. Owing to ease of generation/ expansion, the T4 vector has been chosen for further clinical translation.

1.2.4 Pre-Clinical Safety Testing

Pre-clinical safety testing data are presented in greater detail in the **Investigator Brochure** and the **Investigational Medical Product Dossier**. Findings are summarized briefly below.

We reasoned that it would be appropriate to test toxicity of the therapeutic product (eg human T4⁺ T-cells) in mice for the following reasons.

- Human T-cells can elicit profound toxicity in mice, as illustrated by their ability to induce xenogeneic graft versus host disease following appropriate conditioning treatment (57).
- All human ErbB ligands (including EGF, TGF-α and heregulins) are active on murine target cells (58, 59). This means that human T1E28z⁺ T-cells would be expected to engage murine cells that express relevant ErbB receptors. In agreement with this, we have shown that human T-cells engrafted with the human T1E28z fusion receptor can recognize and destroy a murine ErbB⁺ SCCHN tumour cell line, B7E3 (60).
- Consequently, we examined the toxicity of human T1E28z⁺ T-cells following adoptive transfer into SCID Beige recipient mice. T-cells were transferred either by the intra-tumoural or intravenous routes, directly following gene transfer or after *ex-vivo* activation on ErbB⁺ tumour cells. In these studies, we observed no alteration in clinical status, weight or histological appearance of harvested organs in animals treated in this manner. Histology was assessed by an independent veterinary histopathologist, soon after *in-vivo* T-cell disappearance.
- In several studies that addressed the efficacy of T1E28z⁺ or T4⁺ T-cell immunotherapy, we observed no clinical evidence of T-cell mediated toxicity in mice, following intraperitoneal administration of T-cells. Animals were followed up for up to 128 days in these studies.
- Despite the above, dose-dependent toxicity has been demonstrated following intraperitoneal administration of larger doses of T4⁺ T-cells. Toxicity appears to be aggravated by high tumour burden, and high T-cell transduction efficiency. The minimum dose at which toxicity has been observed in mice is 10 million transduced cells. By contrast, efficacy has been observed at lower doses indicating that even using this route of administration, there is a therapeutic window. Dose-dependent toxicity is observed in tumour-free mice at even higher T-cell doses. Evidence indicates that cytokine storm accounts for this finding.

Extrapolation to man of these findings is supported by the ability of the CAR to cross the species barrier and by the fact that dose-dependent toxicity can be elicited. However, it should be borne in mind that SCID Beige mice (in which these pre-clinical studies were undertaken) are highly immunodeficient.

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This may enhance the toxic potential of this approach since animals lack "cytokine sinks" that would be present in man in the absence of lymphodepletion.

We conclude that cautious dose escalation should be undertaken during clinical testing. Target cell doses should reflect the efficiency of transduction. Use of the intra-tumoural route should be safest since preclinical imaging studies suggest that the cells remain at this site. We will initiate dosing in man at 10^7 T4⁺ T-cells - a level that, proportionately for weight, equates to 3000-fold below the toxic threshold as determined by IP injection in mice. This initial dose level has resulted in reproducible tumour regression in mice following regional (eg intraperitoneal) administration. Consequently, we have set 10^7 T4⁺ T-cells as the "minimum anticipated biological effect level" (MABEL) from which dose escalation will proceed cautiously, monitoring for dose-limiting toxicity as specified elsewhere in this Clinical Trial Protocol. In man however, efficacy at a starting dose of 10^7 cells is a remote possibility, considering that a typical 1cm^3 tumour mass contains approximately 10^9 cells (representing an effector to target ratio of 1:100).

1.2.5 Immunomodulation using Cyclophosphamide

Several factors are believed to limit the success of adoptive T-cell immunotherapy (ACT) in patients with malignant disease. These include the presence of expanded populations of immunosuppressive cells in patients, including regulatory T-cells (Treg) and myeloid suppressor cells. Furthermore, access to supportive cytokines in-vivo is also believed to limit the survival of infused Tcells. To address these limitations. investigators increasingly are combinations of cytotoxic agents in order to "pre-condition" patients prior to ACT. This commonly approach, known lymphodepletion, pioneered was by Rosenberg to improve the efficacy of immunotherapy of metastatic melanoma using ex-vivo expanded tumour-infiltrating lymphocytes (TIL) (61). Figure 2 shows that ACT achieves an increased response rate when TIL cells are administered after lymphodepletion with fludarabine

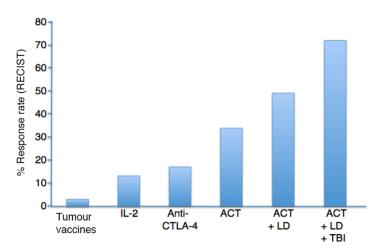


FIGURE 2. Preparatory lymphodepletion enhances response rate in patients with metastatic melanoma treated with adoptive cell therapy (ACT) using *ex-vivo* expanded tumour infiltrating lymphocytes. Results are compared to those achieved with tumour vaccines, IL-2 or anti-CTLA-4 alone. LD — non-myeloablative lymphodepletion using fludarabine and cyclophosphamide; TBI — total body irradiation. Data from the Surgery Branch, National Cancer Institute (adapted from reference 61).

cyclophosphamide. Furthermore, when total body irradiation is added to intensify conditioning, the resultant myeloablation leads to a further improvement in clinical response rate. While these data do not derive from randomized controlled studies, they do nonetheless raise the possibility that appropriate lymphodepletion may enhance the efficacy of ACT using CAR-engineered T-cells.

In keeping with this, early clinical studies using CAR-based immunotherapy which did not incorporate a lymphodepletion step achieved very limited clinical efficacy in a spectrum of malignancies (62-65). By contrast, lymphodepletion has been included in several more recent clinical studies in which regression

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of malignant disease has been repeatedly observed (66-70). Interpretation of these data is complicated by several factors. For example, CAR design has also improved over this period. Most current studies involve so-called second or third generation CARs in which signalling domains comprise two or three elements respectively, leading to enhanced potency of T-cell activation. However, in an ongoing study in which a second generation CAR is being used without lymphodepletion to treat patients with lymphoma, no clinical responses have been seen as yet beyond disease stabilization (71). Taken together, while evidence is clearly limited, these observations raise the possibility that lymphodepletion has been an important contributory factor to the improved efficacy of ACT using CAR-engineered T-cells

Currently, three mechanisms are believed to account for the beneficial effect of lymphodepletion, namely the depletion of Treg, the removal of competing cytokine sinks and the creation of "space" within which adoptively infused T-cells may expand, particularly in response to homeostatic cytokines such as IL-7 and IL-15.

Adoptive T-cell transfer in the absence of pre-conditioning generally results in poor T-cell engraftment in the patient and subsequent poor clinical responses. In this trial, we aim to address this issue in the first instance by intra-tumoural injection of T-cells. By this means, we hope that T-cells will locate at the site of the disease for a sufficient period to elicit a meaningful therapeutic effect. Should this approach prove non-toxic but poorly efficacious, even at the highest dose tested, it is then logical to explore immunomodulatory approaches that may improve T-cell survival and function *in-vivo*.

The primary concern associated with the use of lymphodepletion relates to its potential toxicity, particularly in heavily pre-treated patients with malignant disease. Lymphodepletion has been a cofactor in two fatal Suspected Unexpected Serious Adverse Reactions (SUSAR), both of which occurred in patients treated with CAR-engineered T-cells. Both fatal reactions were characterized by uncontrolled immune cell activation and resulting cytokine storm (72, 73). In one case, toxicity may have been a manifestation of undetected sepsis (73). However, death of the second patient was clearly attributed to the uncontrolled activation of the T-cells, which were targeted against ErbB2 (72). A full description of that event and its implications for the design of our trial is provided in the Risk Benefit analysis section of the IMPD. Furthermore, a UK trial in which lymphodepletion has been used prior to infusion of CAR-engineered T-cells has recently been terminated owing to toxicity (74). Although details of that study have not been published other than in abstract form, it entailed the use of a first generation (eg lowest potency) CAR targeted against carcinoembryonic antigen and administered to a patient population with a similar performance status and life expectancy to ours.

In all three cases, toxicity is likely to have been multi-factorial. Nonetheless, the ability of lymphodepletion to remove several cell populations and cytokine sinks is likely to have been a co-factor in the uncontrolled progression of these toxic events. Consequently, we do not feel that it would be appropriate to include a lymphodepletion step in the design of this clinical trial.

Instead, we have elected to include a final cohort in our study design in which metronomic low-dose cyclophosphamide will be used to pre-condition patients prior to administration of T4 immunotherapy. We will only proceed to this step should we not identify a maximum tolerated dose of T4 immunotherapy during the dose escalation phase of the study. Metronomic cyclophosphamide leads to selective (albeit incomplete) depletion of Treg (75, 76) and is extremely well tolerated by patients with terminal malignancy (77). In some pre-clinical studies, metronomic cyclophosphamide alone can induce anti-tumour immune responses and tumour regression (78). We have selected a dose of 50mg per day for 14 days, which achieves a reproducible albeit partial depletion of circulating Treg cells (76). In SCCHN,

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increased numbers of Treg cells have been observed in the peripheral circulation and the tumour of patients when compared with healthy controls (79-81). Consequently, we will evaluate the combination of this depletion strategy with T4 immunotherapy in patients with SCCHN. Our rationale is that selective depletion of Treg may enhance efficacy without achieving non-specific lymphodepletion or removal of cytokine sink cellular populations, buffering against the cytokine-mediated effects of widespread T-cell activation.

We did consider whether it would be appropriate to reduce the dose of T4 immunotherapy in patients who receive metronomic cyclophosphamide. However, in light of the extremely low dose involved and the mild (and incomplete) immunomodulatory effects elicited by metronomic cyclophosphamide, we consider that it is reasonable to add this preparatory therapy to the same dose of T4 immunotherapy as is administered to cohort 5. By this means, the need to include an additional cohort in the study is avoided.

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2. OBJECTIVES OF THE TRIAL

2.1 Trial Objectives

The overall goal of this study is to investigate the safety of T4 immunotherapy when administered to treat loco-regional disease in SCCHN that is not suitable for conventional active therapy.

2.1.1 Primary Objectives

- ◆ To define dose limiting toxicities for T4 immunotherapy in SCCHN.
- ◆ To determine a safe and feasible recommended dose for phase II testing of intra-tumoural T4 immunotherapy.

2.1.2 Secondary Objectives

- ◆ To investigate serum cytokine levels after administration of T4 immunotherapy.
- ◆ To investigate persistence of T4⁺ T-cells at the site of administration and in the peripheral circulation.
- ◆ To achieve preliminary assessment of anti-tumour activity, using cross-sectional imaging to quantify objective responses.
- ◆ To investigate tumour ErbB receptor phenotype, before and after administration of T4 immunotherapy.
- To investigate immunomodulatory effects of low dose cyclophosphamide on T4 immunotherapy.
- ◆ To investigate effect of T4 immunotherapy upon immune reactivity against endogenous tumour antigens.

2.2 Trial Endpoints

2.2.1 Primary Endpoint

Dose limiting toxicity of T4 immunotherapy graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (see **Appendix 1**).

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2.2.2 Secondary Endpoints

- Cytokine levels present in serum taken pre-injection, at 30 min after injection, and at 1, 4, 24, 48-96 and 120-168 hours post T-cell infusion (flexible time points, to allow for weekends). Analysis will be performed using a multiplex cytokine bead array platform.
- Persistence of T4⁺ T-cells in tumour biopsies (measured by quantitative PCR) at two or, if necessary, four weeks post therapy. If T-cell persistence is seen at the two-week time point in any patient, <u>subsequent</u> enrolled patients will instead have biopsies performed at four weeks post therapy.
- Presence of T4⁺ T-cells in the circulation measured by quantitative PCR and flow cytometry analysis for T1E28z⁺ T-cells at 4, 24, 48-96 and 120-168 hours (flexible time points, to allow for weekends), and days 8, 15, 29 and 43 days post injection.
- Evidence of response evaluated by appropriate cross-sectional imaging 6 weeks post therapy. Clinical response will be assessed according to RECIST 1.1 criteria.
- Effect of T4 immunotherapy upon endogenous T-cell reactivity against MAGE-A3 and MAGE-A4 cancer/testis antigens. Analysis will be performed 3 days before and 29 days after T4 immunotherapy is administered on day +1. Responses will be quantified using interferon-γ ELISPOT after stimulation with overlapping peptides derived from each antigen.
- Evidence of immunomodulation by cyclophosphamide, as measured by circulating numbers of CD4⁺ CD25^{HIGH} CD127^{DIM/NEG} cells. Cells will be quantified by flow cytometry, performed at initiation and completion of a 14 day course of cyclophosphamide (50mg PO daily).

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3. PATIENT SELECTION CRITERIA

3.1 Inclusion Criteria

- 1) Histologically and/ or cytologically confirmed SCCHN.
- 2) 18 years or older.
- 3) Locally advanced and/ or recurrent head and neck cancer with or without metastatic disease (excluding brain metastases) for whom no standard therapy remains or is suitable.
- 4) Regarding previous treatment, patients may have received prior systemic therapy, including platinum chemotherapy, at least one month earlier. In the presence of metastatic disease, recent short-course palliative radiotherapy to non-target site(s) is allowed.
- 5) Those who refuse palliative treatment may be eligible for participation. However, their reasons for not opting for palliative treatment must be explored thoroughly.
- 6) At least one loco-regional target lesion measurable by RECIST v1.1 criteria on CT or MRI scanning within four weeks of enrolment*, and amenable to intra-tumoural injection.
- 7) Eastern Co-operative Oncology Performance Status of 0-2.
- 8) Normal cardiac function as assessed by electrocardiography and either echocardiography (ECHO), or multi-gated acquisition (MUGA) scanning. Left ventricular ejection fraction must be \geq 50%. Assessment must take place within four weeks of enrolment*.
- 9) Haematology results within seven days of enrolment*: neutrophils $\ge 1.5 \times 10^9 / L$, platelets $\ge 100 \times 10^9 / L$, haemoglobin $\ge 90 g / L$, INR < 1.5.
- 10) Biochemistry results within seven days of enrolment*:
- serum creatinine <1.5 upper limit of normal
- bilirubin <1.25 times normal;
- ALT/ AST <2.5 times upper limit of normal (<5 times upper limit of normal if liver metastases present)
- 11) Female patients must be postmenopausal (12 months of amenorrhea), surgically sterile or they must agree to use a physical method of contraception. Oral or injectable contraceptive agents cannot be the sole method of contraception. Women of childbearing potential (WOCB) who receive cyclophosphamide must adhere to these contraceptive requirements during the trial and until 3 months after the last dose of cyclophosphamide. Male patients, even if sterilized, must agree to use a barrier method of contraception. Male subjects must also commit to use a barrier method of contraception until at least 3 months after the end of study treatment.
- 12) Written informed consent prior to registration*.

^{*} enrolment/ registration occurs on the day that blood is collected to manufacture T4 immunotherapy

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3.2 Exclusion Criteria

- 1) The presence of or imminent occurrence of airway obstruction, unless tracheostomy in place.
- 2) The presence of or imminent occurrence of tumour-mediated infiltration of major blood vessels.
- 3) Positive history of HIV-1, HIV-2, HTLV-1, HTLV-2, Hepatitis B, Hepatitis C or syphilis infection.
- 4) Prior splenectomy.
- 5) Clinically active autoimmune disease. Sub-clinical or quiescent autoimmune disease does not exclude from participation.
- 6) Treatment in the week preceding the administration of T4 immunotherapy (or in cohort 6, cyclophosphamide followed by T4 immunotherapy) with any of the following: (i) systemic corticosteroids (\geq 20mg prednisolone/ day); (ii) any systemic immunomodulatory agent; (iii) radiotherapy; (iv) chemotherapy or (v) any investigational medicinal product.
- 7) Concurrent use of anticoagulant therapy is not permissible.
- 8) The presence of major co-morbidity likely to impair ability to undergo trial therapy, such as recent myocardial infarction, congestive cardiac failure or uncontrolled hypertension.
- 9) The presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.
- 10) Cyclophosphamide allergy (Cohort 6 only).
- 11) Pregnancy.
- 12) Breastfeeding.
- 13) Prior T4 immunotherapy.

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4. TRIAL DESIGN

This is a phase 1 dose-finding open label study of T4 immunotherapy in ErbB1-expressing SCCHN, following loco-regional relapse.

4.1 Justification for a 3 + 3 trial design

A key guiding principle for dose escalation in phase I trials is to avoid exposing too many patients to sub-therapeutic doses while preserving safety. Rule-based designs (including the traditional 3+3 design) have two advantages in this respect. First, they do not stipulate any prior assumption of the dose—toxicity curve, which is appropriate for a first in man study involving T-cell immunotherapy. Second, the traditional 3+3 design is simple to implement and is generally safe. However, a potential disadvantage of this design is that it may involve an excessive number of dose escalation steps, which results in a large proportion of patients who are treated at low (ie, potentially sub-therapeutic) doses. To counterbalance this risk, only five dose escalation steps have been included in our study.

Using a 3+3 trial design, the occurrence of two dose-limiting toxicities (at a given dosing level) would indicate that the maximum tolerated dose has been exceeded. In light of this, measures are required to minimise the risk that three or more trial participants within a single dosing cohort suffer a dose-limiting toxicity. To achieve this, participants will be enrolled and treated in a staged manner (**Figure 3**). This approach is described in **section 4.5** below, which deals with methods to be used in this study. By this means, we aim to minimize the risk that two or more patients will suffer dose-limiting toxicities within a short time window so that appropriate actions are taken promptly throughout the trial.

In the event that dose-limiting toxicities occur, the independent safety review committee will be notified in all cases. The safety review committee will also review data pertaining to each cohort of treated patients prior to dose escalation.

4.2 Starting Dose of T4 Immunotherapy

The starting dose will be $1 \times 10^7 \, \text{T4}^+$ transduced T-cells. Since this is a first in man study, the optimal dose of T-cells for intra-tumoural CAR therapy is unknown. Due to the widespread low-level distribution of the ErbB receptor family in normal tissues, there is the potential for toxicity with this approach. The chosen dose of 1×10^7 cells for intra-tumoural injection represents a low starting point relative to other studies of intra-tumoural T-cell administration (82) or intravenous phase 1 CAR studies (62, 63, 65-69, 71, 72, 83-87). Allowing for a typical tumour volume for injection of $1 \, \text{cm}^3$, this corresponds to approximately 10^9 tumour cells (88). Consequently, the initial effector to target cell ratio is 1:100, which is unlikely to be associated with either substantial efficacy or toxicity.

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4.3 Dose Escalation of T4 Immunotherapy

T4 immunotherapy T-cell doses will be escalated in fixed increments according to the dose escalation scheme outlined in **Table 1**. Because cell products do not expand in a standardized manner, we have defined a target dose accompanied by an acceptable range (to be used in the event that expansion to the target cell number is not attained at end of production). Three patients will be enrolled at each dose level. If a dose-limiting toxicity (DLT) occurs, the cohort will be expanded by enrolment of a further three patients. If the highest dose level is reached without achieving the maximum tolerated dose of T4 immunotherapy (**section 4.4**), a final cohort of patients will be enrolled at the same dose level, administered immediately after receiving an immunomodulatory dose of cyclophosphamide for 14 days.

The maximum dose for this study is $1 \times 10^9 \text{ T4}^+$ transduced T-cells. However, a density of 1×10^9 cells is the highest that can feasibly be re-suspended in 1mL. Consequently, a TOTAL of 10^9 cells will be the maximum cell dose administered to cohorts 5 and 6 (82).

4.4 Immunomodulation with Cyclophosphamide

In the event that the MTD is not defined following administration of T4 immunotherapy at the highest possible dose level (cohort number 5; Target dose of 1 x 10⁹ cells **Table 1**), the next and final cohort will be treated with cyclophosphamide 50mg administered once daily by mouth for 14 days. Cyclophosphamide treatment will commence on the day blood is provided in order to manufacture the T4 immunotherapy cell product. This means that the final (eg 14th) dose of cyclophosphamide will be taken on the day before T4 immunotherapy will be administered.

Table 1. Dose Escalation Protocol (T4⁺ T-cells).

Notes	Dose Level (Cohort number)	Target dose	Acceptable dose range of T4 ⁺ cells	Volume for injection (mL)
	-1*	3 x 10 ⁶ cells	3 x 10 ⁶ cells	1 <u>+</u> 0.2
Starting T4 Dose level	1	1 x 10 ⁷ cells	3 x 10 ⁶ - 10 ⁷ cells	1 <u>+</u> 0.2
	2	3 x 10 ⁷ cells	1.1 – 3 x10 ⁷ cells	1 <u>+</u> 0.2
	3	1 x 10 ⁸ cells	3.1 – 10 x10 ⁷ cells	1 <u>+</u> 0.2
+	4	3 x 10 ⁸ cells	1.1 – 3 x10 ⁸ cells	1 <u>+</u> 0.2
Final T4 dose level	5	1 x 10 ⁹ cells**	3.1 – 10 x10 ⁸ cells	1 <u>+</u> 0.2
Cyclophosphamide 50mg	6	1 x 10 ⁹ cells**	3.1 – 10 x10 ⁸ cells	1 <u>+</u> 0.2
PO once daily for 14 days				
prior to T4 immunotherapy				

^{*} a "-1" dose level has been included in case dose de-escalation is required from dose level 1. Please note that doses relate to the number of T4⁺ transduced cells (not total cell number).

4.5 Methods

The rate of subject entry and escalation to the next dose level will depend upon safety profile assessment of patients entered at the previous dose level. Toxicity will be evaluated according to the NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (**Appendix 1**), as described below.

^{**} Maximum 1 x 10⁹ cells in total, which is the maximum that can be accommodated in this volume.

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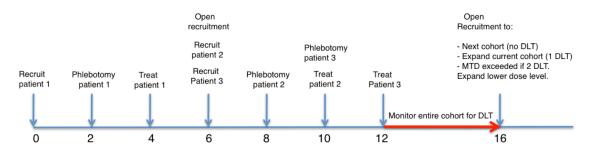


FIGURE 3. Timelines for consecutive patient treatment with T4 immunotherapy. The indicated timeline indicates that there would be a minimum 6 week gap between the treatment of patients 1 and 2 within a cohort. The minimum interval would be 2 weeks between patients 2 and 3. In the even of DLT in patients 1 and 2, the independent safety review committee would consider whether patient 3 could be enrolled at the lower dose level.

Enrolment within each cohort will be consecutive and is summarized in **Figure 3**. After treatment, patients will be evaluated for 24 hours as an inpatient and then again after 72 hours as an outpatient. If no DLT has occurred within the ensuing two-week period for that patient, recruitment will open for the next two patients in that cohort (meaning that they will not receive T4 immunotherapy for at least a further 2 weeks). However, since only one patient cell product can be manufactured at a time, this means that patients 2 and 3 within each cohort will be treated with a minimum gap of 2 weeks. Once three patients are enrolled in a cohort, all will be evaluated for DLT for 28 days before escalation to the next dose level.

The expected sample size in this study is 21.

All participants enrolled in the study will be provided with a patient alert card. This provides contact details of clinical staff who can be contacted at any time by patients on the trial.

4.6 Maximum Tolerated Dose

A 3+3 dose escalation design will be followed in order to determine the maximum tolerated dose (MTD) and thus the recommended dose for phase 2 testing (RDPT). Trial design has been modelled on dose escalation methods used in cancer drug trials (89).

The maximum <u>administered</u> dose occurs when 2 out of 3 patients (or 2 out of 6 with cohort expansion) experience a dose-limiting toxicity (DLT) at a given dose level. In this event, the MTD will have been exceeded. The MTD will then be taken as the dose level administered to the cohort below the maximum administered dose (89).

If one DLT occurs in a cohort of 3 patients, the cohort will be expanded with at least three further patients. If a second DLT occurs in the cohort, the MTD will have been exceeded and the next lowest dose level will be expanded to establish the MTD. Thus the MTD is the highest dose at which <33% of subjects experience a DLT.

If two DLT occur in the first three patients enrolled in any cohort, the MTD will also have been exceeded. If this occurs in cohort 1 (**Table 1**), de-escalation to a -1 dosing regimen will proceed.

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If MTD is not reached, the trial will be completed when the last patient in cohort 6 has completed final evaluation at their last visit, 6 weeks after receiving T4 immunotherapy.

Before opening the next dose level, all adverse events recorded at the previous dose level (within 28 days of dosing) will be reviewed and discussed by the investigators.

4.7 **Dose Limiting Toxicity**

Dose limiting toxicities will be graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (see **Appendix 1**). Any DLT must be a toxic event that is considered at least possibly related to T4 immunotherapy. The period of evaluation for DLT after administration of T4 immunotherapy will be 6 weeks. Dose limiting toxicity is defined as follows:

- 1. <u>Cytokine storm and severe hypotension</u>: There is a theoretical risk that if T4⁺ T-cells activate, expand and pass in large numbers into the circulation that a rapid rise in serum cytokine levels could occur. To monitor for this eventuality, serum cytokine levels will be measured at multiple time points after injection of T4⁺ T-cells. Although investigators will be vigilant for this toxic event, cytokine storm is considered unlikely in view of the low dose of cells, use of the intra-tumoural route and the absence of lymphodepletion using *cytotoxic* doses of cyclophosphamide and fludarabine.
- 2. <u>Haematological</u>: It is not anticipated that significant haematological toxicity will occur. This is because ErbB receptors are not expressed at significant levels by haemopoietic cells and the proposed dosing regimen with cyclophosphamide is not intensive. However the following events would constitute dose-limiting toxicities:
- Febrile neutropenia (Absolute neutrophil count < 1.0 x 10^9 /L with fever $\geq 38.5^0$ C; absolute neutrophil count < 1.0 x 10^9 /L for more than one week).
- Platelet count $< 25 \times 10^9$ /L or thrombocytopenia associated with bleeding.
- 3. <u>Cardiac:</u> ECG will be performed at day 8, 15, 28 and 43. Echocardiography will be performed on days 15, 29 and 43 (see section 6). Any suspected new cardiac symptom will be assessed urgently with the appropriate investigations. A decline in ejection fraction of ≥10% between ECHO investigations will be considered a DLT.
- 4. Any other grade ≥3 <u>non-haematological toxicity</u> except incompletely treated nausea, vomiting or diarrhoea. Grade 3 fatigue will not be a DLT unless patients were grade 0 or 1 at baseline.
- 5. Any other toxicity agreed by the investigators to be dose-limiting.

