Clinical Study Report

Study Title:

Visualisation of Indocyanine Green in Primary and Interval Debulking for Ovarian Cancer

Acronym:

VIPIDO

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Sponsor
University Hospitals Leuven (UZ Leuven)
Herestraat 49, B-3000 Leuven, Belgium

Coordinating Investigator
Toon VAN GORP, MD, PhD; University Hospitals Leuven (UZ Leuven)

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Synopsis

Brief Summary

The study aimed to evaluate the diagnostic accuracy of Indocyanine Green (ICG) [the IMP] in visualizing peritoneal lesions of epithelial ovarian cancer (EOC) during primary and interval debulking surgeries. The primary endpoint was to determine the sensitivity and specificity of ICG in identifying malignant peritoneal implants. The study aimed to include 40 patients, divided into two arms: primary debulking and interval debulking. However, due to futility, the study was terminated prematurely with only 2 participants inclued in the primary debulking arm and 11 in the interval debulking arm.
Key findings indicated a sensitivity of 70.7% and a specificity of 34.9% for ICG in the interval debulking group. The positive predictive value was 50.9%, and the negative predictive value was 55.6%.

Study Design

This was an open-label, therapeutic exploratory trial. The investigational medicinal product (IMP), Indocyanine Green (Verdye®), was used off-label as a diagnostic tool. The study involved intravenous administration of ICG followed by visualization using a near-infrared (NIR) fluorescence camera during surgery. The trial included two arms: primary debulking and interval debulking, with 20 patients in each arm.

Objectives

Primary Objective

- The primary objective of this Trial is to determine the diagnostic accuracy of ICG in visualising peritoneal lesions of EOC *in vivo*. By using the NIR fluorescence camera, peritoneal malignant implants should be fluorescent after intravenous injection of ICG. Benign lesions should not be fluorescent after intravenous injection of ICG.

Secondary Objectives

- Obtaining the false positive and false negative rate of *in vivo* ICG fluorescence signal by correlating these results with the pathological report.
- Determine the difference of estimated ICG uptake *in vivo* of peritoneal lesions between primary debulking and interval debulking.
- Correlation between the pre-operative radiographic examination(s) and the ICG signal *in vivo* and the pathological examination.
- Determination of the tumor-to-background ratio of fluorescence in peritoneal lesions, lymph nodes and other anatomical structures. Correlation of this ratio with the pathological examination.
- Assessment of the number and type of adverse effects, severe adverse effects and adverse reactions with the trial dose of the IMP.

Methodology

The study enrolled 40 patients with advanced-stage EOC (FIGO stage IIIb, IIIc, or IV). Participants underwent either primary or interval debulking surgery. ICG was administered intravenously at a dose of 0.25 mg/kg of body weight. The NIR fluorescence camera was used to visualize peritoneal lesions during surgery. Fluorescence signals were correlated with pathological findings to assess diagnostic accuracy.

Key Findings

	Primary Debulking (n=2)	Interval Debulking (n= 11)
Final pathology shows HGSOC (n,%)	2 (100.0%)	9 (81,8%)
Number of assessed lesions per participant (n,%)		
0	1 (50.0%)	1 (9,1%)
5	0	1 (9,1%)
6	0	1 (9,1%)
7	0	1 (9,1%)
8	1 (50.0%)	2 (18,2%)
10	0	5 (45.5%)
Sensitivity (95%CI)	Not calculated	70.7% (54.5 - 83.9%)
Specificity (95%CI)	Not calculated	34.9% (21.0 - 50.9%)
Positive Predictive Value (95%CI)	Not calculated	50.9% (43.6 - 58.2%)
Negative Predictive Value (95%CI)	Not calculated	55.6% (40.0 - 70.1%)
Accuracy (95%CI)	Not calculated	52.4% (41.2 - 63.4%)
Diagnostic odds ratio (95%CI)	Not calculated	1.30 (0.52 - 3.25)

Conclusion

The study concludes that ICG fluorescence imaging has potential as an adjunctive tool for visualizing malignant peritoneal lesions in EOC surgeries. However, its diagnostic accuracy is limited by a high false positive rate and therefore without any clear added value during the surgical proces.

Future research should focus on optimizing the technique, possibly by combining ICG with other imaging modalities, to enhance specificity and overall diagnostic performance.

Table of Contents

List of Abbreviations and Definitions

Abbreviation	Definition
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
APR	Annual Progress Report
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Coordinating Investigator
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CM	Concomitant Medication
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
DMP	Data Management Plan
DPA	Data Processing Annex
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
DTA	Data Transfer Agreement
EC	Ethics Committee
ECG	Electrocardiogram
(e)CRF	(electronic) Case Report Form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOC	Epithelial ovarian cancer
EoT	End of Trial
EPR	Enhanced permeability and retention
ESGO	European Society of Gynaecological Oncology
EU	European Union
FIGO	International Federation of Gynaecology and Obstetrics
FPFV	First Patient First Visit
GCP	Good Clinical Practice (latest version of ICH E6)
GDPR	General Data Protection Regulation
IB	Investigator's Brochure
ICF	Informed Consent Form
ICG	Indocyanine green
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ISF	Investigator Site File
JCI	Joint Commission International
LPLV	Last Patient Last Visit
MAH	Marketing Authorisation Holder