If a DLT occurs, recruitment will pause until all toxic events have been reviewed by the investigators and the independent safety review committee.

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4.8 Recommended Dose for Phase II Testing

If a MTD is identified, this defines the RDPT of T4 immunotherapy. If the MTD is not reached in the trial, the RDPT is defined as the highest dose level tested.

4.9 Feasibility

Guy's and St Thomas' NHS Trust is a large tertiary referral center for SCCHN. Although the percentage of patients with disease able to meet the eligibility criteria will be small (approximately 2 per month), study recruitment is feasible.

4.10 Patient Replacement

If after T-cell expansion, a sample fails end of production quality control (EOP QC), the patient will not be treated with T4 immunotherapy. In that event, the patient will be offered a second opportunity for treatment. Should they agree to this, the patient will be re-consented for treatment and a new blood sample taken. Alternatively, another patient will be enrolled at the same dose level as a replacement. The frequency of failure of EOP QC will be recorded.

4.11 End of the Trial

In compliance with EU guidance (Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial - ENTR/CT1, Revision 2, October 2005), the end of the trial will be deemed to occur on the date of the last visit of the last patient undergoing the trial.

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5. THERAPEUTIC REGIMENS, EXPECTED TOXICITY, DOSE MODIFICATIONS

5.1 Treatment Plan

5.1.1 Preparation of T4 Immunotherapy

T4 immunotherapy consists of an autologous patient-derived cell product in which T-cells are genetically engineered and expanded *ex-vivo* thereafter (**section 1.2**). Figure 4 presents an outline of the two-week closed manufacturing process whereby T4 immunotherapy is generated. A detailed description of this process is provided in the Investigational Medicinal Product Dossier.

5.1.2 Immunophenotypic analysis

Cells will be analyzed by flow cytometry for %T1E28z expression. Expression of T1E28z is detected using biotinylated anti-human EGF antibody (R&D systems, code BAF236) followed by PE-conjugated streptavidin (Invitrogen, code S866). This analysis will be performed 2-4 days after retroviral transduction and also at end of production.

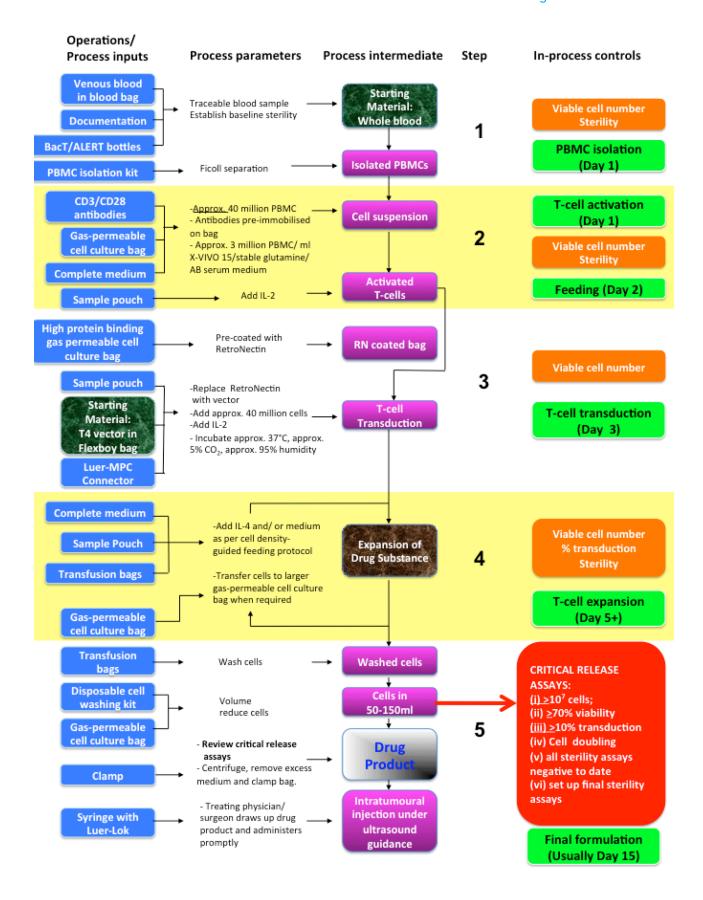
Additional polychromatic flow cytometry will be performed <u>for information only</u> in order to characterise the immunophenotype of the product, detecting expression of CD3, CD4, CD8, CD27, CD28, CD45RA, CD45RO, CD57, CD62L, CCR7, NKG2D, CD25, CD124 (to detect $4\alpha\beta$), CD19 (B-cells), CD16+56 (NK cells), CD14 (monocytes) and PD1.

Figure 4: Outline of Manufacturing Process.

Cell products are manufactured using the indicated process over a period of 14-16 days from phlebotomy to release of the final product. The process is closed meaning that cells are contained in gas-permeable bags throughout the manufacturing process. In step 1, peripheral blood mononuclear cells (PBMC) are isolated from patient blood. T-cells within the PBMC fraction are activated using immobilized antibodies, causing them to reproduce and rendering them suitable for retrovirus-mediated gene transfer (step 2). Gene-transfer is facilitated by the use of RetroNectin (RN)-coated bags. In step 3, gene-modified T-cells are selectively expanded by addition of IL-4, a drug that causes only the genetically engineered cells to grow well. This expansion phase continues through to the final day of manufacture (step 4) on which cells are washed and formulated for injection. In process control tests are shown in orange boxes and assist in maintaining the quality of the manufacturing process. Critical release assays are shown in the red box and indicate that the cell product is safe to release for patient administration.

Cell product manufacture will take place in the Good Manufacturing Process (GMP) Cell Therapy Suite of the Clinical Research Facility at Guy's Hospital.

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5.1.3 T4 Immunotherapy Release and Administration

End of production (EOP) quality control (QC) assays will be performed on therapeutic cell products as summarized in **Table 2**. T4 immunotherapy products that pass QC will be volume reduced, centrifuged and re-suspended at the appropriate cell number in a final volume of 1mL X-VIVO 15 plus 20% AB serum. All cell handling will be undertaken in the GMP Cell Therapy Suite of the Clinical Research Facility at Guy's Hospital. Final cell products will be administered to patients in an adjacent treatment suite, immediately upon formulation.

Table 2. End of Production Quality Control.

Table 2: End of Froduction Quality Control.	
End Point	Method
>70% cell viability	DAPI staining and Flow cytometry analysis on day of
	release.
>10 ⁷ T4-transduced cells	Flow cytometry analysis on day of release
>2 fold-increase in cell number, compared to the	Cell count
number of cells transduced on day 3.	
Cell surface phenotype >10% T1E28z+	Flow cytometry analysis on day of release
Bacterial, fungal and mycoplasma sterility	Initiate sterility tests on day 1 (BacT/ ALERT), day 8
	(BacT/ ALERT & mycoplasma PCR) and on day of
	release (day 15; BacT/ ALERT, fungal &
	mycoplasma PCR). Final and interim culture results
	should be negative.

The autologous T4 immunotherapy cell product will be administered to the patient by a head and neck cancer surgeon, using ultrasound guidance to identify the viable tissue within the tumour. Infiltration of the maximum possible volume of the target lesion will be achieved by injection along multiple radial paths. Cells will be delivered via a minimum number of puncture sites required to achieve as even a distribution of T4 immunotherapy throughout the viable area of the tumour. T4 immunotherapy will be delivered using a syringe with a Luer connection, via a 21-gauge needle. The total volume to be administered is 1mL and this volume will be distributed between the injection sites in accordance with the area of viable tumour seen at ultrasound. This means that the maximum volume that would be administered to a single site within the tumour would be 1mL.

5.1.4 Pre-medication

Skin overlying the areas to be injected with T4 immunotherapy will be anaesthetised with lidocaine or bupivacaine, administered prior to treatment injection.

5.1.5 Patient Monitoring

Patient monitoring immediately prior to and over the 24-hour period following injection of T4 immunotherapy is summarized in **Figure 5**. Blood samples at T-30 minutes are for retrospective analysis. Baseline safety blood tests will be performed within a seven-day period prior to treatment as summarized in **Table 3**. All patients will remain in hospital for the first 24 hours post administration of T4 immunotherapy. This is to enable close monitoring in case of acute toxicity and to facilitate ease of

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regular sample collection for safety monitoring. In most cases, patients will be accommodated in an Oncology ward overnight.

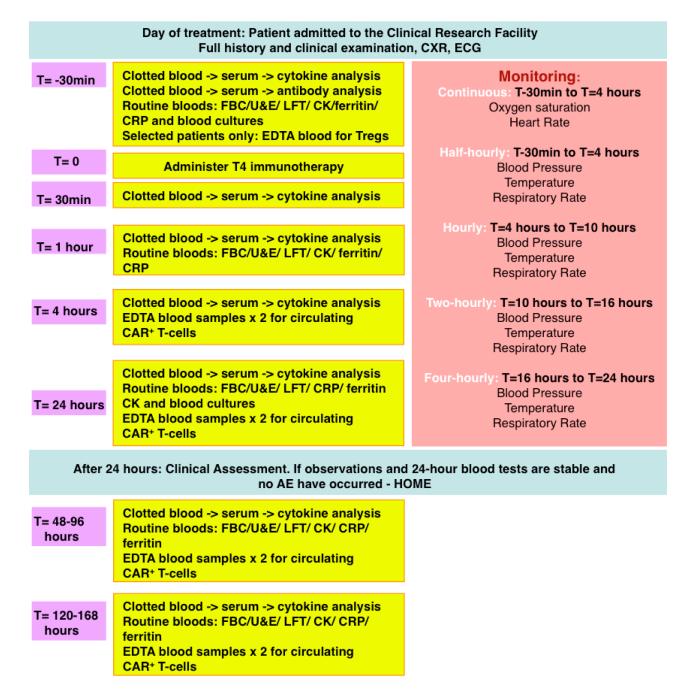


Figure 5: Patient Monitoring: Hours 0 – 168. Patients in cohort 6 who receive cyclophosphamide should also have a blood sample taken at T-30 minutes for measurement of CD4⁺ CD25^{HIGH} CD127^{DIM/NEG} regulatory T-cells.

The term "AE" refers to adverse events that are deemed clinically significant.

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5.1.6 Dose Adjustments

Dose adjustments are not applicable. Once administered in a single dose, T4 immunotherapy cannot be adjusted.

5.1.7 **Duration of Therapy**

T4 immunotherapy will be administered once to each patient.

Patients will be followed up until six weeks post T4 immunotherapy administration when the final response evaluations will be performed. They will then have completed protocol therapy. Follow up thereafter will be as per referring clinician's normal practice.

5.1.8 Concomitant therapy

- Systemic corticosteroids and other immunomodulatory agents are not permitted, unless prescribed by the investigators for the management of T4 immunotherapy-related toxicity.
- Chemotherapy or other anti-cancer agents are not permitted in conjunction with T4 immunotherapy (other than the use of immunomodulatory dose cyclophosphamide in cohort 6).
- Radiotherapy is permitted for palliation of painful metastatic disease excluding the site of administration of T4 immunotherapy and target lesions used for RECIST evaluation.
- Otherwise there are no restrictions on concomitant medications. Palliative care interventions for symptom management are permitted.
- Once the final response evaluation has been completed at six weeks post administration of T4 immunotherapy, these restrictions no longer apply.

5.2 Management of Toxicities

If cytokine storm is suspected, the treatment algorithm described in **Appendix 2** will be followed. Agents will be stored on the ward. The proposed approach is justified as follows.

- Increasing evidence indicates that IL-6 is an important mediator of cytokine storm in patients treated with CD19 CAR-specific T-cells and that the anti-IL-6 receptor antibody, tocilizumab, can ameliorate toxicity (91, 92).
- With ongoing pyrexia, give consideration to administration of levetiracetam since seizures may occur in these patients.
- Corticosteroids are of established value in the management of cytokine storm induced by biologicals such as OKT3. Recent pre-clinical evidence also supports the value of these agents in the amelioration of cytokine storm induced by CD28 superagonist antibodies (93).
- Use of infliximab is supported by evidence that T-cell derived tumour necrosis factor (TNF)- α is a driver of superantigen-mediated toxic shock (94). TNF- α was greatly elevated in both patients who suffered fatal SUSARs following CAR-based immunotherapy (72, 73).

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6. CLINICAL EVALUATION, LABORATORY TESTS, FOLLOW-UP

6.1 Prior to Commencement of Therapy

- **♣** Within four weeks before treatment:
 - Check against Inclusion criteria
 - Medical history/ Concomitant medication
 - Physical examination
 - ECHO and ECG
 - Screening blood tests (Full blood count, biochemical profile, HIV-1, HIV-2, HTLV-1, HTLV-2, HBV (HBsAg and anti-HB core (HBc) antibody), HCV, syphilis serology)
 - Contrast-enhanced CT: head, neck, thorax, abdomen (Where deemed more useful, MRI imaging will be used to evaluate local tumour status)
 - **Selected patients only**: ¹⁸Fluorodeoxyglucose (FDG) positron emission tomography (PET)-CT head, neck and half-body body scanning. The scan will be repeated on the same patients after treatment
 - Selected patients only: In up to six patients, two core biopsies will be taken from the target lesion selected as amenable to immunotherapy. These will be fixed, paraffin embedded and analyzed for (i) H&E staining and (ii) immunohistochemistry for EGF receptor, cleaved caspase 3 and anti-CD3. If possible, biopsies will also be taken from some of the same patients after treatment.
- ♣ On the day of blood harvest (Day -14):
 - HIV-1, HIV-2, HTLV-1, HTLV-2, HBV (HBsAg and anti-HBc antibody), HCV, syphilis serology on the harvested blood.
 - **Selected patients only**: Baseline blood sample to measure circulating Tregs in patients scheduled to receive cyclophosphamide (4mL whole blood in EDTA anticoagulant). Testing will be repeated on the same patients immediately after completion of cyclophosphamide (eg on the day that T4 immunotherapy is administered).

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- ₩ Within three days before treatment (baseline safety screen/ testing):
 - Clinical history
 - Physical examination
 - Bloods: FBC, U&E, LFT, CRP, creatine kinase, ferritin, MAGE-reactive T-cell ELISPOT (22.5mL whole blood in citrate anticoagulant).
 - ECG

6.2 During Treatment

♣ Day 1:

- The patient is admitted as an inpatient for the first 24 hours.
- Clinical history.
- Physical examination.
- ECG.
- For monitoring and blood sampling over the first 24 hours please refer to the patient monitoring flow chart, section 5.1.5 (Figure 5).
- **Selected patients only**: Those patients who received cyclophosphamide Blood sample to measure circulating Treg (4mL whole blood in EDTA anticoagulant) immediately prior to administration of T4 immunotherapy.
- **Selected patients only**: SPECT-CT T-cell imaging following *ex-vivo* ¹¹¹In labelling of T4 engineered T-cells (first of three scans to be performed on these patients). Labelled T-cells will account for 10% of total T-cell dose and will be administered at a single site within the tumour.

♣ Day 2:

- Bloods: FBC, U&E, LFT, CRP, creatine kinase, ferritin.
- Whole blood in EDTA (2 x 4mL) for circulating T1E28z⁺ cell analysis (FACS, qPCR).
- Clotted sample for cytokine analysis on serum.
- **Selected patients only**: SPECT-CT T-cell imaging following *ex-vivo* ¹¹¹In labelling (second of three scans).

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♣ Day 3-4:

- Bloods: FBC, U&E, LFT, CRP, creatine kinase, ferritin.
- Whole blood in EDTA (2 x 4mL) for circulating T1E28z⁺ cell analysis (FACS, qPCR).
- Clotted sample for cytokine analysis on serum.
- **Selected patients only**: On day 3, SPECT-CT T-cell imaging will be repeated following *ex-vivo* ¹¹¹In labelling (third of three scans).

4 Day 5-7:

- Bloods: FBC, U&E, LFT, CRP, creatine kinase, ferritin.
- Whole blood in EDTA (2 x 4mL) for circulating T1E28z⁺ cell analysis (FACS, qPCR).
- Clotted sample for cytokine analysis on serum.

♣ Day 8:

- Clinical History.
- Physical examination.
- Bloods: FBC, U&E, LFT, CRP, creatine kinase, ferritin.
- Whole blood in EDTA (2 x 4mL) for circulating T1E28z⁺ cell analysis (FACS, qPCR).
- ECG.

4 Day 15:

- Clinical History.
- Physical examination.
- Bloods: FBC, U&E, LFT, CRP, creatine kinase, ferritin.
- Whole blood in EDTA (2 x 4mL) for circulating T1E28z⁺ cell analysis (FACS, qPCR).
- Clotted sample for separation and storage of serum at -80°C. This will be used to examine for emerging anti-CAR antibodies.
- ECG.

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- ECHO.
- CXR.
- **Selected patients only**: In up to six patients, three core biopsies will be taken from the target lesion after immunotherapy. Ideally, some of these patients will have had preceding core biopsies taken prior to immunotherapy.
 - Two core biopsies will be fixed, paraffin embedded and analyzed for (i) H&E staining and (ii) immunohistochemistry for EGF receptor, cleaved caspase 3 and anti-CD3.
 - One fresh core biopsy will be processed for qPCR analysis to detect T1E28z⁺ T-cells. If any patient has detectable T1E28z⁺ T-cells, biopsies will be performed on day 29 instead of day 15 in subsequent patients.

♣ Day 29

- Clinical History.
- Physical examination.
- Bloods: FBC, U&E, LFT, CRP, creatine kinase, ferritin.
- Whole blood in citrate for circulating T1E28z⁺ cell analysis (2 x 4mL in EDTA) and MAGE-reactive T-cell ELISPOT (22.5mL in citrate anticoagulant).
- ECG.
- ECHO.
- CXR.
- **Selected patients only**: Three core biopsies from the target lesion after immunotherapy (see above for reasons that this may be delayed to Day 29 instead of Day 15).

♣ Day 43

- Clinical History.
- Physical Examination.
- Contrast-enhanced CT: head, neck, thorax, abdomen (Where deemed more useful at enrolment, MRI imaging will be used to evaluate local tumour status).
- Bloods: FBC, U&E, LFT, CRP, creatine kinase, ferritin.

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- Whole blood in EDTA (2 x 4mL) for circulating T1E28z⁺ cell analysis (FACS, qPCR).
- Clotted sample for separation and storage of serum at -80°C. This will be used to examine for emerging anti-CAR antibodies.
- ECG.
- ECHO.
- **Selected patients only**: FDG PET-CT head, neck and half-body body scanning (incorporated with contrast-enhanced CT scan).

A 48-hour window will operate for visits at Days 8, 15, 29 and 43, to allow for weekend breaks.

Should circulating T1E28z⁺ T-cells be detectable at the end of the study period, we would request that clinicians who follow up the patient after the study period has been completed would request that patients provide blood samples at each outpatient visit to monitor the persistence and proportion of these cells that remain.

6.3 Following Completion of Treatment (Follow Up)

After completion of the six weeks on protocol:

- The patients will be followed up as per the referring clinician's practice.
- Appropriate cross-sectional imaging will be performed when clinically indicated.
- The Sponsor will continue safety follow-up for least two years and report safety data as per pharmacovigilance regulations. To achieve this, we will telephone patients every two months to enquire about status.
- Time to progressive disease defined clinically or radiologically will be documented.

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6.4 Summary Table

Table 3. Summary of Patient Monitoring Studies

Table 3. Sullill	Screen T4 Manufacture			Treat ⁶							Follow Up	
	I			_								
Days	<u>-3 to</u> -28	-14	<u><</u> -3	1	2	3-4	5-7	8	15	29	43	
Clinical History	X		Х	Х				Χ	Х	Х	Х	
Examination	Х		Х	Х				Χ	Χ	Χ	Χ	
Entry criteria	Х											
assessment/ bloods,												
including serology												
Blood harvest &		Х										
serology												As per
CT (+/- MRI) ¹	X										Х	referring
Biopsy ²	Х								Х	or X		clinician's practice
¹⁸ FDG PET-CT ³	Х										Χ	1
111In SPECT-CT4				Х	Χ	Х						
FBC/U&E/LFT	X		Х	X ⁷	Χ	Х	Х	Χ	Х	Х	Х	1
CK/CRP/ferritin												
Intra-tumoural T4				Х								
immunotherapy												
Serum for cytokines				X'	Χ	Χ	Х					
Serum for emerging				Х					Χ		Χ	
antibodies												
Blood for CAR				Х	Х	Χ	Χ	Χ	Χ	Χ	Χ	
analysis												_
Blood for MAGE-			Χ							Χ		
reactive T-cells				\ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \ \								4
Blood for Tregs ⁵		Х		X					V			4
CXR	V								X	X		-
ECG	X		Χ	X				Χ	X	X	X	4
ECHO	Х								Χ	Χ	Χ	

Manuf. – manufacture; Tregs – regulatory T-cell number

- 1. CT scanning of head, neck, thorax and abdomen. MRI scanning (tumour site only) will only be conducted where considered to be more informative than CT.
- 2. a). Screening biopsy: fixed paraffin embedded for H&E, EGFr, cleaved caspase 3 and anti-CD3.
 - b). Biopsies performed on days 15/29: 2-3 cores: (i) fixed and paraffin embedded for H&E staining; (ii) fixed and paraffin embedded for immunohistochemistry to detect EGFr, cleaved caspase 3, cytokeratins and anti-CD3; (ii) fresh qPCR for T1E28z⁺ T-cells.
- 3. Head, neck and half-body PET-CT scan will be performed on selected patients.
- 4. Selected patients will receive T4-engineered T-cells in which approximately 10% of the T-cell dose is labelled with ¹¹¹In oxine. This will permit tracking of the migration of T4⁺ T-cells over the ensuing 72 hours.
- 5. Selected patients (cohort 6) will receive cyclophosphamide 50mg PO x 14 days between blood harvest and administration of T4 immunotherapy. Effect on circulating Tregs (regulatory T-cells) will be assessed in these patients only.
- 6. A 48-hour window will operate for all visits from day -14 onwards, to allow for weekend and holiday breaks and duration of manufacture of 14-16 days.
- 7. Tests performed more than once on this day.

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7. CRITERIA OF EVALUATION

7.1 Evaluation of Efficacy

7.1.1 Primary End Point

The primary end point of this study is determination of the dose limiting toxicity induced by T4 immunotherapy, up to 6 weeks post administration. Dose limiting toxicity will be graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (**Appendix 1**).

All patients will be evaluable for toxicity from the time of their injection of T4 immunotherapy.

7.1.2 Secondary End Points

The secondary end points in this study and methods of evaluation are listed below.

Cytokine levels will be analyzed in serum taken pre-injection, at 30 minutes after injection, and at 1, 4, 24, 48-96 and 120-168 hours post T-cell injection. Please consult the CAR Research Group manual of standard operating procedures for current methodologies.

Presence of persistent T4⁺ T-cells in tumour biopsies will be measured two weeks post therapy in up to 6 patients. Please consult the CAR Research Group manual of standard operating procedures for current methodologies used (qPCR for T1E28z⁺ T-cells). If T-cell persistence is seen at the two-week time point, the remaining enrolled patients will have a biopsy performed at four weeks post therapy. Otherwise biopsies will continue at two weeks post injection of T4 immunotherapy.

Presence of T4⁺ T-cells in the circulation will be analyzed at 4, 24, 48-96 and 120-168 hours, and on days 8, 15, 29 and 43 days post injection. Please consult the CAR Research Group manual of standard operating procedures for current methodologies used (FACS analysis and qPCR for T1E28z⁺ T-cells).

Objective tumour response and time of progression will be measured according to RECIST criteria (95).

All eligible patients will be included in the response rate calculation. The subset that will be assigned a response category (CR, PR, SD or PD; see definitions below) are all patients who have received a single treatment with T4 immunotherapy and have had their disease re-evaluated.

Effects of low dose cyclophosphamide on T4 immunotherapy will be evaluated by measurement of dose-limiting toxicity as described in **section 7.1.1** and objective tumour response rate and time of progression.

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The effect of T4 immunotherapy upon immune reactivity against endogenous tumour antigens will be assessed by measurement of T-cell reactivity against overlapping peptides derived from MAGE-A3 and MAGE-A4. Assessment will be performed by ELISPOT analysis of interferon-γ production. Tumours will be assessed for MAGE-A3/ A-4 status by RT-PCR and immunohistochemistry. Please consult the CAR Research Group manual of standard operating procedures for current methodologies used.

7.1.3 Measurability of Tumour Lesions at Baseline

7.1.3.1 Definitions

- **Measurable disease** the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
- Measurable lesions tumour lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray, and as ≥ 10 mm with CT scan or clinical examination [using calipers]. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥ 10 mm by CT scan). Malignant lymph nodes must be ≥ 15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumour measurements must be recorded in millimeters (or decimal fractions of centimeters) by use of a ruler or calipers. Tumour lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. If the only loco-regional site of disease is in a radiation field, which is likely in locally recurrent SCCHN, lesions will be considered measurable if there has been documented radiological evidence of disease progression at that site.
- Non-measurable lesions All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Nodes that have a short axis <10 mm at baseline are considered non-pathological and should not be recorded or followed.
- Target Lesions When more than one measurable tumour lesion or malignant lymph node is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. Note that pathological nodes must meet the criterion of a short axis of ≥ 15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. At baseline, the sum of the target lesions (longest diameter of tumour lesions plus short axis of lymph nodes: overall maximum of 5) is to be calculated and recorded.

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• Non-target Lesions - All non-measurable lesions (or sites of disease) including pathological nodes (those with short axis ≥ 10 mm but < 15 mm), plus any measurable lesions over and above those listed as target lesions are considered non-target lesions. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent".

All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

7.1.3.2 Methods of Measurements

In general, contrast-enhanced CT scanning will be used for response assessment. CT is the most reproducible method currently available to measure lesions selected for response assessment. "Measurability" of lesions on CT scan is based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

In some cases, MRI imaging is preferable to CT, particularly for tumours that are located close to the skull base. The decision to use MRI in preference to CT will be taken in conjunction with an appropriately qualified radiologist.

The same method of assessment and the same technique should and will be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule. While on study, all target lesions recorded at baseline should have their actual measurements recorded on the CRF at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split, add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

In selected patients ¹⁸FDG PET-CT scanning will be performed to examine tumour status. Scans will be performed on patients who are willing to undergo this procedure at any stage of the trial, but preferably in those who receive at least 10⁸ T4⁺ cells.

In selected patients, a proportion (approximately 10%) of the T4-engineered T-cells will be passively labelled with ¹¹¹In-oxine, prior to intra-tumoural injection. This will permit tracking of T-cell migration for up to 96 hours by SPECT-CT scanning. It is envisioned that this will be performed once the highest tolerated dose has been determined. Ten percent of the injected dose of T4 immunotherapy will be labelled with indium oxine and then injected at a single site. By this means, the patient will receive a dose in which 90% of the cells are unlabelled and thus have the maximum potential for function. Furthermore, this approach ensures that the largest possible number of T-cells are amenable to *in-vivo* tracking, maximizing the utility of the imaging procedure.

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7.1.4 Tumour Response Evaluation

All patients will have their best response from the start of study treatment until the end of treatment classified as outlined below.

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point at least 4 weeks later (please refer to **Table 4**).

<u>Complete Response</u> (CR): disappearance of all target and non-target lesions and normalization of tumour markers. Pathological lymph nodes must have short axis measures < 10 mm (<u>Note</u>: continue to record the measurement even if < 10 mm and considered CR). Tumour markers must have normalized. Residual lesions (other than nodes < 10 mm) thought to be non-malignant should be further investigated (by cytology or PET scans) before CR can be accepted.

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

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

Table 4. Integration of target, non-target and new lesions into response assessment.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this category also requires				
Patients with Target lesions ± non target lesions								
CR	CR	No	CR	Normalization tumour nodes < 10 mm				
CR	Non-CR/Non-PD	No	PR					
CR	Not all evaluated	No	PR					
PR	Non-PD/ not all evaluated	No	PR					
SD	Non-PD/ not all evaluated	No	SD	Documented at least once ≥ 6 weeks from baseline				
Not all evaluated	Non-PD	No	NE					
PD	Any	Any	PD					
Any	PD	Any	PD					
Any	Any	Yes	PD					

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

NE: not evaluable.

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<u>Progressive Disease</u> (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5 mm. Appearance of new lesions will also constitute PD (including lesions in previously un-assessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumour burden has increased sufficiently to merit discontinuation of treatment, for example where the tumour burden appears to have increased by at least 73% in volume (which is the increase in volume when all dimensions of a single lesion increase by 20%). Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but on further documentation, the earlier date must be used.

Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point at least 4 weeks later. The best overall response can be interpreted as per **Table 5**.

Table 5.Best Overall Response.

Response: First time point Subsequent time point CR		BEST overall response	Also requires Normalization tumour nodes < 10 mm		
		CR			
CR	PR	SD, PD or PR (see comment*)			
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD			
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD			
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE			
PR	CR	PR			
PR	PR	PR			
PR	SD	SD			
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD			
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE			
NE	NE	NE			

^{*} may consider PR providing initial "CR" likely PR on subsequent review – then original CR should be corrected. Recurrence of lesion after true CR is PD.

NE: not evaluable.

7.1.4.1 Frequency of Tumour Re-evaluation

In the present study, tumours will be revaluated six weeks after administration of T4 immunotherapy. After discontinuation of protocol treatment, patients who have not progressed will still be re-evaluated according to the referring surgeons standard practice.

7.1.4.2 Date of Progression

This is defined as the first day when the RECIST (version 1.1) criteria for PD are met.

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7.1.5 Reporting of Tumour Response

All patients included in the study must be assessed for response to treatment, even if there is a major protocol treatment deviation or if they are ineligible, or not followed/re-evaluated. Each patient will be assigned one of the following categories: complete response, partial response, stable disease, progressive disease, early death from malignant disease, early death from toxicity, early death from other cause or unknown (not assessable, insufficient data).

Early death is defined as any death occurring before six weeks from administration of T4 immunotherapy. The responsible investigator will decide if the cause of death is malignant disease, toxicity or other cause.

Patients for whom response is not confirmed will be classified as "unknown", unless they meet the criteria for stable disease (or the criteria for partial response in case of an unconfirmed complete response). Patients' response will also be classified as "unknown" if insufficient data were collected to allow evaluation per these criteria.

7.1.6 Response Duration

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented.

7.1.7 Stable Disease Duration

Stable disease duration will be measured from the time of start of treatment (or randomization for randomized studies) until the criteria for progression are met.

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8. STATISTICAL CONSIDERATIONS

8.1 Statistical Design

This is a phase I, dose finding, open label study. A classic 3+3 design will be used (section 4.1).

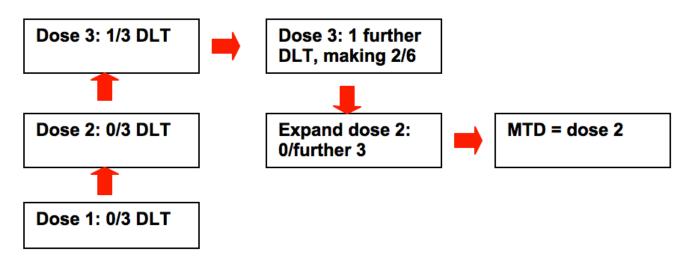


Figure 6: Statistical Design of the Study

Primary End Point:

• Dose limiting toxicity of T4 immunotherapy graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (see **Appendix 1**).

Secondary End Points:

- Cytokine levels present in serum taken pre-injection, at 30 min after injection, and at 1, 4, 24, 48-96 and 120-168 hours post T-cell infusion (later time points flexible, to allow for weekends). Analysis will be performed using a multiplex platform as per the CAR Research Group manual of standard operating procedures.
- Persistence of T4⁺ T-cells in tumour biopsies (measured by qPCR analysis) at two and, if necessary, four weeks post therapy. Analysis will be conducted as per the CAR Research Group manual of standard operating procedures. If T-cell persistence is seen at the two-week time point in any case, further enrolled patients will have a biopsy performed at four weeks post therapy.
- Presence of T4⁺ T-cells in the circulation measured by qPCR and flow cytometry analysis for T1E28z⁺ T-cells at 4, 24, 48-96 and 120-168 hours (flexible time points, to allow for weekends), and days 8, 15, 29 and 43 days post injection. Analysis will be conducted as per the CAR Research Group manual of standard operating procedures.
- Evidence of response evaluated by appropriate cross-sectional imaging 6 weeks post therapy. Clinical response will be assessed according to RECIST 1.1 criteria.

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- Effect of T4 immunotherapy upon endogenous T-cell reactivity against Cancer Tests antigens. ELISPOT analysis will be performed, measuring interferon-γ production upon stimulation by overlapping peptides derived from MAGE-A3 and MAGE-A4. Assays will be conducted as per the CAR Research Group manual of standard operating procedures.
- Evidence of immunomodulation by cyclophosphamide, as measured by circulating numbers of Treg cells. Analysis will be conducted as per the CAR Research Group manual of standard operating procedures.

Entry to the next dose level: The primary end point of DLT will define entry to the next dose level. The period of evaluation for DLT is 28 days. After 3 patients have been enrolled in a cohort the next dose level cohort cannot be opened until there have been no DLT detected for 28 days for the last patient enrolled.

Estimate of patient numbers: Up to 21 patients.

8.2 Statistical Analysis

All patients who started the treatment will be described. Patients without DLT who withdraw within 28 days from administration of T4 immunotherapy will not be included in the toxicity analysis.

Statistical tests will be non-parametric due to the limited sample size. All analysis will be exploratory.

Analysis of the primary end point: The presence of DLT will be analyzed by tables of frequency compared with dose level. All other documented toxicity of any grade according to NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (see **Appendix 1**) will be similarly analyzed. Toxic side effects of all grades will be given by grade and dose level.

Serum cytokine levels: These data will be presented using median and ranges. Evolution in time will be given.

Presence of persistent T4⁺ **T-cells in tumour biopsies:** Analysis will be performed by generating tables of frequency compared with dose level.

Presence of T4⁺ **T-cells in the circulation:** Analysis will be performed by generating tables of frequency compared with dose level.

Evidence of response: disease status at six weeks after administration of T4 immunotherapy will be analyzed by generating tables of frequency compared with dose level. Patients will be followed up for survival after leaving the study.

Endogenous T-cell reactivity against MAGE antigens: These data will be presented using median \pm SEM. Evolution in time will be given.

Immunomodulation by cyclophosphamide: Frequency of circulating Treg cells will be compared prior to and after completion of cyclophosphamide. Evolution in time will be given.

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9. TRANSLATIONAL RESEARCH/ PHARMACODYNAMIC STUDIES

9.1 Cytokine Analysis

9.1.1 Objectives

To analyse the level of cytokines in the peripheral circulation of patients who undergo T4 immunotherapy.

9.1.2 Materials Collected

Five mL of whole blood will be collected into a clotted sample collection tube by peripheral venous puncture. Blood samples will be taken at time points specified in **Table 6**.

Table 6. Timing of blood sampling for serum cytokine analysis.

1	2	3	4	5	6	7
-30 min	30 min	1 hour	4 hours	24 hours	48-96 hours	120-168
						hours

9.1.3 Sample Handling

Full details of the current assay technologies in use to characterize clinical samples are described in the CAR Research Group manual of standard operating procedures.

The blood sample will stand at room temperature for 20min to permit clot retraction and is then centrifuged at 1500g for 15min. The serum layer will be gently aspirated and transferred to a cryovial for storage in a designated locked -80° C freezer.

Cytokine analysis may be performed using a variety of platform technologies. Please see the CAR Research Group manual of standard operating procedures for currently used techniques. Using this type of approach, samples can be stored in the freezer for analysis either at the end of the study or when sufficient patients have had all blood samples collected to allow the use of 1 complete set of reagents.

In the event of a severe reaction consistent clinically with a cytokine storm, samples collected from patients will be analyzed immediately for the most clinically relevant cytokines.

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9.1.4 Statistical Analysis

The evolution in time of cytokine levels will be monitored. Where relevant, the trend by dose level of particular cytokines will be analyzed using mixed models to account for repeated measurements and intra-patient variability paired tests will be used.

9.2 Tumour Biopsies

9.2.1 Objectives

- Evaluation of the target lesion designated for intra-tumoural injection of T4 immunotherapy for levels of cell surface expression of ErbB1 on malignant cells, for apoptosis within the tumour and for cellular architecture.
- Evaluation of the persistence of T1E28z⁺ T-cells within the tumour target lesion following injection with T4 immunotherapy.

9.2.2 Materials Collected

Within four weeks prior to administration of T4 immunotherapy, one or more core biopsies will be taken by the head and neck cancer surgeon, using ultrasound guidance if necessary.

Either two or four weeks after administration of T4 immunotherapy, further core biopsies will be taken from the lesion into which T4 immunotherapy was administered.

9.2.3 Sample Handling

Full details of the current assay technologies in use to characterize clinical samples are described in the CAR Research Group manual of standard operating procedures.

The core biopsy taken pre-enrolment and one of the core biopsies taken post treatment will be fixed in formalin and paraffin embedded. The necessary number of sections will be cut for any or all of the following analyses: (i) analysis of ErbB1 expression; (ii) dual staining of Cytokeratin A1/A3 and cleaved caspase 3 (apoptosis); (iii) detection of (CD3⁺) T-lymphocytes; (iv) H&E staining. Details of the assays are described in the Oral Pathology (Guy's Hospital) and CAR Research Group manual of standard operating procedures. The remainder of the block will be stored in the Head and Neck and Oral Pathology Tissue Bank Archives of Guy's Hospital for future evaluation.

Genomic DNA will be extracted from the fresh sample and stored at -20° C until PCR analysis for T1E28z⁺ T-cells.

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9.2.4 Statistical Analysis

ErbB1 expression will be recorded as % positive tumour cells. Expression of ErbB1 following treatment will be compared across dose levels. Levels of apoptosis will be compared between the pre and post therapy biopsies for each individual patient.

The presence of T1E28z⁺ T-cells will be analyzed by tables of frequency compared with dose level.

9.3 Circulating T4⁺ T-cells

9.3.1 Objectives

To evaluate the presence and (if present) levels of circulating T4⁺ T-cells in the circulation of patients after treatment with intra-tumoural T4 immunotherapy.

9.3.2 Materials Collected

Two samples containing 4mL of EDTA anti-coagulated whole blood will be collected by peripheral venous puncture. Blood samples will be taken at:

- ➤ 4 hours
- > 24 hours
- ➤ 48-96 hours
- > 120-168 hours
- > 8 days
- > 15 days
- > 29 days
- > 43 days

A 48-hour window will be allowed for visits at Days 8, 15, 29 and 43 at which point these samples will be collected

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9.3.3 Sample Handling

Full details of the current assay technologies in use to characterize clinical samples are described in the CAR Research Group manual of standard operating procedures.

Using the first sample, genomic DNA will be extracted from whole blood and will be stored at -20° C until PCR analysis.

Using the second sample, T-cells will be immunostained in whole blood (using anti-CD3 and anti-EGF) to detect expression of the T1E28z CAR.

9.3.4 Statistical Analysis

The presence of T1E28z⁺ cells detectable by FACS and/or PCR will be analyzed by tables of frequency compared with dose level.

9.4 Antibody Analysis

9.4.1 Objectives

To store serum for analysis of antibody generation as a response to T4 immunotherapy.

9.4.2 Materials Collected

Five mL of whole blood will be collected by peripheral venous puncture. Blood samples will be taken at:

- > -30 minutes
- > 15 days
- > 43 days

9.4.3 Sample Handling

A clotted blood sample will be obtained. After centrifugation, the serum layer will be gently aspirated, transferred to a cryovial and immediately transferred to a designated locked minus 80°C freezer.

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9.4.4 Statistical Analysis

This is a stored serum sample for potential future analysis.

9.5 Circulating Regulatory T-cells

9.5.1 Objectives

To evaluate the level of circulating regulatory T-cells in the circulation of patients before and after treatment with low dose cyclophosphamide 50mg orally per day for 14 days. Cyclophosphamide treatment will be administered to the sixth cohort of patients enrolled in the study, commencing on the day of blood harvest, until the day prior to administration of T4 immunotherapy. By this means, it is hoped to deplete circulating regulatory T-cells, thereby promoting enhanced efficacy of T4 immunotherapy.

9.5.2 Materials Collected

Four mL of EDTA anti-coagulated whole blood will be collected by peripheral venous puncture. Blood samples will be taken 14 days prior to and on the day of administration of T4 immunotherapy.

9.5.3 Sample Handling

Full details of the current assay technologies in use to characterize clinical samples are described in the CAR Research Group manual of standard operating procedures.

In brief, anti-coagulated blood will be stained using a Treg detection kit. Following lysis of red blood cells, regulatory T-cells will be enumerated by flow cytometry as CD4⁺ CD25^{HIGH} CD127^{DIM/NEG} events.

9.5.4 Statistical Analysis

Pre- and post-treatment absolute number of circulating CD4⁺ CD25^{HIGH} CD127^{DIM/NEG} cells will be compared.

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9.6 Circulating MAGE-reactive T-cells

9.6.1 Objectives

To evaluate the number of circulating T-cells capable of producing interferon-γ upon stimulation with overlapping peptides derived from MAGE-A3 and MAGE-A4. Comparison will be made before and after treatment with T4 immunotherapy.

9.6.2 Materials Collected

Citrate anti-coagulated whole blood (22.5mL) will be collected by peripheral venous puncture. Blood samples will be taken within 3 days prior to T4 immunotherapy and 29 days after administration of T4 immunotherapy.

9.6.3 Sample Handling

Full details of the current assay technologies in use to characterize clinical samples are described in the CAR Research Group manual of standard operating procedures.

Anti-coagulated blood will be separated by density gradient centrifugation over ficoll leading to isolation of peripheral blood mononuclear cells, which will be cryopreserved. Prior to analysis, thawed cells will be transferred to pre-prepared ELISPOT plates to quantify cytokine producing cells.

9.6.4 Statistical Analysis

Pre- and post-treatment cytokine levels and cytokine-producing cells (quantified as spots) will be compared.

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10. INVESTIGATOR AUTHORISATION PROCEDURE

This is a single centre Phase I trial.

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

This protocol and related documents will be submitted for review to a Research Ethics Committee (REC), to the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation and to the Gene Therapy Advisory Committee.

The Chief Investigator will submit a final report at conclusion of the trial to the KHP CTO (on behalf of the Sponsor), the REC and the MHRA within the timelines defined in the Regulations.

11. PATIENT REGISTRATION / RANDOMIZATION PROCEDURE

This is a single centre Phase 1 trial.

Patients will be recruited via the head and neck cancer clinic and multidisciplinary team meeting or from external institution referral to the Phase I clinical trials unit at Guy's Hospital. Patients will be registered, and eligibility criteria checked against the inclusion and exclusion criteria. Subject numbers will be allocated sequentially beginning with 001.

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12. FORMS AND PROCEDURES FOR COLLECTING DATA

All data collection will be captured in the medical notes on designated visit specific forms. Data will then be transcribed from the medical notes into an electronic case report form (CRF).

Data will be compiled on an Excel spreadsheet. All statistical analysis will be performed using SPSS and/ or GraphPad Prism software.

12.1 Data Flow

Personalised study data will be maintained at the study site in paper and/or electronic format. Paper records will be kept in a locked room or cabinet at all times. Access to the records is restricted to researchers working on the study and to representatives of regulatory authorities required to audit the conduct of the research study.

Electronic data containing personalised information will be saved on local study site computers only in password protected files and backed up regularly to hard copy (CD, flash disk), which will be kept in a secure cabinet or backed up to a remote server.

All data collection will be the responsibility of the Chief Investigator. All data will be collected by the data managers, research team members and investigators. After the final patient in a cohort has been recruited and observed for 28 days for DLT, all data from the cohort will be reviewed by the Chief Investigator and Co-Investigators. By this means, any missing or inconsistent data will be obtained and/or corrected, if possible.

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13. REPORTING ADVERSE EVENTS

13.1 **Definitions**

Definitions used will be those under the Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 as follows:

Adverse Event (AE):

This is defined as any untoward medical occurrence in the patient administered a medicinal product that does not necessarily have a causal relationship with this treatment. An AE is therefore described as any unfavourable and unintended sign (including abnormal laboratory results), symptoms or disease temporally (timely) associated with the use of a medicinal product whether or not related to the product.

Adverse Reaction (AR):

This is defined as any untoward and unintended response in a subject to an investigational medicinal product, which is related to any dose administered to that subject. This means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out

Unexpected Adverse Reaction (UAR):

An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in:

- The summary of product characteristics (SmPC) for that product (for products with a marketing authorisation)
- The Investigator's Brochure (IB) relating to the trial in question (for any other investigational product)

Serious adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction (USAR):

Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that

- Results in death;
- Is life-threatening;
- Required hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability or incapacity;
- Consists of a congenital anomaly or birth defect.

Although not a serious adverse event, any unplanned pregnancy should be reported via the SAE reporting system.

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Suspected Serious Adverse Reaction (SSAR):

This is defined as an adverse reaction that is classified in nature as serious and which <u>is consistent</u> with the information about the medicinal product in question – in the case of a licensed product in the Investigator Brochure for that product.

Suspected Unexpected Serious Adverse Reaction (SUSAR):

The definition of a SUSAR is a serious adverse drug reaction, the nature or severity of which <u>is not consistent</u> with the applicable product information, e.g. summary of product characteristics (SmPC) or Investigator Brochure.

A serious event or drug reaction is not defined as a SUSAR when:

- > It is serious but expected
- It does not fit the definition of a SAE, whether expected or not

13.2 Severity of Adverse Events

Severity for each adverse event, including any laboratory test abnormality, will be determined by using the National Cancer Institute Common Toxicity Criteria (NCI CTCAE, version 4.03) as a guideline, wherever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html and are appended to this Clinical Trial Protocol. In those cases where NCI CTCAE criteria do not apply, severity should be defined according to the following criteria:

Mild Awareness of sign or symptom but easily tolerated

• Moderate Discomfort enough to cause interference with normal daily activities

• Severe Inability to perform normal daily activities

• Life Threatening Immediate risk of death from the reaction as it occurred

13.3 Determining Causality

Relationship to study drug administration will be determined as follows:

- None No relationship between the experience and the administration of the study drug; related to other aetiologies such as concomitant medications or patient's clinical state.
- Unlikely The current state of knowledge indicates that the relationship is unlikely.

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- Possible A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction might also have been produced by the patient's clinical state or other modes of therapy administered to the patient.
- Likely A reaction that follows a plausible temporal sequence from administration of the study drug and follows a known response pattern to the suspected study drug. The reaction cannot be reasonably explained by the known characteristics of the patient's clinical state or other modes of therapy administered to the patient.
- Definitely An adverse event, which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation, e.g., a concomitant drug(s), concomitant disease(s).

13.4 Procedures for Adverse Event Reporting

Toxicity will be monitored from the first study-related procedure until 6 weeks post administration of T4-transduced T-cells. All adverse reactions and serious adverse reactions that occur during this period will be recorded by the Chief Investigator. All SAEs/ SAR designated as reportable (see below) and all SUSARs will be reported to the sponsor (the KHP CTO). Those meeting the definition of serious adverse events must be reported using the Serious Adverse Event Form.

Adverse events that are not considered serious should be included on the relevant case report forms (CRFs) as defined in the trial Protocol. This data will be included in the final trial report.

Investigators must record in the CRF and the patient notes their opinion concerning details of nature, onset, duration, severity, seriousness, expectedness and relationship to T4-transduced T-cells. In cases of doubt, Investigators will liaise in order to come to a final decision, which will be documented as above. Medical terminology should always be used to describe any event. Investigators should avoid vague terms such as "sick".

13.5 Investigator Reporting to the KHP CTO and Research Ethics Committee

The Chief Investigator (CI) will report all SAEs and SARs to the KHP CTO as soon as he is aware of and has assessed the event. It is the responsibility of the Chief Investigator to report all SUSARs to the Research Ethics Committee.

All SAEs, SARs & SUSARs (including any follow up information), must be reported using the SAE Report form. This form will be completed and faxed to the KHP CTO using the number quoted on the

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SAE Report Form. This form should also be e-mailed to the KHP CTO using the address quoted on the form.

The KHP CTO will acknowledge receipt of the SAE Report using the KHP CTO SAE Form Receipt Form. If the CI has not received receipt within 24 hours of sending the report (during office hours), the SAE Report Form should be re-sent to the KHP CTO by email or fax.

Additional information, as it becomes available, will also be reported on the SAE Report Form and returned to the KHP CTO by email or fax as above.

The original SAE Report Form will be filed in the Trial Master File (TMF), with copies filed in the patient's hospital notes, the case record form and the Sponsor file.

13.6 Sponsor Reporting Responsibilities

The co-sponsors have delegated the delivery of the Sponsor's responsibility for Pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004 to the King's Health Partners Clinical Trials Office (KHP CTO)).

All SAEs, SARs and SUSARs (excepting those specified in this protocol as not requiring reporting) will be reported immediately by the Chief Investigator to the KHP CTO in accordance with the current Pharmacovigilance Policy.

Death as a result of disease progression and other events that are primary or secondary outcome measures are not considered to be SAEs and should be reported in the normal way, on the appropriate CRF.

The KHP CTO will report SUSARs to the regulatory authorities (MHRA only in this case, since this is a single site trial).

The Chief Investigator will report to the relevant ethics committee. Reporting timelines are as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.
- The Chief Investigator and KHP CTO (on behalf of the co-sponsors), will submit a Development Safety Update Report (DSUR) relating to this trial IMP to the MHRA and REC annually.

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13.7 Urgent Safety Measures

The Regulations allow the sponsor and investigator to take appropriate urgent safety measures to protect clinical trial subjects from any immediate hazard to their health and safety, these measures should be taken immediately but the sponsor must notify the MHRA and the Main REC in writing, of the measures taken and the reason for the measures within 3 days by submitting a substantial amendment. The CI must inform the KHP CTO as soon as possible after the implementation of the urgent safety measures. The CI should phone the Clinical Trials Unit at the MHRA and discuss the issue with a medical assessor immediately.

The substantial amendment should be faxed and emailed to the Clinical Trials Unit marked 'Urgent Safety Measure' (contact details on MHRA website) or sent as a PDF document on disk to:

Information Processing Unit,

Area 6.

Medicines and Healthcare products Regulatory Agency,

151 Buckingham Palace Road

Victoria

London

SW1W 9SZ

The decision to undertake appropriate safety measures may be taken by:

The CI

The KHP CTO - on behalf of the Sponsor and in consultation with the CI.

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14. QUALITY ASSURANCE

14.1 Control of Data Consistency

After the final patient in a cohort has been recruited and observed for 28 days for DLT, all data from the cohort will be reviewed by the Chief Investigator, and Co-Investigators to ensure consistency.

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15. ETHICAL CONSIDERATIONS

15.1 Patient Protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West and Edinburgh amendments) or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice (ref: http://www.ifpma.org/pdfifpma/e6.pdf).

15.2 Subject Identification

Subject data will be anonymised by the use of study numbers. These will be assigned at the start of the study and all blood samples and results reports will be identified by study number. A copy of the study number code identifying subjects will be kept in a secure cabinet at study site accessible to the Chief Investigator and Co-Investigators at all times. It is not anticipated that any information will be sent outside the study site. However, in the event that it is, it will be fully anonymised.

Analysis will be conducted by the study team. Analysis will only be conducted on anonymised data.

The Chief Investigator will act as custodian of the data on behalf of co-sponsors.

Personal data will be stored for a minimum of 15 years. Access will be controlled by the Chief Investigator.

The following guidelines will be strictly adhered to:

- All anonymised data will be stored on a password-protected computer.
- All trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the Joint KHP CTO Archiving SOP.

15.3 Informed Consent

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorised individuals other than their treating physician.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent

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care. Documented informed consent must be obtained for all patients included in the study before they are registered or randomised in the study. This will be done in accordance with the national and local regulatory requirements.

15.4 Quality Assurance

Monitoring of this trial will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed and oversight retained, by the KHP CTO Quality Team.

The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsor(s), Regulators and REC direct access to source data and other documents (eg patients' case sheets, blood test reports, X-ray reports, histology reports etc).

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16. ADMINISTRATIVE RESPONSIBILITIES

Ultimate responsibility for Trial Administration rests with the Chief Investigator.

17. TRIAL SPONSORSHIP AND FINANCING

The trial is co-sponsored by Guy's and St Thomas' NHS Foundation Trust and King's College London as the employer of the Chief Investigator. Full details are provided on the front cover of this Clinical Trial Protocol.

Funding to support this trial has been provided by the J.P. Moulton Charitable Foundation, the Wellcome Trust and from the National Institute for Health Research (NIHR) Biomedical Research Centre based at Guy's and St Thomas' NHS Foundation Trust and King's College London.

18. PUBLICATION POLICY

The data generated from this trial will be submitted for publication in a peer-reviewed journal. Authorship will include all Investigators listed in the Clinical Trial Protocol in addition to other scientific and clinical staff who contribute to the study.

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APPENDIX 1

NCI Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03

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 <u>not</u> 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.

[†] 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).

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	В	lood and lymphatic syste	em disorders		
			Grade		
Adverse Event	1	2	3	4	5
Anemia	Hemoglobin (Hgb) <lln -="" 10.0<br="">g/dL; <lln -="" -<br="" 6.2="" <lln="" l;="" mmol="">100 g/L</lln></lln>	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
	ed by an reduction in the amount of palpitations of the heart, soft syst	-	- :	ay include pallor of the skin and m	nucous
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 characteriz	ed by the inability of the bone mar	row to produce hematopoietic eler	ments.		
Disseminated intravascular coagulation	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
	ed by systemic pathological activa s depleted of platelets and coagula	-	which results in clot formation thro	oughout the body. There is an incr	rease in the
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 characteriz degrees F) for more than one ho	ed by an ANC <1000/mm3 and a s ur.	single temperature of >38.3 degre	es C (101 degrees F) or a sustaine	ed temperature of >=38 degrees C	C (100.4
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 characteriz	ed by laboratory test results that ir	ndicate widespread erythrocyte ce	Il 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 characteriz	ed by a form of thrombotic microal	ngiopathy with renal failure, hemo	lytic anemia, and severe thromboo	ytopenia.	
Leukocytosis	-	-	>100,000/mm3	Clinical manifestations of leucostasis; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by laboratory test results that ir	ndicate an increased number of w	nite blood cells in the blood.		
Lymph node pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by a sensation of marked disco	omfort 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 splee	en.				
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
	ed by the presence of microangion		cytopenic purpura, fever, renal abr	normalities and neurological abnor	malities such
as seizures, hemiplegia, and visu	ual disturbances. It is an acute or s	subacute condition.	T	Г	
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 disorde	ers		
			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
	ed by signs and symptoms related unstable angina to myocardial infa		lium secondary to coronary artery	disease. The clinical presentation	covers a
Aortic valve disease	Asymptomatic valvular	Asymptomatic; moderate	Symptomatic; severe	Life-threatening consequences;	Death
	thickening with or without mild valvular regurgitation or stenosis by imaging	regurgitation or stenosis by imaging	regurgitation or stenosis by imaging; symptoms controlled with medical intervention	urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Beaut
	ed by a defect in aortic valve funct	tion or structure.			
Asystole	Periods of asystole; non-urgent medical management indicated ed by a dysrhythmia without cardia		is accompanied by acception of the	Life-threatening consequences; urgent intervention indicated	Death
		1	1	T	Darath
Atrial fibrillation	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	controlled medically, or controlled with device (e.g., pacemaker), or ablation	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz originates above the ventricles.	ed by a dysrhythmia without disce	rnible P waves and an irregular ve	entricular response due to multiple	reentry circuits. The rhythm distur	bance
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 characteriz atria.	ed by a dysrhythmia with organize	d rhythmic atrial contractions with	a rate of 200-300 beats per minut	te. The rhythm disturbance origina	tes in the
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 characteriz	ed by a dysrhythmia with complete	e failure of atrial electrical impulse	conduction through the AV node t	to the ventricles.	•
Atrioventricular block first degree	Asymptomatic, intervention not indicated	Non-urgent intervention indicated	-	-	-
Definition: A disorder characteriz	ed by a dysrhythmia with a delay i interval greater than 200 milliseco	n the time required for the conduc	າ tion of an electrical impulse throug	gh the atrioventricular (AV) node b	eyond 0.2
Cardiac arrest	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by cessation of the pumping fu	nction of the heart.	_	,	
Chest pain - cardiac	Mild pain	Moderate pain; limiting instrumental ADL	Pain at rest; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by substernal discomfort due to	insufficient myocardial oxygenati	on.		
Conduction disorder	Mild symptoms; intervention not indicated	Moderate symptoms	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed 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 characteriz	ed by a thickened and fibrotic peri	cardial sac; these fibrotic changes	impede normal myocardial function	on by restricting myocardial muscle	e 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	1	Death
Definition: A disorder characteriz in the filling pressure.	ed by the inability of the heart to p	ump blood at an adequate volume	e to meet tissue metabolic requirer	ments, or, the ability to do so only a	at an elevatior

		Cardiac disorde	ers		
			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
	ed by failure of the left ventricle to nea, orthopnea, and other signs ar		= :	e and in end-diastolic volume. Clin	ical
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 characteriz	ed by a defect in mitral valve funct	ion or structure.	I		1
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
	ed by a dysrhythmia with relatively atrioventricular (AV) node to the ve	·	block of an atrial impulse. This is the	ne result of intermittent failure of a	trial electrical
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
	ed by a dysrhythmia with a progre through the atrioventricular (AV)	· · ·	or to the blocking of an atrial impu	lse. This is the result of intermitter	nt failure of
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 characteriz	ed by gross necrosis of the myoca	rdium; this is due to an interruptio	n 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		Death
Definition: A disorder characteriz	ed by inflammation of the muscle t	tissue of the heart.	T	T	
Palpitations	Mild symptoms; intervention not indicated	Intervention indicated	-	-	-
Definition: A disorder characteriz	ed by an unpleasant sensation of i				
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 characteriz originates in the atria.	ed by a dysrhythmia with abrupt o	nset and sudden termination of atr	rial contractions with a rate of 150-	250 beats per minute. The rhythm	disturbance
Pericardial effusion	-	Asymptomatic effusion size small to moderate	Effusion with physiologic consequences	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by fluid collection within the per	ricardial sac, usually due to inflam	mation.		1
Pericardial tamponade	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by an increase in intrapericardi	al pressure due to the collection o	f 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 characteriz	ed by irritation to the layers of the	pericardium (the protective sac are	ound the heart).		

		Cardiac disorde	ers		
			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 characteriz	zed by a defect in pulmonary valve	function or structure.	T	1	1
Restrictive cardiomyopathy	-	-	Symptomatic heart failure or other cardiac symptoms, responsive to intervention	Refractory heart failure or other poorly controlled cardiac symptoms	Death
	ed by an inability of the ventricles		1		
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
	zed by impairment of right ventricul				
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 characteriz	zed by a dysrhythmia with alternatio	ng periods of bradycardia and atria	al tachycardia accompanied by syl	ncope, fatigue and dizziness.	1
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 characteriz	red by a dysrhythmia with a heart r	ate less than 60 beats per minute	that originates in the sinus node.	1	1
Sinus tachycardia	Asymptomatic, intervention not indicated	Symptomatic; non-urgent medical intervention indicated	Urgent medical intervention indicated	-	-
Definition: A disorder characteriz	ed by a dysrhythmia with a heart r	ate greater than 100 beats per mi	nute that originates in the sinus no	ode.	
Supraventricular tachycardia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	red by a dysrhythmia with a heart r	ate greater than 100 beats per mi	nute that originates above the ven	tricles.	
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
	zed by a defect in tricuspid valve fu				
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 characteriz	ed by a dysrhythmia that originate	s in the ventricles.			
Ventricular fibrillation	-	-	-	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characteriz ventricles.	zed by a dysrhythmia without disce	rnible QHS complexes due to rapi	d repetitive excitation of myocardi	al fibers without coordinated contra	action of the
Ventricular tachycardia	-	Non-urgent medical intervention indicated	Medical intervention indicated	Life-threatening consequences; hemodynamic compromise; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by a dysrhythmia with a heart r	ate greater than 100 beats per mi	nute that originates distal to the bu	undle 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 characteriz	ed by the presence of an accesso	ry conductive pathway between th	e atria and the ventricles that cau	ses premature ventricular activatio	n.
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	• • • • • • • • • • • • • • • • • • • •	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 dis	sorders		
			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 characteri	zed by a sensation of marked disco	mfort 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 characteri	' zed by inflammation, swelling and r	' edness to the outer ear and ear ca	anal.	1	1
External ear pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteri	zed by a sensation of marked disco	mfort 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 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.	Pediatric: Audiologic indication for cochlear implant and additional speech-language related services indicated.	-
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 characteri	। zed by inflammation (physiologic re	ı	1	•	'
Tinnitus	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteri	zed by noise in the ears, such as rir	nging, buzzing, roaring or clicking.	Τ	Г	
Vertigo	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterity vertigo).	zed by a sensation as if the externa	al world were revolving around the	patient (objective vertigo) or as if	he himself were revolving in space	e (subjective
Vestibular disorder	-	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteri	zed by dizziness, imbalance, nause	ea, and vision problems.	T	Г	1
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 disord	lers		
			Grade		
Adverse Event	1	2	3	4	5
Adrenal insufficiency	Asymptomatic; clinical or diagnostic observations only; intervention not indicated when the adrenal cortex does not	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death to a disorder
	on's disease or primary adrenal ins		cortisor and in some cases, the no	imone aldosterone. It may be due	to a disorder
Cushingoid	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms, medical intervention or hospitalization indicated	-	-
Definition: A disorder characterizosteoporosis, usually due to exo	zed by signs and symptoms that regenous corticosteroids.	semble Cushing's disease or sync	lrome: buffalo hump obesity, striat	ions, adiposity, hypertension, diab	etes, and
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 characteriz	zed by unusually late sexual maturi	ty.			
Growth accelerated	-	>= +2 SD (standard deviation) above mid parental height or target height	-	-	-
Definition: A disorder characterize	zed by greater growth than expecte	ed for age.	T	T	1
Hyperparathyroidism	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterize the blood).	zed by an increase in production of	parathyroid hormone by the parat	thyroid glands. This results in hype	ercalcemia (abnormally high levels	of calcium in
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 characteriz	zed by excessive levels of thyroid h	ormone in the body. Common cau	uses include an overactive thyroid	gland or thyroid hormone overdos	e.
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 characterize	zed by a decrease in production of	parathyroid hormone by the parat	hyroid 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
	zed by a decrease in production of		and. T		
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 characteriz 9 for boys.	zed by unusually early developmen	t of secondary sexual features; th	e onset of sexual maturation begir	ns usually before age 8 for girls an	d before age
Virilization	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characteriz	zed by inappropriate masculinizatio	n occurring in a female or prepub	ertal 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

Definition: A disorder characterized diaginate interpretated. Definition: A disorder characterized untreated. Conjunctivitis Asy symindi Definition: A disorder characterized corneal ulcer Definition: A disorder characterized diaginate interpretated. Definition: A disorder characterized diaginate interpretated and interpretated diaginate interpretated and interpretated diaginate interpretated diaginate interpretated diaginate interpretated diaginate interpretated diagrams. Definition: A disorder characterized diagrams diagrams disorder characterized diagrams	ed by visual perception of ur symptomatic; clinical or agnostic observations only; tervention not indicated ed by partial or complete op- symptomatic or mild imptoms; intervention not dicated	Symptomatic; moderate decrease in visual acuity (20/40 or better) acity of the crystalline lens of comparison of comparis	Limiting self care ADL	Blindness (20/200 or worse) in the affected eye a decrease in visual acuity an	- d eventual blindness if
Blurred vision Interpretation Interpretation: A disorder characterized diaginite interpretation: A disorder characterized interpretated. Definition: A disorder characterized symmetric indicates and interpretation in the	ed by visual perception of ur symptomatic; clinical or agnostic observations only; tervention not indicated ed by partial or complete ope symptomatic or mild imptoms; intervention not dicated	Symptomatic; limiting instrumental ADL nclear or fuzzy images. Symptomatic; moderate decrease in visual acuity (20/40 or better) acity of the crystalline lens of comparison of crystalline lens of crystalline lens of comparison of crystalline lens of crystallin	Symptomatic with marked decrease in visual acuity (worse than 20/40 but better than 20/200); operative intervention indicated (e.g., cataract surgery) one or both eyes. This results in Limiting self care ADL	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characterized diaginter interested. Definition: A disorder characterized intreated. Definition: A disorder characterized symmetric individual interested. Definition: A disorder characterized corneal ulcer - Definition: A disorder characterized in individual interested in individual interested in individual individ	ed by visual perception of ur symptomatic; clinical or agnostic observations only; tervention not indicated ed by partial or complete ope symptomatic or mild imptoms; intervention not dicated	instrumental ADL nclear or fuzzy images. Symptomatic; moderate decrease in visual acuity (20/40 or better) acity of the crystalline lens of control of control of the crystalline lens of control of control of control of the crystalline lens of control	Symptomatic with marked decrease in visual acuity (worse than 20/40 but better than 20/200); operative intervention indicated (e.g., cataract surgery) one or both eyes. This results in Limiting self care ADL	in the affected eye	d eventual blindness if
refinition: A disorder characterized interested. refinition: A disorder characterized symmetric individual interested. refinition: A disorder characterized rorneal ulcer - refinition: A disorder characterized interested in the property eye - Asymite individual interested in the property eye - Asymite in the property eye - Asymite individual interested in the property eye - Asymite	symptomatic; clinical or agnostic observations only; tervention not indicated ed by partial or complete operations, intervention not dicated ed by inflammation, swelling	Symptomatic; moderate decrease in visual acuity (20/40 or better) acity of the crystalline lens of comparison of the comparis	decrease in visual acuity (worse than 20/40 but better than 20/200); operative intervention indicated (e.g., cataract surgery) one or both eyes. This results in	in the affected eye	d eventual blindness if
refinition: A disorder characterized interested. Asy symindical interested interested interested in the interested interested in the inte	agnostic observations only; tervention not indicated ed by partial or complete operations symptomatic or mild imptoms; intervention not dicated ed by inflammation, swelling	decrease in visual acuity (20/40 or better) acity of the crystalline lens of comparity of the conjunctive symptomatic; medical	decrease in visual acuity (worse than 20/40 but better than 20/200); operative intervention indicated (e.g., cataract surgery) one or both eyes. This results in	in the affected eye	d eventual blindness if
Conjunctivitis Asy symindi Definition: A disorder characterized Corneal ulcer Definition: A disorder characterized Dry eye Asy diag mild lubr Definition: A disorder characterized Extraocular muscle paresis Asy	mptoms; intervention not dicated ed by inflammation, swelling	intervention indicated (e.g., antibiotics); limiting instrumental ADL and redness to the conjunctiv Symptomatic; medical		-	-
symindi definition: A disorder characterized corneal ulcer definition: A disorder characterized by eye Asy diag mild lubr definition: A disorder characterized corneal ulcer Asy Asy diag mild lubr definition: A disorder characterized xtraocular muscle paresis Asy	mptoms; intervention not dicated ed by inflammation, swelling	intervention indicated (e.g., antibiotics); limiting instrumental ADL and redness to the conjunctiv Symptomatic; medical		-	-
Definition: A disorder characterized diag mile lubr Definition: A disorder characterized Extraocular muscle paresis Asy		Symptomatic; medical	a of the eye.	ı	
Definition: A disorder characterized Asy diag mild lubr Definition: A disorder characterized extraocular muscle paresis Asy		· ' '	1	T	<u> </u>
Ory eye Asy diag mild lubr Definition: A disorder characterized Extraocular muscle paresis Asy	ed by an area of epithelial tis	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	-
diaç milc lubr Definition: A disorder characterized Extraocular muscle paresis Asy		ssue loss on the surface of the	cornea. It is associated with in	flammatory cells in the cornea	and anterior chamber.
Extraocular muscle paresis Asy	· · · · ·	Symptomatic; multiple agents indicated; limiting instrumental ADL	Decrease in visual acuity (<20/40); limiting self care ADL	-	-
	ed by dryness of the cornea	and conjunctiva.			
· ·	symptomatic; clinical or agnostic observations only	Symptomatic; limiting instrumental ADL	Limiting self care ADL; disabling	-	-
Definition: A disorder characterized	ed by incomplete paralysis of	of an extraocular muscle.			
Eye pain Mild	•	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized	ed by a sensation of marked	discomfort in the eye.	Т	Т	Г
diag	agnostic observations only;	Symptomatic; nonoperative intervention indicated; limiting instrumental ADL	Limiting self care ADL; operative intervention indicated	-	-
Definition: A disorder characterized	ed by impaired eyelid function				Γ
lashing lights Syn ADI	mptomatic but not limiting DL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized	-				_
ADI	DL	Limiting instrumental ADL	Limiting self care ADL	-	-
efinition: A disorder characterized					or or lens.
pre: topi	essure (EIOP) with single pical agent for intervention;	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 characterize	ed by an increase in pressur	e in the eyeball due to obstruc	tion of the aqueous humor outf	flow.	
Ceratitis -		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	ed by inflammation to the co	rnea of the eye.	Т	Т	г
light blindness Syn ADI	· · · · · · · · · · · · · · · · · · ·	Limiting instrumental ADL	Limiting self care ADL	Blindness (20/200 or worse) in the affected eye	-

		Eye dis	sorders		
		·	Grade		
Adverse Event	1	2	3	4	5
Optic nerve disorder	Asymptomatic; clinical or diagnostic observations only erized by involvement of the op	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	-
	1		Marked visual field defect	Plindness (20/200 or worse)	
Papilledema	Asymptomatic; no visual field defects	vision; visual field defect present sparing the central 20 degrees	(worse than 20/40 but better than 20/200)	Blindness (20/200 or worse) in the affected eye	-
Definition: A disorder characte	erized by swelling around the o	ptic disc.			
Photophobia	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characte	erized 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 characte	erized by the separation of the i	nner retina layers from the unc	lerlying 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 characte	erized by a small laceration of t	he retina, this occurs when the	vitreous separates from the re	tina. Symptoms include flashes	and floaters.
Retinal vascular disorder	-	Topical medication indicated	Intravitreal medication; operative intervention indicated	-	-
Definition: A disorder characte	erized by pathological retinal blo	ood vessels that adversely affe	cts 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	g the retina.	'	1	1	'
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 characte	erized by involvement of the sol	era 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 characte	erized by inflammation to the uv	yea 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 characte	erized by blood extravasation in	to the vitreous humor.	ı	ı	T
Watering eyes	Intervention not indicated	Intervention indicated	Operative intervention indicated	-	-
Definition: A disorder of exces	ssive tearing in the eyes; it can	be caused by overproduction of	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 dis	orders		
			Grade		
Adverse Event	1	2	3	4	5
Abdominal distension	Asymptomatic; clinical or diagnostic observations only; intervention not indicated rized by swelling of the abdomen.	Symptomatic; limiting instrumental ADL	Severe discomfort; limiting self care ADL	-	-
		Mandauska usaisa liusikin u	0		
Abdominal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder character	rized by a sensation of marked disco	omfort in the abdominal region.	Τ	T	
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 character	rized 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
	rized 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 character	rized by inflammation of the mucous	membrane of the anus.	Τ	T	
Anal necrosis	-	-	TPN or hospitalization indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder character	rized by a necrotic process occurring	T T			
Anal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder character	rized by a sensation of marked disco	omfort in the anal region.	Т	Т	1
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 character	rized 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 character	rized by a circumscribed, inflammato	ory and necrotic erosive lesion on	the mucosal surface of the anal ca	nal.	
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 character	ized by accumulation of serous or h	emorrhagic 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 character	rized by subject-reported feeling of u	incomfortable fullness of the abdo	men.		
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 character	rized 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	-	-
D. C. W A P	ized by inflammation of the lip.				

		Gastrointestinal dis	orders		
			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 characte	erized 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 characte	erized by an abnormal communication	between the large intestine and a	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 characte	erized by bleeding from the colon.				1
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
	erized by blockage of the normal flow			I if the second of the second	Der !!
Colonic perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	erized 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 characte	erized 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 characte	erized by a circumscribed, inflammato	ry and necrotic erosive lesion on t	he 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 characte	erized by irregular and infrequent or di	ifficult 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	-	-
	erized by the decay of a tooth, in whic				
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 characte	erized by frequent and watery bowel n	novements.	1		1
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	-	-
	l erized by reduced salivary flow in the	I	I	1	l

		Gastrointestinal dis	orders		
			Grade		1
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 characteri	ized by an abnormal communication	between the duodenum and ano	ther organ or anatomic site.	T	1
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 characteri	ized by bleeding from the duodenur	n.	T	T	
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 characteri	ized 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 characteri	ized by a rupture in the duodenal w	all.	1	<u> </u>	1
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 characteri	ized 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
	ized by a circumscribed, inflammato	Ī		nal wall. T	
Dyspepsia	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	-
	ized by an uncomfortable, often pair	nful feeling in the stomach, resulting	ng from impaired digestion. Sympt	oms include burning stomach, bloa	ating,
heartburn, nausea and vomiting			T	I	l
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 characteri	ized 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 characteri	ized by inflammation of the small ar	nd large intestines.	1	<u> </u>	1
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 characteri	ized 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 characteri	ized by an abnormal communication	between the esophagus and and	ther 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 characteri	ized by bleeding from the esophagu	s.			

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 characteriz	ed by a necrotic process occurring	g 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 characteriz	ed by blockage of the normal flow	of the contents in the esophagus	T	Т				
sophageal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteriz	ed by a sensation of marked disco	omfort 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 characteriz	ed by a rupture in the wall of the e	sophagus.						
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 characteriz	ed 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 characteriz	ed by a circumscribed, inflammato	ory and necrotic erosive lesion on	the mucosal surface of the esopha	geal wall.				
Esophageal varices nemorrhage	-	Self-limited; intervention not indicated	Transfusion, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder characteriz	ed by bleeding from esophageal v	rarices.						
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		Death			
	ted by inflammation of the esopha		T					
Fecal incontinence	Occasional use of pads required		Severe symptoms; elective operative intervention indicated	-	-			
	ted by inability to control the escap							
Flatulence	Mild symptoms; intervention not indicated	psychosocial sequelae	-	-	-			
	ed by a state of excessive gas in t							
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 characteriz	ed by an abnormal communication	between the stomach and anoth	ner 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 characteriz	ed by bleeding from the gastric wa	all. T						
Gastric necrosis	-	-	Inability to aliment adequately by GI tract; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			

		Gastrointestinal dis	orders		
			Grade		
Adverse Event	1	2	3	4	5
Gastric perforation Definition: A disorder characterize	- ed by a rupture in the stomach wa	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Gastric stenosis	Asymptomatic; clinical or	Symptomatic; altered GI	Severely altered GI function;	Life-threatening consequences;	Death
Gasure steriosis	diagnostic observations only; intervention not indicated	function	tube feeding; hospitalization indicated; elective operative intervention indicated	urgent operative intervention indicated	Death
Definition: A disorder characterize	ed 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
			the mucosal surface of the stomac		
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 characterize	ed by inflammation of the stomach	l.	T		
Gastroesophageal reflux disease	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; surgical intervention indicated	-	-
	ed by reflux of the gastric and/or d esult in injury to the esophageal m		sophagus. It is chronic in nature ar urn and acid indigestion.	nd usually caused by incompetend	e of the lower
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 characterize	ed by an abnormal communication	between any part of the gastroin	testinal 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 characterize	ed by a sensation of marked disco	mfort in the gastrointestinal region	1.		
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 characterize	ed by an incomplete paralysis of the	ne muscles of the stomach wall re	sulting in delayed emptying of the	gastric contents into the small inte	estine.
Gingival pain	Mild pain	Moderate pain interfering with oral intake	Severe pain; inability to aliment orally	-	-
Definition: A disorder characterize	ed by a sensation of marked disco	mfort 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 characterize	ed by bleeding from the hemorrho	ids.	T		
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 characterize	ed by the presence of dilated vein:	s in the rectum and surrounding a	rea.		
lleal 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 characterize	ed by an abnormal communication	between the ileum and another o	organ or anatomic site.	r	1
lleal 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 characterize	ed by bleeding from the ileal wall.				

Gastrointestinal disorders								
			Grade					
Adverse Event	1	2	3	4	5			
lleal 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 characteriz	ed by blockage of the normal flow	of the intestinal contents in the ile	eum.	T	1			
lleal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characteriz	ed by a rupture in the ileal wall.		1	_				
lleal 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 characteriz	red by a narrowing of the lumen of	the ileum.	1	T	1			
lleal 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 characteriz	ed by a circumscribed, inflammato	ory and necrotic erosive lesion on	the mucosal surface of the ileum.	T	1			
Refinition: A disorder characterist	- ted by failure of the ileum to transp	Symptomatic; altered GI function; bowel rest indicated	Severely altered GI function; TPN indicated	Life-threatening consequences; urgent intervention indicated	Death			
Intra-abdominal hemorrhage	Lea by failure of the fleath to transp	Medical intervention or minor	Transfusion, radiologic,	Life-threatening consequences;	Death			
inii a-abdoniinai nemonnage		cauterization indicated	endoscopic, or elective operative intervention indicated	urgent intervention indicated	Deali			
Definition: A disorder characteriz	ed by bleeding in the abdominal c	avity.		T	1			
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 characteriz	ed by an abnormal communication	h between the jejunum and anothe	er organ or anatomic site.	'	1			
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 characteriz	ed by bleeding from the jejunal wa	all.	•	•	'			
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 characterize	ed by blockage of the normal flow	of the intestinal contents in the je	junum.	T				
Jejunal perforation		Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characteriz	ed 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 characteriz	ed 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 characteriz	ed by a circumscribed, inflammato	ory and necrotic erosive lesion on	the mucosal surface of the jejunun	n.				
Lip pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteriz	ed by a sensation of marked disco	omfort of the lip.						

Gastrointestinal disorders								
			Grade					
Adverse Event	1	2	3	4	5			
ower gastrointestinal. Demorrhage	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 characte	rized by bleeding from the lower gas	trointestinal 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 characte	rized by inadequate absorption of nu	trients in the small intestine. Sym	ptoms include abdominal marked o	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 characte	rized by inflammation of the oral mu	cosal.	T	T				
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 characte	rized by a queasy sensation and/or t	1	1	1				
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 characte	rized 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 characte	rized by an abnormal communication	between the oral cavity and another	ther 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 characte	rized by a burning or tingling sensati	on on the lips, tongue or entire mo	outh. T	<u> </u>				
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 characte	rized by bleeding from the mouth.							
Oral pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characte	rized by a sensation of marked disco	pmfort 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 characte	rized 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 characte	rized by an abnormal communication	n between the pancreas and anoth	ner organ or anatomic site.	T				
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 characte	rized by bleeding from the pancreas		1	1				
Pancreatic necrosis	-	-	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death			
Definition: A disorder characte	rized by a necrotic process occurring	g in the pancreas.	1	T				
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 dis	orders		
			Grade		
Adverse Event	1	2	3	4	5
Definition: A disorder characterize	ed by inflammation of the pancrea	S.	_		
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 ginging	val tissue around the teeth.		T	T	
Peritoneal necrosis	-	-	Tube feeding or TPN indicated; radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterize	ed by a necrotic process occurring	in the peritoneum.	1	Γ	
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 characterize	ed 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 characterize	ed 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 characterize	ed 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
	ed 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 characterize	ed by a necrotic process occurring	in the rectal wall.	1	I	1
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 characterize	ed by blockage of the normal flow	of the intestinal contents in the re	ctum.	Γ	
Rectal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterize	ed by a sensation of marked disco				
Rectal perforation	-	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterize	ed by a rupture in the rectal wall.	1	1	ı	1
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 characterize	ed by a narrowing of the lumen of	the rectum.		T	
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 characterize	ed by a circumscribed, inflammato	ry and necrotic erosive lesion on	the mucosal surface of the rectum		

		Gastrointestinal dis	orders		
			Grade		
Adverse Event	1	2	3	4	5
Retroperitoneal hemorrhage	- ed by bleeding from the retroperito	Self-limited; intervention indicated	Transfusion, medical, radiologic, endoscopic, or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	_ · _ ·		A	l ife the extension of	Daath
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 characteriz	ed 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 characteriz	ed by an abnormal communication	between a salivary gland and an	other 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 characteriz	ed 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 characteriz	ed 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 characteriz	ed by a rupture in the small intesti	ne 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 characteriz	ed 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 characteriz	ed by a circumscribed, inflammato	ry and necrotic erosive lesion on t	the mucosal surface of the small in	ntestine.	
tomach pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
efinition: A disorder characteriz	ed by a sensation of marked disco	mfort in the stomach.	I	T	1
ooth development disorder	Asymptomatic; hypoplasia of tooth or enamel	Impairment correctable with oral surgery	Maldevelopment with impairment not surgically correctable; disabling	-	-
Definition: A disorder characteriz	ed by a pathological process of the	e teeth occurring during tooth deve	elopment.	T	1
ooth discoloration	Surface stains	-	-	-	-
efinition: A disorder characteriz	ed by a change in tooth hue or tint				
oothache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	l ed by a sensation of marked disco	1	ı	ı	I

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 character	zed by inflammation of the cecum.	l	Joigno	I				
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 character	zed by bleeding from the upper gas	strointestinal tract (oral cavity, pha	rynx, 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 character	zed by the reflexive act of ejecting	the contents of the stomach through	gh 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;	Life-threatening consequences; urgent intervention indicated	Death			
			disabling; limiting self care ADL					

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 charact	terized by a sensation of cold that often	n marks a physiologic response to	sweating after a fever.					
Death neonatal	-	-	-	-	Death			
Definition: A disorder charact	terized by cessation of life occurring du	uring 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 charact	terized by swelling due to excessive flu	uid accumulation in facial tissues.	1	1				
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 charact	terized by swelling due to excessive flu	ı	I wer extremities	I	I			
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 charact	terized by swelling due to excessive flu	uid accumulation in the trunk area.						
acial pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder charact	terized by a sensation of marked disco	mfort in the face.	,	•	·			
atigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	-	-			
Definition: A disorder charact	terized by a state of generalized weak	ness with a pronounced inability to	summon sufficient energy to acc	omplish daily activities.				
-ever	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)	>39.0 - 40.0 degrees C (102.3 - 104.0 degrees F)	degrees F) for <=24 hrs	>40.0 degrees C (>104.0 degrees F) for >24 hrs	Death			
	terized by elevation of the body's temp							
Flu like symptoms	Mild flu-like symptoms present	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-			
Definition: A disorder charact cough.	terized by a group of symptoms similar	r to those observed in patients with	n the flu. It includes fever, chills, b	ody aches, malaise, loss of appeti	te and dry			
aait 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 charact	terized 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			

	S.STIGIAL V		ation site conditions Grade		
Adverse Event	1	2	3	4	5
nfusion 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	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement;	Life-threatening consequences; urgent intervention indicated	Death
		hrs	hospitalization indicated for clinical sequelae		
Definition: A disorder characteriz	ed by adverse reaction to the infus	sion of pharmacological or biologic	cal substances.	T	1
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
	ed by leakage of a pharmacologic atton and marked discomfort at the	-	nfusion site into the surrounding ti	ssue. Signs and symptoms include	e induratio
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 characteriz	red by an intense adverse reaction	(usually immunologic) developing	at the site of an injection.	T	1
Irritability	Mild; easily consolable	Moderate; limiting instrumental ADL; increased attention indicated	Severe abnormal or excessive response; limiting self care ADL; inconsolable	-	-
Definition: A disorder characteriz condition.	red by an abnormal responsivenes	s to stimuli or physiological arousa	al; may be in response to pain, frig	ht, a drug, an emotional situation o	or a medic
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 characteriz	ed by swelling due to excessive flu	id accumulation at a specific anal	omic site.	'	
Malaise	Uneasiness or lack of well being	Uneasiness or lack of well being; limiting instrumental ADL	-	-	-
Definition: A disorder characteriz	ed by a feeling of general discomf	ort 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 characteriz	ed by progressive deterioration of	the lungs, liver, kidney and clotting	g 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 characteriz	ed by swelling due to an accumula	tion 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 characteriz	ed by discomfort in the chest unre	ated to a heart disorder.			
Pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by the sensation of marked dis	comfort, distress or agony.			
Sudden death NOS	-	-	-	-	Death
Definition: An unexpected cessa	tion of life that cannot be attributed	to a CTCAE term associated with	n Grade 5.	,	•
General disorders and administration site conditions - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention	Moderate; minimal, local or noninvasive intervention indicated; limiting age-	Severe or medically significant but not immediately life- threatening; hospitalization or	Life-threatening consequences; urgent intervention indicated	Death
	not indicated	appropriate instrumental ADL	prolongation of existing hospitalization indicated; disabling; limiting self care ADL		

		Hepatobiliary diso	rders		
			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 characteriz	ed 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 characterize	ed by an abnormal communication	between the bile ducts and anoth	ner 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 characteriz	ed by inflammation involving the g	allbladder. It may be associated w	rith 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 characteriz	ed by an abnormal communication	between the gallbladder and and	ther organ or anatomic site.	T	1
Gallbladder necrosis	-	-	-	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characteriz	ed 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
	ed by blockage of the normal flow	of the contents of the gallbladder.	I	I	
Gallbladder pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
	ed by a sensation of marked disco	mfort in the gallbladder region.	Τ	Τ	
Gallbladder perforation	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by a rupture in the gallbladder	vall.	T	T	1
Hepatic failure	-	-	Asterixis; mild encephalopathy; limiting self care ADL	Moderate to severe encephalopathy; coma; life-threatening consequences	Death
	ed by the inability of the liver to me	etabolize chemicals in the body. La	aboratory test results reveal abnor	rmal plasma levels of ammonia, bi	lirubin, lactic
dehydrogenase, and alkaline pho		0	Turnet size to Protect	I the share and the same	Death
Hepatic hemorrhage	Mild; intervention not indicated	Symptomatic; medical intervention indicated	Transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by bleeding from the liver.			Ī	
Hepatic necrosis	-	-	-	Life-threatening consequences; urgent radiologic or operative intervention indicated	Death
Definition: A disorder characteriz	ed by a necrotic process occurring	in the hepatic parenchyma.		.	1
Hepatic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterize	ed by a sensation of marked disco	omfort 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 characteriz	ed by a rupture in the wall of the e	xtrahepatic or intrahepatic bile due	ot.	•	

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 characterize	ed by an increase in blood pressu	re in the portal venous system.							
Portal vein thrombosis	-	Intervention not indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death				
Definition: A disorder characterize	ed 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 dis	orders		
			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
	ed by an adverse local or general	response from exposure to an alle			
Anaphylaxis	-		Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
	ed by an acute inflammatory react resents with breathing difficulty, dia	-		-	ypersensitivity
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 frontissue constituents.	om loss of function or tissue destru	nction of an organ or multiple orga	ns, arising from humoral or cellula	r immune responses of the individe	ual to his own
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 characteriz	ed by nausea, headache, tachyca	rdia, hypotension, rash, and shorti	ness of breath; it is caused by the	release of cytokines from the cells	
Serum sickness Definition: A disorder characteriz	Asymptomatic; clinical or diagnostic observations only; intervention not indicated ted by a delayed-type hypersensitive.	Moderate arthralgia; fever, rash, urticaria, antihistamines indicated vity reaction to foreign proteins de	Severe arthralgia or arthritis; extensive rash; steroids or IV fluids indicated rived from an animal serum. It occ	Life-threatening consequences; pressor or ventilatory support indicated urs approximately six to twenty-on	Death ne days
	e foreign antigen. Symptoms inclu				-
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						
			Grade	Ι .	l _	
Adverse Event	1	2	3	4	5	
Abdominal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative	Life-threatening consequences; urgent intervention indicated	Death	
			intervention indicated			
Definition: A disorder charact	erized by an infectious process in	volving the abdominal cavity.		1	1	
Anorectal infection	Localized; local intervention	Oral intervention indicated (e.g.,	IV antibiotic, antifungal, or	Life-threatening consequences;	Death	
	indicated	antibiotic, antifungal, antiviral)	antiviral intervention indicated; radiologic, endoscopic, or	urgent intervention indicated		
			operative intervention indicated			
Definition: A disorder charact	erized by an infectious process in	volving the anal area and the rectum.				
Appendicitis	-	-	IV antibiotic, antifungal, or	Life-threatening consequences;	Death	
			antiviral intervention indicated;	urgent intervention indicated		
			radiologic or operative intervention indicated			
Definition: A disorder charact	l erized by acute inflammation to th	। ne vermiform appendix caused by a pa	1		I	
Appendicitis perforated	-	Symptomatic; medical	Severe symptoms; elective	Life-threatening consequences;	Death	
P. P. S.		intervention indicated	operative intervention indicated	urgent intervention indicated	_ 3001	
Definition: A disorder charact	erized by acute inflammation to the	ne vermiform appendix caused by a pa	athogenic agent with gangrenous o	changes resulting in the rupture of	the	
appendiceal wall. The append	diceal wall rupture causes the rele	ease of inflammatory and bacterial cor	ntents from the appendiceal lumen	into the abdominal cavity.	1	
Arteritis infective	-	-	IV antibiotic, antifungal, or	Life-threatening consequences;	Death	
			antiviral intervention indicated;	urgent intervention indicated		
			radiologic or operative intervention indicated			
Definition: A disorder charact	erized by an infectious process in	volving an arterv.		ı	Į.	
Biliary tract infection	-	-	IV antibiotic, antifungal, or	Life-threatening consequences;	Death	
smary wast innocuon			antiviral intervention indicated;	urgent intervention indicated	204	
			radiologic or operative			
			intervention indicated			
Definition: A disorder charact	erized by an infectious process in	volving the biliary tract.		T		
Bladder infection	-	Oral intervention indicated (e.g.,	IV antibiotic, antifungal, or	Life-threatening consequences;	Death	
		antibiotic, antifungal, antiviral)	antiviral intervention indicated; radiologic, endoscopic, or	urgent intervention indicated		
			operative intervention indicated			
Definition: A disorder charact	erized by an infectious process in	volving the bladder.	•	•		
Bone infection	-	-	IV antibiotic, antifungal, or	Life-threatening consequences;	Death	
			antiviral intervention indicated;	urgent intervention indicated		
			radiologic or operative intervention indicated			
Definition: A disorder charact	l erized by an infectious process in	volving the hones	intervention indicated	I	l	
Breast infection	-	Local infection with moderate	Severe infection; axillary	Life-threatening consequences;	Death	
Brodot Imoodon		symptoms; oral intervention	adenitis; IV antibacterial,	urgent intervention indicated	Dodin	
		indicated (e.g., antibiotic,	antifungal, or antiviral			
		antifungal, antiviral)	intervention indicated			
Definition: A disorder charact	erized by an infectious process in	volving the breast.		T		
Bronchial infection	-	Moderate symptoms; oral	IV antibiotic, antifungal, or	Life-threatening consequences;	Death	
		intervention indicated (e.g., antibiotic, antifungal, antiviral)	antiviral intervention indicated; radiologic, endoscopic, or	urgent intervention indicated		
		anusiono, anniungai, anniviral)	operative intervention indicated			
Definition: A disorder charact	erized by an infectious process in	volving the bronchi.	•	1	1	
Catheter related infection	-	Localized; local intervention	IV antibiotic, antifungal, or	Life-threatening consequences;	Death	
		indicated; oral intervention	antiviral intervention indicated;	urgent intervention indicated		
		indicated (e.g., antibiotic,	radiologic or operative			
		antifungal, antiviral)	intervention indicated		[
	erized by an infectious process th	at arises secondary to catheter use.			I_	
Cecal infection	-	-	IV antibiotic, antifungal, or	Life-threatening consequences;	Death	
			antiviral intervention indicated; radiologic, endoscopic, or	urgent intervention indicated		
			operative intervention indicated	1		

		Infections and infes	tations			
		Grade				
Adverse Event	1	2	3	4	5	
Definition: A disorder characterize	d by an infectious process invol	ving the cecum.				
Cervicitis infection	d by an infectious process involves	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 characterize Conjunctivitis infective	a by an infectious process invol	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 characterize	d by an infectious process invol	ving the conjunctiva. Clinical manif	estations 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 characterize	d by an infectious process invol	ving 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 characterize	d by an infectious process invol	ving a cranial nerve.		1		
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 characterize	d by an infectious process invol	ving 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 characterize	d by an infectious process invol	ving 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 characterize	d by an infectious process invol	ving 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 characterize	d by an infectious process invol	ving the brain and spinal cord tissu	es.			
Endocarditis infective	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characterize	d by an infectious process invol	ving the endocardial layer of the he	eart.			
Endophthalmitis	-	Local intervention indicated	Systemic intervention or hospitalization indicated	Blindness (20/200 or worse)	-	

		Infections and infes			
			Grade		
Adverse Event	1	2	3	4	5
Enterocolitis infectious	-	Passage of >3 unformed stools	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
		per 24 hrs or duration of illness	antiviral intervention indicated;	urgent intervention indicated	
		>48 hrs; moderate abdominal	radiologic, endoscopic, or		
		pain	operative intervention indicated;		
			profuse watery diarrhea with		
			signs of hypovolemia; bloody		
			diarrhea; fever; severe		
			abdominal pain; hospitalization		
Offinition: A disorder characteri	and by an infactious process involve	ing the small and large intestines	indicated		
	zed by an infectious process involv		IV andibitation and formal and	1 16- 41	D = =41=
sophageal infection	-	Local intervention indicated	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
		(e.g., oral antibiotic, antifungal,	antiviral intervention indicated;	urgent intervention indicated	
		antiviral)	radiologic or operative		
			intervention indicated		
	zed by an infectious process involv				_
Eye infection	-	Localized; local intervention	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
		indicated (e.g., topical antibiotic,	antiviral intervention indicated;	urgent intervention indicated;	
		antifungal, or antiviral)	radiologic or operative	enucleation	
			intervention indicated		
efinition: A disorder characteri	zed by an infectious process involv	ing the eye.	T		
Gallbladder infection	-	-	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
			antiviral intervention indicated;	urgent intervention indicated	
			radiologic, endoscopic, or		
			operative intervention indicated		
Definition: A disorder characteri	zed by an infectious process involv	ing the gallbladder.	1	T	
Gum infection	Local therapy indicated (swish	Moderate symptoms; oral	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
	and swallow)	intervention indicated (e.g.,	antiviral intervention indicated;	urgent intervention indicated	
		antibiotic, antifungal, antiviral)	radiologic or operative		
			intervention indicated		
Definition: A disorder characteri	zed by an infectious process involv	ing the gums.			
Hepatic infection	-	-	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
			antiviral intervention indicated;	urgent intervention indicated	
			radiologic or operative		
			intervention indicated		
Definition: A disorder characteri	zed by an infectious process involv	ing the liver.	1	T	
Hepatitis viral	Asymptomatic, treatment not	-	Symptomatic liver dysfunction;	Decompensated liver function	Death
	indicated		fibrosis by biopsy; compensated	(e.g., ascites, coagulopathy,	
			cirrhosis; reactivation of chronic	encephalopathy, coma)	
			hepatitis		
Definition: A disorder characteri	zed by a viral pathologic process in	volving the liver parenchyma.	1		1
nfective myositis	-	Localized; local intervention	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
		indicated (e.g., topical antibiotic,	antiviral intervention indicated;	urgent intervention indicated	
		antifungal, or antiviral)	radiologic or operative		
			intervention indicated		
Definition: A disorder characteri	zed by an infectious process involv	ing the skeletal muscles.	ı		1
loint infection	-	Localized; local intervention	Arthroscopic intervention	Life-threatening consequences;	Death
		indicated; oral intervention	indicated (e.g., drainage) or	urgent intervention indicated	
		indicated (e.g., antibiotic,	arthrotomy (e.g., open surgical		
		antifungal, antiviral); needle	drainage)		
		aspiration indicated (single or			
		multiple)			
Definition: A disorder characteri	zed by an infectious process involv	ing a joint.			
Kidney infection	-	-	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
			antiviral intervention indicated;	urgent intervention indicated	
			radiologic, endoscopic, or		
			operative intervention indicated		

		Infections and infes	tations		
			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 characterization	zed by an inflammatory process inv	volving 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 characterize	zed by an infectious process involv	ing the lips.	T	1	1
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 characterize	zed by an infectious process involv	ing the lungs.	I	1	
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 characterization	zed by an infectious process involv	ing the lymph nodes.	Τ	1	
Mediastinal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	zed by an infectious process involv	ing 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 characteriz	zed by acute inflammation of the m	eninges 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 characteriz	zed by an infectious process involv	ing 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 characteriz	zed by an infectious process involv	ing the nail.			1
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
	zed by an infectious process involvtoms include fullness, itching, swell	-		ive water exposure (swimmer's ea	r infection)
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 characterization	zed by an infectious process involv	ing the middle ear.	•	•	1
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 characterize	zed by an infectious process involv	ing the ovary.		1	ı

		Infections and infes	tations		
			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 characterize	zed by an infectious process involvi	ing the pancreas.	<u> </u>	<u> </u>	1
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; lifethreatening consequences	Death
	red by an eruption consisting of pa				o, and upper
	rash does not present with whiteh		i i	esions.	
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 characterize	red by an infectious process involvi	ing the soft tissues around the nai	l.		
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 characterize	ed by an infectious process involvi	ing 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 characteriz	ed by an infectious process involvi	ing the penis.			
Periorbital infection	- red by an infectious process involvi	antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; radiologic or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
	ed by an injectious process involvi		N/ antibiation antibused as	l ife the extension of	Daath
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
	zed by an infectious process involvi	ту тте реприетат пегуеs.	IV antibiatio antibus a	Life threatering	Dooth
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 characteriz	red by an infectious process involvi	ing 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 characteriz	zed 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 infes	tations		
		T	Grade	T	
Adverse Event	1	2	3	4	5
Definition: A disorder character of the infected vein.	rized by an infectious process involv	ing the vein. Clinical manifestation	is include erythema, marked disco	omfort, swelling, and induration alo	ng the cours
Pleural infection	-	Localized; local intervention	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
r rourdi imodion		indicated (e.g., topical antibiotic,	antiviral intervention indicated;	urgent intervention indicated	Boain
		antifungal, or antiviral)	radiologic, endoscopic, or		
			operative intervention indicated		
Definition: A disorder character	rized by an infectious process involv	ing the pleura.	T	T	
Prostate infection	-	Moderate symptoms; oral	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
		intervention indicated (e.g., antibiotic, antifungal, antiviral)	antiviral intervention indicated; radiologic, endoscopic, or	urgent intervention indicated	
			operative intervention indicated		
Definition: A disorder character	rized by an infectious process involv	ing the prostate gland.			
Rash pustular	-	Localized; local intervention	IV antibiotic, antifungal, or	-	-
		indicated (e.g., topical antibiotic,	antiviral intervention indicated;		
		antifungal, or antiviral)	radiologic or operative intervention indicated		
Definition: A disorder character	ized by a circumscribed and elevate	l ed skin lesion filled with nus	Intervention indicated	l	ļ
Rhinitis infective	-	Localized; local intervention	-	_	_
		indicated (e.g., topical antibiotic,			
		antifungal, or antiviral)			
Definition: A disorder character	rized by an infectious process involv	ing the nasal mucosal.	T	T	
Salivary gland infection	-	Moderate symptoms; oral	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
		intervention indicated (e.g., antibiotic, antifungal, antiviral)	antiviral intervention indicated; radiologic or operative	urgent intervention indicated	
		antibiotio, antifungai, antiviral)	intervention indicated		
Definition: A disorder character	rized by an infectious process involv	ing the salivary gland.	1	'	1
Scrotal infection	-	Localized; local intervention	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
		indicated (e.g., topical antibiotic,	antiviral intervention indicated;	urgent intervention indicated	
		antifungal, or antiviral)	radiologic or operative intervention indicated		
Definition: A disorder character	 rized by an infectious process involv	ing the scrotum	Intervention indicated	l	
Sepsis	-	-	_	Life-threatening consequences;	Death
Сороло				urgent intervention indicated	Boain
Definition: A disorder character	rized by the presence of pathogenic	microorganisms in the blood strea	Im that cause a rapidly progressin	g systemic reaction that may lead	to shock.
Sinusitis	-	Localized; local intervention	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
		indicated (e.g., topical antibiotic,	antiviral intervention indicated;	urgent intervention indicated	
		antifungal, or antiviral)	radiologic, endoscopic, or operative intervention indicated		
Definition: A disorder character	 rized by an infectious process involv	ing the mucous membranes of the	1 .	I	
Skin infection	Localized, local intervention	Oral intervention indicated (e.g.,	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
	indicated	antibiotic, antifungal, antiviral)	antiviral intervention indicated;	urgent intervention indicated	Death
			radiologic or operative		
			intervention indicated		
	rized by an infectious process involv		1		
Small intestine infection	-	Moderate symptoms; oral	IV antibiotic, antifungal, or antiviral intervention indicated;	Life-threatening consequences;	Death
		intervention indicated (e.g., antibiotic, antifungal, antiviral)	radiologic or operative	urgent intervention indicated	
			intervention indicated		
Definition: A disorder character	rized by an infectious process involv	ing the small intestine.			
Soft tissue infection	-	Localized; local intervention	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
		indicated (e.g., topical antibiotic,	antiviral intervention indicated;	urgent intervention indicated	
		antifungal, or antiviral)	radiologic or operative intervention indicated		
Definition: A disorder character	 rized by an infectious process involv	ing soft tissues		I	I
Splenic infection	-	-	IV antibiotic, antifungal, or	Life-threatening consequences;	Death
-p.50000011			antiviral intervention indicated;	urgent intervention indicated	
			radiologic or operative		
			intervention indicated	ĺ	

		Infections and infes	tations		
			Grade		
Adverse Event	1	2	3	4	5
	ed by an infectious process involvi	Γ .		<u> </u>	1
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 characteriz	ed by an infectious process involvi	ing a stoma (surgically created op	ening on the surface of the body).	T	
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
	ed by an infectious process involvi				
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 characteriz	ed by an infectious process involvi	ing the trachea.	<u> </u>	<u> </u>	1
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 characteriz	ed by an infectious process involvi	ing the upper respiratory tract (nos	se, paranasal sinuses, pharynx, la	rynx, or trachea).	1
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 characteriz	ed by an infectious process involvi	ing 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 characteriz	ed by an infectious process involvi	ing the urinary tract, most commo	nly 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 characteriz	ed by an infectious process involvi	ing the endometrium. It may exten	. Id to the myometrium and parame	trial 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 characteriz	ed by an infectious process involvi	ing 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 characteriz	ed by an infectious process involvi	ing 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 characteriz	ed by an infectious process involvi	ing the wound.		T	
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 procedu	ral 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 affected leg and foot.	the ankle joint characterized by a	break in the continuity of the ank	le bone. Symptoms include marke	d discomfort, swelling and difficult	y moving the
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.	<u> </u>	T		
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.	I	T	T	
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	n of two separate anatomic structur	res).	I
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 blad	der anastomosis (surgical connec	tion of two separate anatomic stru	ctures).	ı
Bruising	Localized or in a dependent area	Generalized	-	-	-
Definition: A finding of injury of th	e soft tissues or bone characterize	ed by leakage of blood into surrou	nding tissues.		
Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
<u> </u>	ntegrity to the anatomic site of an a depends on the length and intensi		an be caused by exposure to chen sion of treatment.	nicals, direct heat, electricity, flame	es and
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 a	as a result of exposure to biologica	ally effective levels of ionizing radia	ation.	
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 du	ue to breakdown of an esophagea	l anastomosis (surgical connection	of two separate anatomic structu	res).	
Fall	Minor with no resultant injuries; intervention not indicated	Symptomatic; noninvasive intervention indicated	Hospitalization indicated	-	-
Definition: A finding of sudden mo	ovement downward, usually result	ing in injury.	1	1	ı
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 du	ue to breakdown of a fallopian tube	e anastomosis (surgical connectio	n of two separate anatomic structu	ures).	
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 i	injury to the bone in which the con	tinuity of the bone is broken.	,		

	injury	, poisoning and procedu			
Advaras Event	1	2	Grade 3	4	5
Adverse Event			-		
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 d	ue to breakdown of a gastric anas	I tomosis (surgical connection of tw	1		1
Gastrointestinal anastomotic	Asymptomatic diagnostic	Symptomatic; medical	Severe symptoms; radiologic,	Life-threatening consequences;	Death
eak	observations only; intervention	intervention indicated	endoscopic or elective operative	urgent operative intervention	Death
	not indicated		intervention indicated	indicated	
Definition: A finding of leakage d	1	ı nal anastomosis (surgical connect	ition of two separate anatomic struc	1	1
Gastrointestinal stoma necrosis		Superficial necrosis;	Severe symptoms;	Life-threatening consequences;	Death
dastrollitestillai stolla necrosis		intervention not indicated	hospitalization or elective operative intervention indicated	urgent intervention indicated	Death
Definition: A finding of a necrotic	process occurring in the gastroint	estinal tract stoma.			
Hip fracture	-	Hairline fracture; mild pain;	Severe pain; hospitalization or	Life-threatening consequences;	-
		limiting instrumental ADL; non-	intervention indicated for pain	symptoms associated with	
		surgical intervention indicated	control (e.g., traction); operative	neurovascular compromise	
			intervention indicated		
Definition: A finding of traumatic	injury to the hip in which the contin	nuity of either the femoral head, fe	moral neck, intertrochanteric or su	btrochanteric regions is broken.	
Injury to carotid artery	-	-	Severe symptoms; limiting self	Life-threatening consequences;	Death
			care ADL (e.g., transient	urgent intervention indicated	
			cerebral ischemia); repair or		
			revision indicated		
Definition: A finding of damage to	the carotid artery.	_	_	.	
Injury to inferior vena cava	-	-	-	Life-threatening consequences;	Death
				urgent intervention indicated	
Definition: A finding of damage to	the inferior vena cava.	T	T		
Injury to jugular vein	-	-	Symptomatic limiting self care	Life-threatening consequences;	Death
			ADL; disabling; repair or	urgent intervention indicated	
			revision indicated		
Definition: A finding of damage to	the jugular vein.	T	1		
Injury to superior vena cava	Asymptomatic diagnostic	Symptomatic; repair or revision	Severe symptoms; limiting self	Life-threatening consequences;	Death
	finding; intervention not	not indicated	care ADL; disabling; repair or	evidence of end organ damage;	
	indicated		revision indicated	urgent operative intervention	
				indicated	
Definition: A finding of damage to	the superior vena cava.	<u> </u>	1		
Intestinal stoma leak	Asymptomatic diagnostic	Symptomatic; medical	Severe symptoms; radiologic,	Life-threatening consequences;	Death
	observations only; intervention	intervention indicated	endoscopic or elective operative	urgent operative intervention	
	not indicated		intervention indicated	indicated	
Definition: A finding of leakage of	f contents from an intestinal stoma	a (surgically created opening on th	e surface of the body).		
Intestinal stoma obstruction	-	Self-limited; intervention not	Severe symptoms; IV fluids,	Life-threatening consequences;	Death
		indicated	tube feeding, or TPN indicated	urgent operative intervention	
			>=24 hrs; elective operative	indicated	
			intervention indicated		
	of the normal flow of the contents				
Intestinal stoma site bleeding	Minimal bleeding identified on	Moderate bleeding; medical	Severe bleeding; transfusion	Life-threatening consequences;	Death
	clinical exam; intervention not	intervention indicated	indicated; radiologic or	urgent intervention indicated	
	indicated		endoscopic intervention		
Definition: A finaling of the sale of	road from the intention to the con-	I	indicated	1	I
nomination: A finding of blood look	age from the intestinal stoma.				
	Primary repair of injured	Partial resection of injured	Complete resection or	Life-threatening consequences;	Death
Intraoperative arterial injury	1 ' ' '		reconstruction of injured	urgent intervention indicated	
	organ/structure indicated	organ/structure indicated	=		
	1 ' ' '	organ/structure indicated	organ/structure indicated;		
Intraoperative arterial injury	organ/structure indicated		=		
Intraoperative arterial injury Definition: A finding of damage to	organ/structure indicated	dure.	organ/structure indicated; disabling		
Intraoperative arterial injury	organ/structure indicated an artery during a surgical proce	dure. Partial resection of injured	organ/structure indicated; disabling Complete resection or	Life-threatening consequences;	Death
Intraoperative arterial injury Definition: A finding of damage to	organ/structure indicated	dure.	organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death

	Injury	, poisoning and proced	lural complications		
			Grade		
Adverse Event	1	2	3	4	5
Definition: A finding of damage to	the breast parenchyma during a	surgical procedure.	1		
Intraoperative cardiac injury	the beaut during a currical pressure	-	Primary repair of injured organ/structure indicated	Life-threatening consequences; urgent intervention indicated	Death
	the heart during a surgical proce			I	I
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 procedu	ire.			
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 sur	gical 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 durin	g 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 surg	ical procedure.			
Intraoperative hemorrhage	-	-	Postoperative radiologic, endoscopic, or operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of uncontrolle	ed bleeding during a surgical proc	edure.			
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 b	piliary tract during a surgical pro	cedure.		
Intraoperative musculoskeletal injury Definition: A finding of damage to	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
		r i	Complete reception or	Life threatening consequences	Dooth
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
	the nervous system during a sur				.
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 proced	ure.	1		
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 proc	edure.	•	•	•
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 procedu	ral complications		
			Grade		1
Adverse Event	1	2	3	4	5
Definition: A finding of damage to	the reproductive organs during a	surgical procedure.	T	T	1
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 s	urgical procedure.	1	.	1
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 proced	ure.			
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
<u> </u>	the spleen during a surgical proc				
Intraoperative urinary injury Definition: A finding of damage to	Primary repair of injured organ/structure indicated the urinary system during a surgi	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; disabling	Life-threatening consequences; urgent intervention indicated	Death
Intraoperative venous injury	Primary repair of injured	Partial resection of injured	Complete resection or	Life-threatening consequences;	Death
intracperative verious injury	organ/structure indicated	organ/structure indicated	reconstruction of injured organ/structure indicated; disabling	urgent intervention indicated	Dealii
Definition: A finding of damage to	a vein during a surgical procedur	e.			
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 kidn	ey anastomosis (surgical connecti	on of two separate anatomic struc	tures).	
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 du	ue to breakdown of an anastomos	is (surgical connection of two sepa	arate anatomic structures) in the la	arge 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 du	ue to breakdown of a pancreatic a		f two separate anatomic structure	S).	1
Pharyngeal anastomotic leak	Asymptomatic diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	indicated	Death
			of two separate anatomic structure	1	
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
	ccurring after a surgical procedure		Established a 70 bir	Life there are the set	D- : !!
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 previous	ly undocumented problem that oc	curs after a thoracic procedure.	T	Τ	
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 procedu	ral 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 su	urface.	
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 displacem	ent of the urostomy.	T	I	T	T
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 chemotherapeut	ic agents, for weeks or months fol	lowing radiotherapy. The inflamma	tory reaction
is confined to the previously irrac	diated skin and the symptoms disa	ppear after the removal of the pha	rmaceutical agent.	T	I
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 d	ue to breakdown of a rectal anasto	omosis (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.	T	Т	T	I
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 d	ue to breakdown of an anastomos	is (surgical connection of two sepa	arate anatomic structures) in the si	mall bowel.	T
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 d	ue to breakdown of a spermatic co	ord anastomosis (surgical connecti	on of two separate anatomic struc	tures).	
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 cor	ntinuity of a vertebral bone is broke	en.	•	,
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 (surg	gically created opening on the surf	ace of the body).	T	T
Stomal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
	ed by a circumscribed, inflammato	ory and necrotic erosive lesion on t	the jejunal mucosal surface close t	to the anastomosis site following a	ı
gastroenterostomy procedure.	Minimal blooding identified	Moderate blooding: madical	Covere blooding: transfining	Life threatening concernances	Dooth
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 f	rom the trachea.	Т	Т	Т	<u> </u>
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								
		T	Grade	<u> </u>				
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 leak	age 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 di	ue to breakdown of a ureteral ana:	stomosis (surgical connection of two	vo separate anatomic structures).	r				
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 di	ue to breakdown of a urethral ana	stomosis (surgical connection of tw	vo 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	f contents from a urostomy.	T	Ι					
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	of the urostomy.	_	_					
Jrostomy 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 for	rom 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.	1.	I	I	1			
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 d	ue to breakdown of a uterine anas	tomosis (surgical connection of tw	o 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 characteriz	ed by a rupture in the uterine wall.							
/aginal 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 d	ue to breakdown of a vaginal anas	tomosis (surgical connection of tw	o separate anatomic structures).					
/as 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 di	ue to breakdown of a vas deferens	s anastomosis (surgical connection	n of two separate anatomic structu	res).				
/ascular 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			
	Í	1	1., 2.0,o.,vaoivo procedure)	I	1			

	Injury	, poisoning and procedu	ral complications		
	,,	, p	Grade		
Adverse Event	1	2	3	4	5
Venous injury Definition: A finding of damage to	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
Wound complication	Incisional separation of <=25%	Incisional separation >25% of	Hernia without evidence of	Hernia with evidence of	Death
	of wound, no deeper than superficial fascia	wound; local care indicated	disruption/dehiscence; primary wound closure or revision by	strangulation; major reconstruction flap, grafting, resection, or amputation indicated	
Definition: A finding of developm	ent 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	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.			1
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 broke	en.		
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

Ad.,									
Grade									
Adverse Event	1	2	3	4	5				
Activated partial thromboplastin ime prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; hemorrhage	-	-				
-	•	romboplastin time is found to be g s and disorders, both primary and		possible indicator of coagulopath	ny, a prolonged				
Alanine aminotransferase	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-				
1	pratory test results that indicate ar	। n increase in the level of alanine a	ı minotransferase (ALT or SGPT) ir	in the blood specimen.	1				
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 labo	oratory test results that indicate ar	n increase in the level of alkaline p	hosphatase in a blood specimen.	•	<u> </u>				
Aspartate aminotransferase ncreased	>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 labo	oratory test results that indicate ar	n increase in the level of aspartate	aminotransferase (AST or SGOT) in a blood specimen.	<u>'</u>				
abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-				
Definition: A finding based on labo	oratory test results that indicate at	onormal levels of antidiuretic horm	one 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 labor	pratory test results that indicate ar	abnormally high level of bilirubin	in the blood. Excess bilirubin is as	ssociated with jaundice.					
·	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-				
Definition: A finding based on labor	pratory test results that indicate ar	n decrease in levels of corticotroph	nin in a blood specimen.	ı					
	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 labo	oratory test results that indicate at	onormal levels of gonadotrophin h	ormone in a blood specimen.	,					
•	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	-	-	-				
		ı onormal levels of prolactin hormor	ı ıe in a blood specimen.	l	1				
	3 - 5 units below LLN; for follow-	6 - 8 units below LLN; for follow-	Asymptomatic decrease of >8	-	-				
. ,	up, a decrease of 3 - 5 units (ml/min/mm Hg) below the baseline value	up, an asymptomatic decrease of >5 - 8 units (ml/min/mm Hg) below the baseline value	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	g function test results that indicate	a decrease in the lung capacity	to absorb carbon monoxide.	Γ					
·	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	-	-				
		of cardiac troponin I in a biologica							
	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 biologica	al specimen.	•	•				
* ' '	<lln -="" 0.5="" 500="" <lln="" mm3;="" x<br="">10e9 /L</lln>	<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 labo	pratory test results that indicate ar	n decrease in levels of CD4 lymph	ocytes in a blood specimen.						
-	>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 labo	pratory test results that indicate hi	gher than normal levels of cholest	erol in a blood specimen.	Γ					
1	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN in increase in levels of creatine pho	>5 x ULN - 10 x ULN	>10 x ULN	-				

		Investigations			
			Grade		
Adverse Event	1	2	3	4	5
Creatinine increased	>1 - 1.5 x baseline; >ULN - 1.5	>1.5 - 3.0 x baseline; >1.5 - 3.0	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-
Definition: A finding based on lab	x ULN	x ULN	 		
	oratory test results that indicate in				
Ejection fraction decreased	-	- 40%; 10 - 19% drop from baseline	Resting ejection fraction (EF) 39 - 20%; >20% drop from baseline	<20%	-
contraction.	uted when the amount of blood eje	ected during a ventricular contracti	on of the heart is compared to the	amount that was present prior to	the
Electrocardiogram QT corrected interval prolonged		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	-
-	dysrhythmia characterized by an a			T	
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 lab	oratory test results that indicate a	n decrease in levels of fibrinogen i	n 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 tes	t results that indicate a relative de	crease in the fraction of the forced	I 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 lab	oratory test results that indicate hi	gher than normal levels of the enz	ryme gamma-glutamyltransferase	in the blood specimen. GGT (gam	nma-
glutamyltransferase) catalyzes th	ne transfer of a gamma glutamyl g	roup from a gamma glutamyl pept	ide to another peptide, amino acid	s 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 lab	oratory test results that indicate al	onormal levels of growth hormone	in a biological specimen.		
Haptoglobin decreased	<lln< td=""><td>-</td><td>-</td><td>-</td><td>-</td></lln<>	-	-	-	-
Definition: A finding based on lab	oratory test results that indicate a	n decrease in levels of haptoglobir	n 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 lab	oratory test results that indicate in	creased 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 lab	oratory test results that indicate a	n increase in the ratio of the patier	nt's prothrombin time to a control s	ample in the blood.	1
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 lab	oratory test results that indicate a	n increase in the level of lipase in	a biological specimen.		
Lymphocyte count decreased	<lln -="" 0.8="" 800="" <lln="" mm3;="" x<br="">10e9 /L</lln>	<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 lab	oratory test results that indicate a	decrease in number of lymphocyte	es in a blood specimen.		
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-
Definition: A finding based on lab	oratory test results that indicate a	n abnormal increase in the numbe	r of lymphocytes in the blood, effu	sions or bone marrow.	1
Neutrophil count decreased	<lln -="" 1.5="" 1500="" <lln="" mm3;="" x<br="">10e9 /L</lln>	<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 lab	oratory test results that indicate a	decrease in number of neutrophils	s in a blood specimen.		
Pancreatic enzymes decreased	<lln and="" asymptomatic<="" td=""><td>Increase in stool frequency, bulk, or odor; steatorrhea</td><td>Sequelae of absorption deficiency</td><td>-</td><td>-</td></lln>	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency	-	-
Definition: A finding based on lab	oratory test results that indicate a	n decrease in levels of pancreatic	enzymes in a biological specimen.		

		Investigations	;		
			Grade		
Adverse Event	1	2	3	4	5
Platelet count decreased	<lln -="" 10e9="" 75,000="" 75.0="" <lln="" l<="" mm3;="" td="" x=""><td><75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L</td><td><50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L</td><td><25,000/mm3; <25.0 x 10e9 /L</td><td>-</td></lln>	<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 lab	oratory 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 lab	oratory test results that indicate ar	n 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 tes	t results that indicate urine produc	tion is less relative to previous ou	tput.	•	,
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 pulvalue.	lmonary function test results that in	ndicate an abnormal vital capacity	(amount of exhaled after a maxim	num inhalation) when compared to	the predicted
Weight gain	5 - <10% from baseline	10 - <20% from baseline	>=20% from baseline	-	-
Definition: A finding characterized	d by an increase in overall body w	eight; for pediatrics, greater than t	he 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	d by a decrease in overall body we	eight; for pediatrics, less than the b	paseline growth curve.		
White blood cell decreased	<lln -="" 3.0="" 3000="" <lln="" mm3;="" x<br="">10e9 /L</lln>	<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 lab	oratory test results that indicate ar	n decrease in number of white blo	od 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	n disorders		
			Grade		
Adverse Event	1	2	3	4	5
Acidosis	pH <normal, but="">=7.3</normal,>	-	pH <7.3	Life-threatening consequences	Death
Definition: A disorder characteriz	ed by abnormally high acidity (high	h hydrogen-ion concentration) of the	ne blood and other body tissues.	T	
Alcohol intolerance	-	Present	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz vomiting, indigestion and headac	ed by an increase in sensitivity to t hes.	the adverse effects of alcohol, whi	ch can include nasal congestion,	skin flushes, heart dysrhythmias, r	nausea,
Alkalosis	pH >normal, but <=7.5	-	pH >7.5	Life-threatening consequences	Death
Definition: A disorder characteriz	ed by abnormally high alkalinity (lo	w 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 characteriz	ed by a loss of appetite.		I	T	1
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 characteriz	ed by excessive loss of water from	the body. It is usually caused by	severe diarrhea, vomiting or diaph	noresis.	
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 characteriz	ed by an inability to properly metal	polize glucose.			
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; lonized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; lonized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; lonized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; lonized calcium >1.8 mmol/L; life-threatening consequences	Death
Definition: A disorder characteriz	ed by laboratory test results that in	dicate an elevation in the concen	tration of calcium (corrected for all	oumin) 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
	ed by laboratory test results that in	dicate an elevation in the concen	tration 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 characteriz the use of diuretic drugs.	ed by laboratory test results that in	dicate an elevation in the concen		1	ometimes with
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 characteriz	ed by laboratory test results that in	dicate an elevation in the concen	tration of magnesium in the blood		1
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 characteriz	ed by laboratory test results that in	dicate an elevation in the concen	tration of sodium in the blood.	Γ	
Hypertriglyceridemia	1	mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	life-threatening consequences	Death
	ed by laboratory test results that in	dicate an elevation in the concen			
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 characteriz	ed by laboratory test results that in	dicate an elevation in the concen	tration of uric acid.	1	
Hypoalbuminemia	<lln -="" 3="" 30="" <lln="" dl;="" g="" l<="" td=""><td><3 - 2 g/dL; <30 - 20 g/L</td><td><2 g/dL; <20 g/L</td><td>Life-threatening consequences; urgent intervention indicated</td><td>Death</td></lln>	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by laboratory test results that in	dicate a low concentration of albu	ımin in the blood.		

		Metabolism and nutrition	n disorders		
			Grade		
Adverse Event	1	2	3	4	5
Hypocalcemia	Corrected serum calcium of <lln -="" 1.0="" 2.0="" 8.0="" <lln="" calcium="" dl;="" l;="" l<="" lonized="" mg="" mmol="" td=""><td>Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; lonized calcium <1.0 - 0.9 mmol/L; symptomatic</td><td>Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; lonized calcium <0.9 - 0.8 mmol/L; hospitalization indicated</td><td>Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; lonized calcium <0.8 mmol/L; life-threatening consequences</td><td>Death</td></lln>	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; lonized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; lonized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; lonized calcium <0.8 mmol/L; life-threatening consequences	Death
Definition: A disorder characteriz	ed by laboratory test results that in	ndicate a low concentration of calc	ium (corrected for albumin) in the	blood.	
Hypoglycemia	<lln -="" 3.0<br="" 55="" <lln="" dl;="" mg="">mmol/L</lln>	<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 characteriz	ed by laboratory test results that in	ndicate a low concentration of gluc	ose in the blood.		
Hypokalemia	<lln -="" 3.0="" l<="" mmol="" td=""><td><pre><lln -="" 3.0="" l;<br="" mmol="">symptomatic; intervention indicated</lln></pre></td><td><3.0 - 2.5 mmol/L; hospitalization indicated</td><td><2.5 mmol/L; life-threatening consequences</td><td>Death</td></lln>	<pre><lln -="" 3.0="" l;<br="" mmol="">symptomatic; intervention indicated</lln></pre>	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Definition: A disorder characteriz	ed by laboratory test results that in	ndicate a low concentration of pota	ssium in the blood.		
Hypomagnesemia	<lln -="" 0.5="" 1.2="" <lln="" dl;="" l<="" mg="" mmol="" td=""><td><1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L</td><td><0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L</td><td><0.7 mg/dL; <0.3 mmol/L; life-threatening consequences</td><td>Death</td></lln>	<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 characteriz	ed by laboratory test results that in	ndicate a low concentration of mag	nesium in the blood.		
Hyponatremia	<lln -="" 130="" l<="" mmol="" td=""><td>-</td><td><130 - 120 mmol/L</td><td><120 mmol/L; life-threatening consequences</td><td>Death</td></lln>	-	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences	Death
Definition: A disorder characteriz	ed by laboratory test results that in	ndicate a low concentration of sodi	um in the blood.		
Hypophosphatemia	<lln -="" 0.8="" 2.5="" <lln="" dl;="" l<="" mg="" mmol="" td=""><td><2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L</td><td><2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L</td><td><1.0 mg/dL; <0.3 mmol/L; life- threatening consequences</td><td>Death</td></lln>	<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 characteriz	ed by laboratory test results that in	ndicate a low concentration of pho	sphates in the blood.		
Iron overload	-	Moderate symptoms; intervention not indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by accumulation of iron in the ti	issues.			
Obesity	-	BMI 25 - 29.9 kg/m2	BMI 30 - 39.9 kg/m2	BMI >=40 kg/m2	-
Definition: A disorder characteriz	ed by having a high amount of boo	dy fat.			
Tumor lysis syndrome	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by metabolic abnormalities that	result from a spontaneous or the	apy-related cytolysis of tumor cell	S.	
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		T			
Adverse Event	1	2	3	4	5			
bdominal 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			
efinition: A disorder characteriz	ed by a necrotic process occurring	in the soft tissues of the abdomir	nal wall.					
rthralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
efinition: A disorder characteriz	ed by a sensation of marked disco	omfort in a joint.		T				
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	-	-			
	ed by inflammation involving a joir							
wascular 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			
	ed by necrotic changes in the bon d the destruction of the bone struc	·	od supply. Most often affecting the	epiphysis of the long bones, the n	ecrotic			
Back pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteriz	ed by marked discomfort sensatio	n in the back region.						
one pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteriz	ed by marked discomfort sensatio	n in the bones.	1	1				
Buttock pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteriz	ed by marked discomfort sensatio	n in the buttocks.	1	T				
Chest wall pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteriz	ed by marked discomfort sensatio	n 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 characteriz	ed by non-neoplastic overgrowth o	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			
	ed by fibrotic degeneration of the	1	1					
lank pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder characteriz	ed by marked discomfort sensatio	n on the lateral side of the body in	the region below the ribs and abo	ove 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 characteriz	ed by a reduction in the strength o	of muscles in multiple anatomic site	es.					
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 discorder elements de	ed by of stature that is smaller tha	n 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 characterize	ed by a necrotic process occurring	in the soft tissues of the head.	1	 						
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 characterize	ed by excessive fluid in a joint, usu	ually as a result of joint inflammation	on.	T						
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 characterize	ed 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 characterize	ed 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	-	-					
Definition: A disorder characterize Kyphosis	ed by a decrease in flexibility of a last Asymptomatic; clinical or	Moderate accentuation; limiting	Severe accentuation; operative	-	-					
	diagnostic observations only; intervention not indicated	instrumental ADL	intervention indicated; limiting self care ADL							
Definition: A disorder characterize	ed by an abnormal increase in the	curvature of the thoracic portion of	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 characterize	ed by an abnormal increase in the	curvature of the lumbar portion of	1	l	l					
Muscle weakness left-sided	Symptomatic; perceived by patient but not evident on	Symptomatic; evident on physical exam; limiting	Limiting self care ADL; disabling	-	-					
Dofinition: A disorder characteriz	physical exam ed by a reduction in the strength o	instrumental ADL	a hady		1					
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 characterize	ed by a reduction in the strength o	f 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 characterize	ed by a reduction in the strength o	ı	he body.	•	1					
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 characterize	ed by a reduction in the strength o	ı	I	I	I					
Muscle weakness upper limb	Symptomatic; perceived by patient but not evident on	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL; disabling	-	-					
	physical exam	Instrumental ADL								

	Muscu	loskeletal and connectiv	e 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 characterize	ed by of a malformation of the mus	sculoskeletal system.		1	1		
Myalgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder characterize	ed by marked discomfort sensation	n originating from a muscle or gro	up 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 characterize	ed by inflammation involving the s	keletal muscles.					
Neck pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
Definition: A disorder characterize	ed by marked discomfort sensation	n in the neck area.	1				
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 characterize	ed by a necrotic process occurring	in the soft tissues of the neck.		T	ı		
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 characterize	ed 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 characterize	ed by reduced bone mass, with a	decrease in cortical thickness and	in the number and size of the trab	peculae of cancellous bone (but no	ormal chemical		
composition), resulting in increas			T		1		
Pain in extremity	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-		
	ed by marked discomfort sensation						
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 characterize	ed by a necrotic process occurring	·	1				
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 characterize	ed by a malformed, lateral curvatu	re 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 characterize	ed by a necrotic process occurring	in the soft tissues of the lower ex	tremity.	Г			
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 characterize	ed by a necrotic process occurring	in the soft tissues of the upper ex	xtremity.				

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

Grade							
1	2	3	4	5			
-	-	-	Present	Death			
ed by leukemia arising as a result	of the mutagenic effect of chemot	herapy agents.					
-	-	-	Life-threatening consequences; urgent intervention indicated	Death			
ed by insufficiently healthy hemata	poietic cell production by the bone	e marrow.					
-	-	Non life-threatening secondary malignancy	Acute life-threatening secondary malignancy; blast crisis in leukemia	Death			
ed by development of a malignanc	y most probably as a result of trea	tment for a previously existing ma	lignancy.				
Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
ed by marked discomfort from a ne	eoplasm that may be pressing on	a nerve, blocking blood vessels, in	flamed or fractured from metastas	is.			
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;	Life-threatening consequences; urgent intervention indicated	Death			
	ed by insufficiently healthy hemata ed by development of a malignance Mild pain ed by marked discomfort from a new Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention	ed by leukemia arising as a result of the mutagenic effect of chemotic	ed by leukemia arising as a result of the mutagenic effect of chemotherapy agents. -	ed by leukemia arising as a result of the mutagenic effect of chemotherapy agents. -			

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	-	-			
efinition: A disorder characteri	zed by involvement of the abducen	s 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	-	-			
efinition: A disorder characteri	zed by involvement of the accessor	y 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 characteri	zed by involvement of the acoustic	nerve (eighth cranial nerve).	<u> </u>		1			
ıkathisia	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 characteri	zed by an uncomfortable feeling of	inner restlessness and inability to	stay still; this is a side effect of so	me psychotropic drugs.	1			
Amnesia	Mild; transient memory loss	Moderate; short term memory loss; limiting instrumental ADL	Severe; long term memory loss; limiting self care ADL	-	-			
	zed by systematic and extensive lo	ss of memory.	W-11					
aphonia	-	-	Voicelessness; unable to speak	-	-			
	zed by the inability to speak. It may				l			
rachnoiditis	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death			
	zed by inflammation of the arachno							
\taxia	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 characteri	zed by lack of coordination of musc	le movements resulting in the imp	airment or inability to perform volu	ntary 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 characteri	zed by regional paresthesia of the b	prachial plexus, marked discomfor	t and muscle weakness, and limite	ed 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 characteri	zed by a necrotic process occurring	in the brain and/or spinal cord.	Τ		1			
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 characteri	zed by loss of cerebrospinal fluid in	to 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 characteri	' zed by a conspicuous change in co	gnitive 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	-	-			
	T. Control of the Con	1	I .	1	I .			

		Nervous system dis	orders		
		T	Grade	T	
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 characteriz	ed by a decrease in ability to perc	eive 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 characteriz	ed by a disturbing sensation of light	ntheadedness, unsteadiness, gidd	liness, spinning or rocking.	_	_
Dysarthria	Mild slurred speech	Moderate impairment of articulation or slurred speech	Severe impairment of articulation or slurred speech	-	-
Definition: A disorder characteriz	ed by slow and slurred speech res	sulting from an inability to coordina	te the muscles used in speech.	Ι	
Dysesthesia	Mild sensory alteration	Moderate sensory alteration; limiting instrumental ADL	Severe sensory alteration; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by distortion of sensory percep	tion, resulting in an abnormal and	unpleasant sensation.	Т	
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 characteriz	ed by abnormal sensual experience	ce with the taste of foodstuffs; it ca	n 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 characteriz	ed by impairment of verbal commi	unication skills, often resulting from	n brain damage.		
Edema cerebral	-	-	-	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characteriz	ed by swelling due to an excessive	e accumulation of fluid in the brain	l. T	T	
Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characteriz	ed by a pathologic process involvi	ng the brain.	T	T	
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 characteriz	ed by abnormal, repetitive, involur	ntary muscle movements, frenzied	speech and extreme restlessness	s.	
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 characteriz	ed by a reduction in the strength o	f 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 characteriz	ed by involvement of the facial ne	rve (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 characteriz	ed by involvement of the glossoph	aryngeal nerve (ninth cranial nerv	e).		
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by a sensation of marked disco	omfort in various parts of the head	, not confined to the area of distrib	ution 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 characteriz	ed by an abnormal increase of cer	rebrospinal fluid in the ventricles o	f the brain.		
Hypersomnia	Mild increased need for sleep	Moderate increased need for sleep	Severe increased need for sleep	-	-
Definition: A disorder characteriz	ed by characterized by excessive	sleepiness during the daytime.			•

Nervous system disorders								
		Ι .	Grade	Ι .				
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 character	rized by involvement of the hypoglos	ssal 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 character	rized by bleeding from the cranium.							
lschemia cerebrovascular	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	-	-	-			
Definition: A disorder character damage.	rized by a decrease or absence of b	lood supply to the brain caused by	obstruction (thrombosis or embol	ism) of an artery resulting in neuro	ological			
IVth nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-			
	rized by involvement of the trochlean		T	I				
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	-	-	-			
Definition: A disorder character	rized by a decrease in consciousnes	ss characterized by mental and phy	ysical 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 character	rized by diffuse reactive astrocytosis	with multiple areas of necrotic foo	i without inflammation.					
Memory impairment	Mild memory impairment	Moderate memory impairment; limiting instrumental ADL	Severe memory impairment; limiting self care ADL	-	-			
Definition: A disorder character	rized by a deterioration in memory fu	unction.	_					
Meningismus	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death			
Definition: A disorder character	rized by neck stiffness, headache, a	nd photophobia resulting from irrita	ation of the cerebral meninges.					
Movements involuntary	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-			
Definition: A disorder character	rized by uncontrolled and purposele	ss movements.	1	1				
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			
	rized by inflammation involving the s	i i	1	marked discomfort and incontiner	nce.			
Neuralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-			
Definition: A disorder character	rized by intense painful sensation al	1	T	I				
Nystagmus	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-			
Definition: A disorder character	rized by involuntary movements of the	ne eyeballs.	T	Ī				
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 character	rized by involvement of the oculomo	tor nerve (third cranial nerve).						
Olfactory nerve disorder	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-			
Definition: A disorder character	rized by involvement of the olfactory	nerve (first cranial nerve)						

		Nervous system dis	orders		
			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 characteriz are experienced in the absence of		ensory neurons resulting in abnorr	mal cutaneous sensations of tingli	ng, numbness, pressure, cold, and	warmth that
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 characteriz	ed by inflammation or degeneration	n of the peripheral motor nerves.		_	1
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 characteriz	ed by inflammation or degeneration	n of the peripheral sensory nerves	S.	T	
Phantom pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by marked discomfort related to	a limb or an organ that is remove	ed from or is not physically part of	the body.	
Presyncope	-	Present (e.g., near fainting)	-	-	-
Definition: A disorder characteriz	ed by an episode of lightheadedne	ess and dizziness which may prec	ede an episode of syncope.	T	
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
	ed by dysfunction of the corticospi and a decrease in fine motor coord		I cord. Symptoms include an incre	ease in the muscle tone in the lowe	er extremities,
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 characteriz connecting nerve root.	ed by inflammation involving a ner	ve root. Patients experience mark	red discomfort radiating along a ne	erve path because of spinal pressu	re on the
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 characteriz	ed by paralysis of the recurrent lar	ryngeal nerve.	1	1	Г
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
		=		indings of posterior leukoencephal	-
		1		s an acute or subacute reversible o	
Seizure	Brief partial seizure; no loss of consciousness	Brief generalized seizure	Multiple seizures despite medical intervention	Life-threatening; prolonged repetitive seizures	Death
	ed by a sudden, involuntary skelet		_		
Sinus pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by marked discomfort in the fac	ce, between the eyes, or upper tee	eth originating from the sinuses.	<u> </u>	
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 characteriz	ed by characterized by excessive	sleepiness and drowsiness.	T	T	
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 characteriz disturbances.	ed by increased involuntary muscl			It results in gait, movement, and sp	peech
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 characteriz	ed by a sudden loss of sensory fu	nction due to an intracranial vascu	ılar event.		
Syncope	-	-	Fainting; orthostatic collapse	-	-
Definition: A disorder characteriz	ed by spontaneous loss of conscio	ousness caused by insufficient blo	od supply to the brain.		

		Nervous system dis	orders				
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 characteriz	ed by a brief attack (less than 24 h	nours) of cerebral dysfunction of va	ascular origin, with no persistent n	eurological deficit.			
Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-		
Definition: A disorder characterize	zed by the uncontrolled shaking mo	evement of the whole body or indiv	vidual 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 characteriz	ed by involvement of the trigemina	l 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 characteriz	zed by involvement of the vagus ne	rve (tenth cranial nerve).	•	•			
Vasovagal reaction	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death		
Definition: A disorder characterizincrease in the stimulation of the	zed by a sudden drop of the blood progression vagus nerve.	pressure, bradycardia, and periph	eral vasodilation that may lead to l	loss of consciousness. It results fro	om an		
Nervous system disorders -	Asymptomatic or mild	Moderate; minimal, local or	Severe or medically significant	Life-threatening consequences;	Death		
Other, specify	symptoms; clinical or diagnostic observations only; intervention not indicated	noninvasive intervention indicated; limiting age-appropriate instrumental ADL	but not immediately life- threatening; hospitalization or prolongation of existing hospitalization indicated;	urgent intervention indicated			
			disabling; limiting self care ADL				

	Pregna	ancy, puerperium and pe	erinatal conditions				
Grade							
Adverse Event	1	2	3	4	5		
Fetal death	-	-	-	-	Fetal loss at any gestational age		
Definition: A disorder characteria	zed by death in utero; failure of the	product of conception to show ev	idence of respiration, heartbeat, or	definite movement of a voluntary	muscle after		
expulsion from the uterus, withou	ut 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 characteria	zed by inhibition of fetal growth res	ulting 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 charactering gestation.	zed by delivery of a viable infant be	fore the normal end of gestation.	Typically, viability is achievable be	tween the twentieth and thirty-sev	enth week of		
Unintended pregnancy	-	-	Unintended pregnancy	-	-		
Definition: A disorder characteria	zed by an unexpected pregnancy a	t 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 disor	aers		
			Grade		
Adverse Event	1	2	3	4	5
gitation	Mild mood alteration	Moderate mood alteration	Severe agitation; hospitalization not indicated	Life-threatening consequences; urgent intervention indicated	Death
efinition: A disorder characte	rized by a state of restlessness asso	ciated with unpleasant feelings of	irritability and tension.	T	1
norgasmia	Inability to achieve orgasm not adversely affecting relationship	Inability to achieve orgasm adversely affecting relationship	-	-	-
Definition: A disorder character	rized by an inability to achieve orgas	im.	T	T	1
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 character stimulus.	rized by apprehension of danger and	d dread accompanied by restlessn	ess, tension, tachycardia, and dys	pnea unattached to a clearly ident	ifiable
Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characte	rized by a lack of clear and orderly the	nought and behavior.			
Delayed orgasm	Delay in achieving orgasm not adversely affecting relationship	Delay in achieving orgasm adversely affecting relationship	-	-	-
Definition: A disorder character	rized by sexual dysfunction characte	rized by a delay in climax.	T	Τ	
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 character reversible condition.	rized by the acute and sudden devel	opment of confusion, illusions, mo	ovement changes, inattentiveness,	agitation, and hallucinations. Usu	ally, it is a
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 characte	rized by false personal beliefs held o	ontrary to reality, despite contradi	tory evidence and common sense). 9.	1
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 character	rized by melancholic feelings of grie	or unhappiness.	'	'	,
Euphoria	Mild mood elevation	Moderate mood elevation	Severe mood elevation (e.g., hypomania)	-	-
Definition: A disorder characte	rized by an exaggerated feeling of w	ell-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 characte	rized by a false sensory perception i	n the absence of an external stimu	ulus.		
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 character	rized by difficulty in falling asleep an	d/or remaining asleep.	T	T	1
Libido decreased	Decrease in sexual interest not adversely affecting relationship	Decrease in sexual interest adversely affecting relationship	-	-	-
Definition: A disorder character	rized by a decrease in sexual desire	T	T	Γ	
ibido 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 characte	rized 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 characte	rized by excitement of psychotic pro	, portions manifested by mental and	1	ation 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 disord	ders				
	Grade						
Adverse Event	1	2	3	4	5		
Definition: A disorder characteriz	ed by a conspicuous change in a p	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 characteriz tumor.	ed by personality change, impaired	d functioning, and loss of touch wi	th reality. It may be a manifestatio	n of schizophrenia, bipolar disorde	er or brain		
Restlessness	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-		
Definition: A disorder characteriz	ed by an inability to rest, relax or b	pe 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 characteriz	ed by thoughts of taking one's owr	n 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 characteriz	ed by self-inflicted harm in an atte	mpt 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 di	sorders		
			Grade		
Adverse Event	1	2	3	4	5
Acute kidney injury Definition: A disorder character	Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0 x above baseline erized by the acute loss of renal functions.	Creatinine 2 - 3 x above baseline	Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	Life-threatening consequences; dialysis indicated	Death
causes (ureteral or bladder ou		on and is traditionally stassified a	o pro ronar (ion blood non into na	noy), ronal (nanoy damago) and p	Joor Torial
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 characte	erized by a rupture in the bladder wall				
Bladder spasm	Intervention not indicated	Antispasmodics indicated	Hospitalization indicated	-	-
Definition: A disorder characte	erized by a sudden and involuntary co	ntraction of the bladder wall.			
Chronic kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <lln -="" 60<br="">ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5</lln>	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 characte	erized by gradual and usually perman	ent loss of kidney function resultir	ng 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 characte	erized by inflammation of the bladder	ı	on of the urinary tract.	ı	ı
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 characte	erized by laboratory test results that in	dicate blood in the urine.			
Hemoglobinuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characte	erized by laboratory test results that ir	dicate the presence of free hemo	globin 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 characte	erized by laboratory test results that in	dicate the presence of excessive	protein in the urine. It is predomin	antly 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 characte	erized by the formation of crystals in t	ne pelvis of the kidney.		1	
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 characte	erized by paroxysmal and severe flan	k marked discomfort radiating to the	he inguinal area. Often, the cause	is the passage of kidney stones.	

		Renal and urinary di	sorders		
			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 characteri	zed 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 characteri	zed by an abnormal communication	between any part of the urinary s	system and another organ or anato	pmic site.	
Urinary frequency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
	zed 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 characteri	zed by inability to control the flow o	f 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 characteri	zed by accumulation of urine within	the bladder because of the inabili	ty 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 characteri	zed 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 characteri	zed by a sensation of marked disco	mfort in the urinary tract.			
Urinary urgency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Definition: A disorder characteri	zed by a sudden compelling urge to	urinate.			
Jrine discoloration	Present	-	-	-	-
Definition: A disorder characteri	zed 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

	Rep	productive system and bi	reast disorders		
			Grade		
Adverse Event	1	2	3	4	5
Azoospermia	-	-	Absence of sperm in ejaculate	-	-
Definition: A disorder characteri	zed by laboratory test results that in	ndicate complete absence of sperr	natozoa in the semen.		1
Breast atrophy	Minimal asymmetry; minimal atrophy	Moderate asymmetry; moderate atrophy	Asymmetry >1/3 of breast volume; severe atrophy	-	-
Definition: A disorder characteri	zed by underdevelopment of the br	1	Tvoidino, develo dil opiny	I	
	· · · · · · · · · · · · · · · · · · ·		Cavara nain, limiting salf sara		
Breast pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteri	zed by marked discomfort sensatio	n in the breast region.			
Dysmenorrhea	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characteri	zed by abnormally painful abdomin	al cramps during menses.	!	!	ll .
Dyspareunia	Mild discomfort or pain	Moderate discomfort or pain	Severe discomfort or pain	_	_
- Jyoparcama	associated with vaginal	associated with vaginal	associated with vaginal		
	penetration; discomfort relieved	penetration; discomfort or pain	penetration; discomfort or pain		
	with use of vaginal lubricants or	partially relieved with use of	unrelieved by vaginal lubricants		
	estrogen	vaginal lubricants or estrogen	or estrogen		
Definition: A disorder characteri	zed by painful or difficult coitus.				
Ejaculation disorder	Diminished ejaculation	Anejaculation or retrograde eiaculation	-	-	-
Definition: Δ disorder characteri	। zed by problems related to ejaculat	,	I ture delayed retrograde and nain	l ful ejaculation	ļ
			1	ilui ejaculation.	
Erectile dysfunction	Decrease in erectile function (frequency or rigidity of	Decrease in erectile function (frequency/rigidity of erections),	Decrease in erectile function (frequency/rigidity of erections)	-	-
	erections) but intervention not	erectile intervention indicated,	but erectile intervention not		
	indicated (e.g., medication or	(e.g., medication or mechanical	helpful (e.g., medication or		
	use of mechanical device,	devices such as penile pump)	mechanical devices such as		
	penile pump)		penile pump); placement of a		
			permanent penile prosthesis		
			indicated (not previously		
			present)		
Definition: A disorder characteri	zed by the persistent or recurrent in	nability to achieve or to maintain a	n erection during sexual activity.		
Fallopian tube obstruction	Diagnostic observations only;	Mild symptoms; elective	Severe symptoms; elective	-	-
	intervention not indicated	intervention indicated	operative intervention indicated		
Definition: A disorder characteri	zed by blockage of the normal flow	of the contents in the fallopian tub)e.	ı	ļi
	Asymptomatic clinical or	Symptomatic and intervention	Severe symptoms; elective	Life-threatening consequences;	Death
Fallopian tube stenosis	diagnostic observations only;	not indicated	operative intervention indicated	urgent operative intervention	Dealli
	intervention not indicated	The maleated	operative intervention indicated	indicated (e.g., organ resection)	
Definition: A disorder characteri	zed by a narrowing of the fallopian	l tuha luman	I		ļ
			0	Let un a la de la companya de la com	D II
Female genital tract fistula	Asymptomatic clinical or	Symptomatic and intervention	Severe symptoms; elective	Life-threatening consequences;	Death
	diagnostic observations only; intervention not indicated	not indicated	operative intervention indicated	urgent intervention indicated	
Definition: A diserder aberester	1	 	vetem ergen and enother ergen a	 	
	zed by an abnormal communication		lystem organ and another organ of	r anatomic site.	
Feminization acquired	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characteri	zed by the development of seconda	ary female sex characteristics in m	ales due to extrinsic factors.		
Genital edema	Mild swelling or obscuration of	Readily apparent obscuration of	Lymphorrhea; gross deviation	-	-
	anatomic architecture on close	anatomic architecture;	from normal anatomic contour;		
	inspection	obliteration of skin folds; readily	limiting self care ADL		
		apparent deviation from normal			
		anatomic contour			
Definition: A disorder characteri	zed by swelling due to an excessive	e accumulation of fluid in the genit	als.		
Gynecomastia	Asymptomatic breast	Symptomatic (e.g., pain or	Severe symptoms; elective	-	-
-	enlargement	psychosocial impact)	operative intervention indicated		
	zed by excessive development of the	ne breasts in males.		•	•
Definition: A disorder characteri				1	
		Moderate bleeding: modical	Severe bleeding: transfusion	Life-threatening consequences:	Death
	Minimal bleeding identified on	Moderate bleeding; medical	Severe bleeding; transfusion indicated: radiologic or	Life-threatening consequences;	Death
Definition: A disorder characteri Hematosalpinx		Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention	Life-threatening consequences; urgent operative intervention indicated	Death

	Rep	productive system and be	reast disorders		
			Grade		ı
Adverse Event	1	2	3	4	5
Definition: A disorder characte	rized by the presence of blood in a fa	allopian tube.	T		
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 characte	rized by irregular cycle or duration of	menses.	T	Т	1
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 characte	rized by disturbances of milk secretic	on. It is not necessarily related to p	pregnancy that is observed in fema	ales and can be observed in males	S.
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 characte	rized by abnormally heavy vaginal bl	eeding 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 characte	rized 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 characte	rized by a decrease in the number of	f spermatozoa in the semen.	I		1
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 characte	rized by bleeding from the ovary.		T		
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 characte	rized by tearing or disruption of the o	varian tissue.	•	•	'
Ovulation pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characte ovarian follicle.	rized by marked discomfort sensation	n in one side of the abdomen betv	veen menstrual cycles, around the	time of the discharge of the ovum	from the
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 characte	rized by a reduction in the strength o	f the muscles of the pelvic floor.	,		
Pelvic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characte	rized by marked discomfort sensation	n in the pelvis.		ı	1
Penile pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characte	rized by marked discomfort sensation	n in the penis.	I		T
Perineal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characte	rized by a sensation of marked disco	omfort in the area between the ger	nital organs and the anus.	ı	1
Premature menopause	-	-	Present	-	-
Definition: A disorder characte	rized by ovarian failure before the ag	e of 40. Symptoms include hot fla	shes, 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

	Rej	productive system and b	reast disorders		
			Grade		
Adverse Event	1	2	3	4	5
efinition: A disorder character	ized by bleeding from the prostate	gland.	1	T	
rostatic obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
efinition: A disorder character tream, and incomplete emptyli	ized by compression of the urethra ng of the bladder).	secondary to enlargement of the p	prostate gland. This results in voidi	ng difficulties (straining to void, slo	ow urine
Prostatic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder character	ized by a sensation of marked disc	1	ı	I	ı
crotal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
efinition: A disorder character	ized by marked discomfort sensation	n in the scrotal area.	1	ı	
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
efinition: A disorder character	ized 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 character	ized by blockage of the normal flow	of the contents of the spermatic of	ord.		
Festicular 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 character	ized by involvement of the testis.				
Festicular 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 character	ized by bleeding from the testis.	T	1	T	
esticular pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder character	ized by a sensation of marked disco	omfort in the testis.		T	
Iterine 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 character	ized by an abnormal communicatio	। n between the uterus and another	organ or anatomic site.	I	Į.
Jterine 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 character	ized by bleeding from the uterus.	T	1	T	
Iterine obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder character	ized by blockage of the uterine outl	et.	I	I	
Iterine pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
efinition: A disorder character	ized by a sensation of marked disco	omfort in the uterus.	1		
aginal discharge	Mild vaginal discharge (greater than baseline for patient)	Moderate to heavy vaginal discharge; use of perineal pad or tampon indicated	-	-	-
efinition: A disorder character	ized by vaginal secretions. Mucus p	•	discharged from the vagina natura	' Illy, especially during the childbear	ring years.
aginal 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	-	-
	en de la companya de la francia de la franci	itching and burning in the vagina.	•	•	ı

	кер	productive system and b	reast 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 characteriz	zed 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 characteria	zed 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 characteria	zed by inflammation involving the v	agina. Symptoms may include red	dness, edema, marked discomfort	and an increase in vaginal dischar	ge.
Vaginal obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characteri:	zed by blockage of vaginal canal.				
Vaginal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteria	zed by a sensation of marked disco	mfort 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 characteria	zed 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 characteria	zed by a narrowing of the vaginal c	anal.		•	,
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 characterizintercourse.	zed by involuntary spasms of the pe	elvic floor muscles, resulting in pa	thologic tightness of the vaginal w	all during penetration such as duri	ng sexua
Reproductive system and breas 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

	Respi	ratory, thoracic and med	iastinal 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 characteriz surgery.	ed by progressive and life-threater	ning pulmonary distress in the abs	ence of an underlying pulmonary o	condition, usually following major t	rauma or
Allergic rhinitis	Mild symptoms; intervention not indicated	intervention indicated	-	-	-
	ed by an inflammation of the nasal of the sinuses, eyes, middle ear, a				ay also
Apnea	-	-	Present; medical intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characteriz			<u> </u>		
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 characteriz	ed by inhalation of solids or liquids	into the lungs.	T	T	
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
	ed by the collapse of part or the er	_			
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 characteriz	ed by an abnormal communication	between the bronchus and anoth	er organ or anatomic site.		Т
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 characteriz	ed by blockage of a bronchus pass	sage, most often by bronchial sec	retions 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 characteriz	red by a narrowing of the bronchial	tube.	Г	Г	T
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 characteriz	ed by an abnormal communication	between a bronchus and the plei	ıral cavity.	Γ	T
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
	1	,	'	'	1

	Respi	ratory, thoracic and med	iastinal 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 characterize	zed by a sudden contraction of the	smooth muscles of the bronchial v	wall.	T	I
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 characteriz	zed by milky pleural effusion (abnor	rmal collection of fluid) resulting fro	om 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 a distinctive sound.	zed by sudden, often repetitive, spa	asmodic contraction of the thoracion	c cavity, resulting in violent release	e of air from the lungs and usually	accompanied
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 characterize	zed by an uncomfortable sensation	of difficulty breathing.		1	Т
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 characteriz	zed 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 characteriz	zed by repeated gulp sounds that re	esult from an involuntary opening	and closing of the glottis. This is a	ttributed to a spasm of the diaphra	ıgm.
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 characteriz	zed by harsh and raspy voice arisir	g 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
	zed by a decrease in the level of ox	İ	Obrida w was a instance distance of	Life the set of a significant	Darath
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
	zed by swelling due to an excessive				
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 characterization	zed 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 characterize	zed by bleeding from the larynx.	I	1	T	T
Laryngeal inflammation	Mild sore throat; raspy voice	Moderate sore throat; analgesics indicated	Severe throat pain; endoscopic intervention indicated	-	-
Definition: A disorder characterization	zed by an inflammation involving th	e 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
		e mucous membrane of the larynx		l.,, ., .	
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 characterize	ed by blockage of the laryngeal ai	rway.			
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 characterize	ed 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 characterize	ed by an uncomfortable persistent	sensation in the area of the laryn	gopharynx.		
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 characterize	ed by paroxysmal spasmodic mus	cular contraction of the vocal cord	S.	•	,
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
	ed by bleeding from the mediastin				
Nasal congestion	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Associated with bloody nasal discharge or epistaxis	-	-
Definition: A disorder characterize	ed by obstruction of the nasal pas	sage due to mucosal edema.	T	Т	ı
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 characterize	ed by an abnormal communication	n between the pharynx and anothe	er organ or anatomic site.	Т	ı
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
	ed 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 characterize	ed by an inflammation involving th	e mucous membrane of the phary	nx.	T .	Т
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

	Respi	ratory, thoracic and med	iastinal disorders		
			Grade		
Adverse Event	1	2	3	4	5
Definition: A disorder characteriz	ed 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 characteriz	ed by a narrowing of the pharynge	al airway.			
Pharyngolaryngeal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by marked discomfort sensation	n in the pharyngolaryngeal region.	T	T	I
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 characteriz	ed by an increase in amounts of flu	uid within the pleural cavity. Symp	toms include shortness of breath,	cough and marked chest discomfo	ort.
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 characteriz	ed by bleeding from the pleural ca	vity.			
Pleuritic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by marked discomfort sensation	n in the pleura.	.	1	1
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
	ed by inflammation focally or diffus				
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 characteriz	ed by abnormal presence of air in	the pleural cavity resulting in the c	collapse of the lung.	'	,
Postnasal drip	Mild symptoms; intervention not indicated		-	-	-
Definition: A disorder characteriz	ed 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		-
	ed by expectorated secretions upo				
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 characteriz	ed by accumulation of fluid in the I	ung tissues that causes a disturba	ance of the gas exchange that may	y lead to respiratory failure.	
Pulmonary fibrosis	Mild hypoxemia; radiologic pulmonary fibrosis <25% of lung volume	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
	ed by the replacement of the lung	tissue by connective tissue, leadir	T i i i i i i i i i i i i i i i i i i i	tory 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

Definition: A disorder characterized by an abnormal communication between the lung and another organ or anatomic site. Minimal dyspenes, thindings on physical sevent or other evaluation physical sevent or other evaluation on physical sevent or other evaluation. Definition: A disorder characterized by an increase in pressure within the pulmonary circulation due to lung or heart disorder. Prespiratory failure: Prespiratory failure	Respiratory, thoracic and mediastinal disorders							
Definition: A disorder characterized by an abnormal communication between the lung and another organ or anatomic site. Minimal dysprines; indings on physical activation of physical activation of physical activation by cardiac catherized by an increase in pressure within the pulmonary cinulation due to lung or heart disorder. Peepiratory failure Peepiratory failure Peepiratory stature Peepiratory by making dispersions of the parameters of the parameters of the catherized system resulting in hypoxemia and a decrease in oxygenation of the tissues that may be associated with an increase in arterial levels of carbon disorder. Pedinition: A disorder characterized by weight gain, oxygenea, pleural and pricardial efficiency and sociated indicated i	A.I			I		_		
Description Number dyspress refurning on physical search or their evaluation Minimal dyspress. Refurning on physical search or their evaluation Minimal dyspress. Refurning on physical search or their evaluation Number of the respiratory failure - -				-	4	5		
physical exam or other evaluation or permitting evaluation by cartiaction with physical catheterization and medical intervention of catheterization and medical intervention incleased (e.g., tracheotomy or infubation). Pelinificin: A disorder characterized by an increase in pressure within the pulmonary circulation due to lung or heart disorder. Prespiratory failure Prespiratory system resulting in hypoxemia and a decrease in congruences; urgent may be associated syndrome. Full resembning again, riteration with this gain, riteration with this gain, riteration with task prespiratory desired and prespiratory system resulting in hypoxemia and a decrease in congruences; urgent may be associated syndrome. Full resembning again, dyspness, pleural and pericardial effusions, leukocytosis and/or renal failure originally described in patients treated with all-transferring consequences; urgent may be associated with a fine particles and consequences and prespiratory system resulting in hypoxemia and a decrease in congruences and consequences and present the particles and present					Life threatening sinusur	Dooth		
Cardiovascular or possibilities - -	rumonary nypenension	physical exam or other	requiring evaluation by cardiac catheterization and medical	with hypoxemia, right heart	consequences; urgent intervention indicated (e.g.,	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 and a decrease in oxygenation of the tissues that may be associated and a decrease in oxygenation of the tissues that may be associated intervention with fluid restriction and/or distriction indicated indicated verticated by weight gain, dyspinea, pleural and pericardial effusions, leukocytosis and/or renal failure originally described in patients treated with all-fraction indicated and obstruction; limiting self care with significant mass and obstruction; limiting self care wi	Definition: A disorder characteri	zed by an increase in pressure with	nin the pulmonary circulation due to	o lung or heart disorder.				
with an increase in arterial levels of cathon disorder. Patinic retrieval or a few plant increase in arterial levels of cathon disorder elements of a kind of unreliced grain, intervention with fluid restriction and/or durrelice indicated Definition: A disorder characterized by weight gain, dyspnea, pleural and pericardial effusions, leukocytosis and/or renal failure originally described in patients treated with all-trocked by weight gain, dyspnea, pleural and pericardial effusions, leukocytosis and/or renal failure originally described in patients treated with all-trocked by weight gain, dyspnea, pleural and pericardial effusions, leukocytosis and/or renal failure originally described in patients treated with all-trocked by the indicated with all-trocked pleural and pericardial effusions, leukocytosis and/or renal failure originally described in patients treated with all-trocked pleural and pericardial effusions, leukocytosis and/or renal failure originally described in patients treated with all-trocked pleural and pericardial effusions, leukocytosis and/or renal failure originally described in patients treated with all-trocked pleural and pericardial effusions, leukocytosis and/or renal failure originally described in patients treated with all-trocked pleural ple	Respiratory failure	-	-	-	urgent intervention, intubation,	Death		
Retinic acid syndrome Fluid retention: < 3kg of weight gain, intervention with fluid retention and/or discretic indicated Service symptoms: hospitalization indicated Life-threatening consequences: hospitalizati			he respiratory system resulting in	hypoxemia and a decrease in oxy	genation of the tissues that may be	e associa		
Definition: A disorder characterized by weight gain, dyspnea, pleural and pericardial effusions, leukocytosis and/or renal failure originally described in patients treated with all-travelence acid. Sinus disorder Asymptomatic mucosal crusting: Symptomatic stenosis or edema/hararowing interfering with airflow; limiting instrumental ADL Definition: A disorder characterized by involvement of the parasass sinuses. Sieep apnea Sororing and nocturnal sleep arousal without apnetic periods indicated; limiting instrumental ADL Definition: A disorder characterized by cessation of breathing for short periods during sleep. Sineazing Mid symptoms; intervention not indicated intervention indicated; limiting instrumental ADL Definition: A disorder characterized by of marked discomfort in the throat 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; limiting intervention indicated; limiting instrumental ADL 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; limiting instrumental ADL Definition: A disorder characterized by an abnormal communication between the trachea and another organ or anatomic site. Tracheal stenosis Endoscopic findings only; minimal hemophysis, pain, or respiratory distress, medical intervention indicated; limiting allowed intervention indicated; limiting instrumental ADL Asymptomatic; clinical or diagnostic observations only; intervention indicated or diagnostic observations only; intervention indicated or approach intervention indicated intervention indicated; limiting allowed intervention indicated (e.g., sent or primary closure) Polinition: A disorder characterized by an abnormal communication between the trachea and another organ or anatomic site. Endoscopic findings		Fluid retention; <3 kg of weight gain; intervention with fluid restriction and/or diuretics	- : :	- ·	_ :	Death		
Asymptomatic mucosal crusting: Symptomatic stenosis or edema/narrowing interfering with ariflow; limiting instrumental ADL Definition: A disorder characterized by involvement of the paranasal sinuses. Sidep apnea		1	al and pericardial effusions, leukoo	ı cytosis and/or renal failure original	ly described in patients treated wit	h all-trans		
Sleep apnea Snoring and nocturnal sleep arousal without apneic periods during sleep. Definition: A disorder characterized by cessation of breathing for short periods during sleep. Sneezing Mild symptoms; intervention not indicated intervention indicated (e.g., tracheotomy or intubation) 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 indicated intervention indicated; limiting instrumental ADL. 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 instrumental ADL. Definition: A disorder characterized by an alternation indicated intervention indicated; limiting instrumental ADL. Moderate symptoms; medical intervention indicated (e.g., stern or primary closure) congenitates or multiple thoraccoplasty, chronic open drainage or multiple thoraccoplasty, chronic open drainage or multiple thoraccoplasty, chronic open drainage or multiple thoraccoplasty, intervention indicated intervention indicated interven			edema/narrowing interfering with airflow; limiting instrumental	obstruction; limiting self care	urgent operative intervention	Death		
arousal without apneic periods destination; excessive daytime associated with hypertension; medical intervention indicated; limiting instrumental ADL Definition: A disorder characterized by cessation of breathing for short periods during sleep. Sneezing Mild symptoms; intervention not indicated intervention indicated (e.g., tracheotomy or intubation) 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 indicated intervention indicated; limiting instrumental ADL 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 Endoscopic findings only; intervention indicated; limiting instrumental ADL Definition: A disorder characterized by an abnormal communication between the trachea and another organ or anatomic site. Tracheal mucositis Endoscopic findings only; intervention indicated; limiting instrumental ADL intervention indicated (e.g., stent or primary closure) Definition: A disorder characterized by an alternation involving the mucous membrane of the trachea. Tracheal stenosis Asymptomatic; clinical or diagnostic observations only; intervention indicated intervention indicated (e.g., stent, laser) Definition: A disorder characterized by an abnormal communication between the trachea and another organ	Definition: A disorder characteri	zed by involvement of the paranasa	al sinuses.	'	'			
Mild symptoms; intervention not indicated Definition: A disorder characterized by the involuntary expulsion of air from the nose. Sore throat Mild pain Moderate pain; limiting instrumental ADL Moderate pain; limiting instrumental ADL; limiting ability to swallow Definition: A disorder characterized by of marked discomfort in the throat Stridor	Sleep apnea		desaturation; excessive daytime sleepiness; medical evaluation indicated; limiting instrumental	associated with hypertension; medical intervention indicated;	neuropsychiatric symptoms; urgent operative intervention	Death		
Indicated Intervention indicated Interve	Definition: A disorder characteri	zed by cessation of breathing for sh	nort periods during sleep.					
Mild pain Moderate pain; limiting instrumental ADL Severe pain; limiting self care ADL; limiting ability to swallow Pefinition: A disorder characterized by of marked discomfort in the throat Tracheal fistula Asymptomatic; clinical or diagnostic observations only; intervention not indicated Endoscopic findings only; minimal hemoptysis, pain, or respiratory symptoms Definition: A disorder characterized by an inflammation involving the mucous membrane of the trachea. Mild pain Moderate pain; limiting self care ADL; limiting instrumental ADL Respiratory distress limiting self care ADL; limitin	Sneezing			-	-	-		
Definition: A disorder characterized by of marked discomfort in the throat Stridor - Respiratory distress limiting self care ADL; medical intervention indicated (e.g., tracheotomy or intubation) 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 Pracheal mucositis Endoscopic findings only; minimal hemoptysis, pain, or respiratory symptoms Endoscopic or diagnostic observations only; minimal hemoptysis, pain, or respiratory symptoms Asymptomatic; clinical or diagnostic observations only; minimal hemoptysis, pain, or respiratory symptoms Asymptomatic; clinical or diagnostic observations only; minimal hemoptysis, pain, or respiratory symptoms Asymptomatic; clinical or diagnostic observations only; minimal hemoptysis, pain, or respiratory symptoms Asymptomatic; clinical or diagnostic observations only; instrumental ADL Definition: A disorder characterized by an inflammation involving the mucous membrane of the trachea. Fracheal stenosis Asymptomatic; clinical or diagnostic observations only; instrumental ADL Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL Life-threatening consequences; urgent intervention indicated intervention indicated; limiting respiratory symptoms; limiting self care ADL Entition: A disorder characterized by an inflammation involving the mucous membrane of the trachea. Fracheal stenosis Asymptomatic; clinical or diagnostic observations only; intervention indicated (e.g., noisy airway breathing), but causing no respiratory distress limiting self care ADL; imiting self ca	Definition: A disorder characteri	zed by the involuntary expulsion of	air from the nose.	'	'	'		
Stridor Respiratory distress limiting self care ADL; medical intervention indicated (e.g., tracheotomy or intubation) 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 indicated (e.g., stent or primary closure) 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 Definition: A disorder characterized by an inflammation involving the mucous membrane of the trachea. Asymptomatic; tube thoracostomy or medical intervention indicated (e.g., stent or primary closure) Death diagnostic observations only; intervention indicated; limiting instrumental ADL Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., thoracoplasty, chronic open drainage or multiple thoracotomies) Death diagnostic observations only; intervention indicated; limiting instrumental ADL Symptomatic (e.g., stent or primary closure) Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL Life-threatening airway consequences; urgent operative intervention indicated (e.g., thoracoplasty, chronic open drainage or multiple thoracotomies) Death diagnostic observations only; intervention indicated; limiting self care ADL; endoscopic intervention indicated (e.g., thoracoplasty, chronic open drainage or multiple thoracotomies) Death diagnostic observations only; intervention indicated; limiting self care ADL; endoscopic intervention indicated (e.g., tracheotomy or intubation) Death diagnostic observations only; intervention indicated (e.g., stent, laser) Death diagnostic observations only; intervention indicated (e.g., stent, laser)	Sore throat	Mild pain	' '	_ ·	-	-		
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 Definition: A disorder characterized by an abnormal communication between the trachea and another organ or anatomic site. Endoscopic findings only; minimal hemoptysis, pain, or respiratory symptoms 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 Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., thoracoplasty, chronic open drainage or multiple thoracotomies) Death diagnostic observations only; intervention indicated; limiting instrumental ADL Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL Self-threatening consequences; urgent intervention indicated (e.g., thoracoplasty, chronic open drainage or multiple thoracotomies) Death diagnostic observations only; intervention indicated; limiting instrumental ADL Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL Self-care ADL Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress limiting self care ADL; endoscopic intervention indicated (e.g., tracheotomy or indicated (e.g., tracheotomy or indicated (e.g., tracheotomy or indicated (e.g., tracheotomy or indicated (e.g., stent, laser) intervention indicated (e.g., tracheotomy or indicated (e.g., stent, laser)	Definition: A disorder characteri	zed by of marked discomfort in the	throat		_			
Tracheal fistula Asymptomatic; clinical or diagnostic observations only; intervention not indicated Definition: A disorder characterized by an abnormal multiple monophysis, pain, or respiratory symptoms 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 Asymptomatic; clinical or diagnostic observations only; intervention indicated; limiting instrumental ADL Severe symptoms; limiting self care ADL; endoscopic or operative intervention indicated (e.g., thoracoplasty, chronic open drainage or multiple thoracotomies) Death urgent operative intervention indicated (e.g., stent or primary closure) Life-threatening consequences; urgent operative intervention indicated (e.g., throacoplasty, chronic open drainage or multiple thoracotomies) Death urgent intervention indicated (e.g., stent or primary closure) Endoscopic findings only; intervention indicated; limiting instrumental ADL Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL Severe pain; hemorrhage or sepiratory symptoms; limiting self care ADL Severe pain; hemorrhage or sepiratory symptoms; l	Stridor	-	-	care ADL; medical intervention	compromise; urgent intervention indicated (e.g., tracheotomy or	Death		
diagnostic observations only; intervention not indicated intervention indicated; limiting instrumental ADL intervention indicated; limiting instrumental ADL intervention indicated (e.g., stent or primary closure) 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 intervention indicated; limiting instrumental ADL 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 Possible for a DL; endoscopic or operative intervention indicated (e.g., thoracoplasty, chronic open drainage or multiple thoracotomies) Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL Useful to a DEFINITION of the Intervention indicated (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., stent, laser) Death of the respiratory distress indicated (e.g., stent, laser) Death of the respiratory distress indicated (e.g., stent, laser)	Definition: A disorder characteri	zed by a high pitched breathing sou	und due to laryngeal or upper airw	ay obstruction.	T	1		
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minimal hemoptysis, pain, or respiratory symptoms intervention indicated; limiting self care ADL 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., stent, laser) minimal hemoptysis, pain, or respiratory symptoms; limiting self care ADL Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress indicated (e.g., stent, laser) Death compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Definition: A disorder characteri	zed by an abnormal communication	between the trachea and another	r organ or anatomic site.				
Asymptomatic; clinical or diagnostic observations only; intervention not indicated 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., indicated (e.g., stent, laser) Symptomatic (e.g., noisy airway breathing), but causing no respiratory distress; medical management indicated (e.g., stent, laser) Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Tracheal mucositis	minimal hemoptysis, pain, or	intervention indicated; limiting	respiratory symptoms; limiting	_ :	Death		
diagnostic observations only; intervention not indicated breathing), but causing no intervention not indicated breathing), but causing no respiratory distress; medical management indicated (e.g., indicated (e.g., stent, laser) indicated (e.g., tracheotomy or intubation)	Definition: A disorder characteri	zed by an inflammation involving th	e mucous membrane of the trache	ea. I	T			
steroids)	Tracheal etenosis	- ·		· · ·		Death		

	Respi	ratory, thoracic and med	iastinal 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 character	ized by a change in the sound and/o	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 character	ized by a high-pitched, whistling sou	und during breathing. It results fro	m the narrowing or obstruction of t	he 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	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;	-	-	-	
	not require a wig or hair piece to	associated with psychosocial				
Definition: A disorder characte	camouflage	impact	 ndividual at a given ago and hady	location		
	rized by a decrease in density of hair	·	ndividual 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 characte	rized by an abnormal body smell res	ulting from the growth of bacteria	on the body.	1	1	
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 characte	rized by inflammation of the skin cha	racterized by the presence of bull	ae which are filled with fluid.	T		
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 characte	rized by flaky and dull skin; the pores	s 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 characte	rized by target lesions (a pink-red rin	g 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 characte	rized by generalized inflammatory er	ythema and exfoliation. The inflan	nmatory process involves > 90% o	f 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 characte	rized by shrinking of adipose tissue.	Г	T	Т		
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 characte androgen control (beard, mous	rized by the presence of excess hair stache, chest, abdomen)	growth in women in anatomic site	s where growth is considered to b	e a secondary male characteristic	and under	
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 characte	rized by excessive perspiration.	•	•	•	•	

Skin and subcutaneous tissue disorders						
		Г	Grade	Г		
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	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)	-	-	-	
	enough about the overgrowth to use any form of hair removal	plus/minus arms] that requires frequent shaving or use of destructive means of hair removal to camouflage; associated with psychosocial impact				
Definition: A disorder characteriz	zed by hair density or length beyon	d the accepted limits of normal in	a particular body region, for a part	icular age or race.		
Hypohidrosis Definition: A disorder characteriz		Symptomatic; limiting instrumental ADL	Increase in body temperature; limiting self care ADL	Heat stroke	Death	
	T .	Covering 10 - 30% BSA and	Covering >30% BSA and	_		
Lipohypertrophy	Asymptomatic and covering <10% BSA	associated tenderness; limiting instrumental ADL	associated tenderness and narcotics or NSAIDs indicated; lipohypertrophy; limiting self care ADL			
Definition: A disorder characteriz	zed by hypertrophy of the subcutan	eous adipose tissue at the site of	multiple subcutaneous injections of	of insulin.		
Nail discoloration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-	
Definition: A disorder characterization	zed by a change in the color of the	nail plate.	1	T		
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 characterization	zed by loss of all or a portion of the	nail.				
Nail ridging	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-	
Definition: A disorder characteriz	zed 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 characterize	zed by marked discomfort sensation	n in the skin.	1			
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	-	-	
	zed by redness, marked discomfort			eet.		
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 characteriz	zed by swelling due to an excessive	e 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 characteria	zed by an increase in sensitivity of t	the skin to light.	•		•	

	Sk	in and subcutaneous tis	sue 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 characteriz	ed by an intense itching sensation	•			
Purpura Definition: A disorder characteriz	Combined area of lesions covering <10% BSA red by hemorrhagic areas of the sk	Combined area of lesions covering 10 - 30% BSA; bleeding with trauma in and mucous membrane. Newer	Combined area of lesions covering >30% BSA; spontaneous bleeding resions appear reddish in color. C	- Dider lesions are usually a darker i	- ourple color
and eventually become a browni	sh-yellow color.	<u> </u>	T	T	
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; lifethreatening consequences	Death
Definition: A disorder characterize	ed by an eruption of papules and p	pustules, typically appearing in fac	e, 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	-	-
	ed by the presence of macules (fla		nown as morbillform rash, it is one	of the most common cutaneous a	dverse
· · · · · ·	pper trunk, spreading centripetally	•			
Scalp pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characteriz	ed by marked discomfort sensation	n in the skin covering the top and	the back of the head.	T	
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 characterize	ed by the degeneration and thinnir	ng of the epidermis and dermis.	T	T	1
Skin hyperpigmentation	Hyperpigmentation covering <10% BSA; no psychosocial impact	Hyperpigmentation covering >10% BSA; associated psychosocial impact	-	-	-
Definition: A disorder characteriz	ed 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 characteriz	ed 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 characteriz	red by an area of hardness in the s	kin.	Т	Т	1
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 characteriz	ed by circumscribed, inflammatory	and necrotic erosive lesion on the	e skin.		

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

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 characteriz	ed by the permanent cessation of	menses, usually defined by 12 cor	nsecutive months of amenorrhea i	n a woman over 45 years of age.			
Social circumstances - Other, specify	-, ,	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	**	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			
	ed by leakage of intravascular fluid syndromes, low-flow states, ischer	•		-				
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 characteriz	ed by episodic reddening of the fa	ce.	T		1			
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 characteriz	ed by a localized collection of bloc	od, usually clotted, in an organ, sp	ace, or tissue, due to a break in th	e 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 characteriz	ed by an uncomfortable and tempor	orary sensation of intense body w	armth, flushing, sometimes accom	panied 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	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	Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	Death			
		>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	indicated Pediatric: Same as adult	Pediatric: Same as adult				
Definition: A disorder characterize	led by a pathological increase in bl	1	ion in the blood pressure exceeding	l og 140 over 90 mm Ha	1			
Hypotension	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	1	Life-threatening and urgent intervention indicated	Death			
Definition: A disorder characteriz	ed by a blood pressure that is belo	ow the normal expected for an indi	ividual 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 characteriz	ed by the loss of lymph fluid into the	ne surrounding tissue or body cavi	ity. T		1			
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 characteriz	ed 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 characteriz	ed by a cystic lesion containing lyr	mph.	T					
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 characteriz	ed by impaired circulation to an ex	ctremity.	1	I	1			
Phlebitis	-	Present	-	-	-			
Definition: A disorder characteriz	ed by inflammation of the wall of a	vein.	1	ı	T			
Superficial thrombophlebitis	-	Present	-	-	-			
Definition: A disorder characteriz	ed by a blood clot and inflammatic	on involving a superficial vein of the	e 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 characteriz cough, orthopnea and headache	ed by obstruction of the blood flow .	in the superior vena cava. Signs	and symptoms include swelling an	d cyanosis of the face, neck, and	upper arms,	
Thromboembolic event	Venous thrombosis (e.g., superficial thrombosis)	Venous thrombosis (e.g., uncomplicated deep vein thrombosis), medical intervention indicated	· ·	Life-threatening (e.g., pulmonary embolism, cerebrovascular event, arterial insufficiency); hemodynamic or neurologic instability; urgent intervention indicated	Death	
Definition: A disorder characteriz	ed by occlusion of a vessel by a th	rombus that has migrated from a	distal site via the blood stream.			
Vasculitis	Asymptomatic, intervention not indicated	Moderate symptoms, medical intervention indicated	\ \ \ \ \ \ \ \	Life-threatening; evidence of peripheral or visceral ischemia; urgent intervention indicated	Death	
Definition: A disorder characteriz	ed by inflammation involving the w	vall 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 characteriz	ed 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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APPENDIX 2

Treatment Algorithm for the Management of Cytokine Release Syndrome

Treatment Algorithm for the Management of Cytokine Release Syndrome (Version to accompany Clinical Trial Protocol version 2.31)

Vigilance for **typical clinical manifestations**: Headache, Lumbar myalgia, restlessness, nausea, vomiting, bowel urgency, diarrhoea, dyspnoea, pyrexia, hypotension, erythema, rigors, tachycardia, tachypnoea, central or peripheral cyanosis, SpO₂ <94%



(ALL PATIENTS MUST BE REVIEWED IMMEDIATELY BY MEDICAL ONCOLOGY AND/ OR IMMUNOLOGY CLINICAL STAFF WITH PROMPT REFERRAL TO AN INTENSIVE CARE PHYSICIAN IF APPROPRIATE)

Administer immediately:

Supplemental oxygen as necessary
1g Paracetamol orally (repeat as required)
10mg Chlorpheniramine (piriton) i.v. (repeat as required)
Fluid replacement (crystalloids or colloids) if hypotensive*
Transfer to ITU should be considered if CRP >20mg/dL (Davila et al. 2014)

Consider (following discussion with consultant medical oncologist and immunologist):

- 1. Tocilizumab 4mg/kg (max. 800 mg) by i.v. infusion over 1 hour. This agent may be repeated once.
- 2. Consider levetiracetam (initially 250mg PO or by i.v. infusion) if ongoing pyrexia for 2 days
- 3. If no improvement after administration of tocilizumab x 2 doses, consider dexamethasone 10mg i.v. every 12 hours.
- 4. In refractory cases, consider infliximab (5mg/kg by i.v. infusion over 2 hours).

Check:

FBC, Coagulation screen, Ferritin, CRP, Group and Save, Serum electrolytes, Renal function and Liver function tests.

Take 10mls serum (clotted sample) and send urgently FAO Dr John Maher, Department of Research Oncology, Bermondsey Wing (T: 020 7188 1468)

Perform Arterial blood gas, ECG and Chest X-ray

Maintain strict fluid balance chart documenting urine output (plus daily weight if patient ambulatory)

Replace blood components as required (packed red cells, fresh frozen plasma, cryoprecipitate and platelet concentrates)

Consider:

Insertion of central venous line to monitor fluid replacement Inotropes to maintain urine output

As indicated:

Renal review with consideration of haemofiltration/haemodialysis for acute renal failure

Respiratory support with continuous positive airways pressure (CPAP) or mechanical ventilation

• Hypotension defined as fall in systolic blood pressure of >20mm Hg