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MP	Monitoring Plan
MRI	Magnetic resonance imaging
NIR	Near-infrared
PC	Paclitaxel & Carboplatin
PET-CT	Positron emission tomography–computed tomography
PI	Principal Investigator (Participating Site)
PRO	Patient Reported Outcome
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBR	Tumor-to-background ratio
TMF	Trial Master File

Introduction

Background

Epithelial ovarian cancer (EOC) is the most lethal gynecological cancer and the fifth largest cause of cancer-related death in women in Europe [1]. Two thirds of diagnoses are made in an advanced stage (International Federation of Gynaecology and Obstetrics (FIGO) stage III and IV), adding to the mortality [2]. The main goal for surgery in these advanced cases is to optimally resect all macroscopically visible tumor deposits, in order to optimize patient prognosis [3]. However, this optimal and complete (R0) resection is not always an option. Peritoneal involvement is a typical aspect from advanced disease, possible leading to large spread disease with bowel involvement or involvement into the portal vessels. This renders primary surgery ("debulking") not feasible. The European Society of Gynaecological Oncology (ESGO) guidelines advice to administer neoadjuvant chemotherapy in unresectable disease or unfit patients [4]. If the disease is less extensive after this neoadjuvant treatment and the patient is deemed fit for surgery, interval debulking surgery is advisable to achieve an R0 resection and to increase overall survival.

However, during interval debulking surgery, the clinician often encounters residual peritoneal lesions. Macroscopically, the surgeon cannot always differentiate these masses between active peritoneal disease or inactive and harmless fibrotic tissue, deprived from tumor cells due to the neoadjuvant therapy. If such a deposit exists on the parietal peritoneal surface, resection is no issue. Nonetheless, if such a deposit is situated next to the portal vein or on the serosa of the bowel, resection could cause significant morbidity and R0 resection could be compromised. Pre-operative imaging such as positron emission tomography–computed tomography (PET-CT) or magnetic resonance imaging (MRI) could aid the surgeon to differentiate active versus non-active lesions, however sensitivity for smaller lesions remains low and localization of the exact lesion is cumbersome [5]. Especially lesions smaller then 5mm are hard to differentiate preoperatively (due to resolution restraints of both PET-CT and MRI) and intra-operatively, mainly during interval debulking surgery, due to less obvious macroscopic aspect and the possible missing very small lesions during debulking surgery [6].

Indocyanine green is an amphiphilic tricarbocyanine iodine dye that rapidly binds to plasma protein, mainly albumin, which maintains the ICG intravascular [7,8]. This allows for easy visualization of the arteriovenous and lymphatic system, including lymph nodes. Furthermore, by bonding to plasma proteins, ICG behaves as a macromolecule. These macromolecules are accumulated in tumor tissues due to increased permeability and reduced drainage [9]. This effect is called the "enhanced permeability and retention" (EPR) effect, allowing to visualize the tumor tissue by using ICG. ICG is visualized by exciting the molecule with near-infrared (NIR) light. Typically, ICG is excited by a wavelength between 750 and 800nm and viewed at 830nm which is the peak emission level [8,10]. This wavelength is an optimal range to visualize *in vivo* tissues, since it is situated between the isosbestic point (around 700nm) of tissues containing hemoglobin and myoglobin and between the wavelengths (above 900nm) absorbed by water and lipids [8,11]. Furthermore, the NIR light can penetrate the tissue deeper than visible light, up to 10mm of tissue [12].

Rationale

The rationale of this Trial is to adequately visualize peritoneal lesions of EOC in both primary and interval debulking surgery by using intravascular ICG and NIR light. Without ICG, macroscopic lesions

in primary surgery are easily visible, however in interval debulking adequate visualization of active peritoneal lesions is challenging. Active peritoneal implants could be mistaken for fibrosis, leading to suboptimal debulking surgery (i.e., not a true R0 resection) with higher rates of recurrence. We want to investigate whether ICG can increase the visibility of peritoneal lesions and can differentiate between peritoneal implants and fibrosis. In previous studies with a limited number of patients, this concept has already been proved feasible [8,12–14]. In this Trial we aim to further optimize this technique with a larger number of patients and in both primary and interval debulking surgery. Furthermore, we will associate operative findings with preoperative imaging, allowing to correlate the visualization of lesions by the IMP with these examinations.

In this Trial patients that undergo either primary or interval debulking surgery are included. The aim of the Trial is to identify active peritoneal implants; in primary debulking surgery we expect that all macroscopic peritoneal lesions will be fluorescence positive, as such this could be considered our positive control arm of the IMP efficacity. However, in interval debulking surgery, the possibility exists that some macroscopic peritoneal lesions are mere fibrotic tissue and as such we would expect the fluorescence signal to be less intense or absent. If such a difference would exist between active (fluorescence positive) peritoneal implants, this could aid in the visualization and selective resection of peritoneal disease in EOC, ultimately reducing the risk for hazardous resections.

Non-peritoneal lesions and in particular lymph nodes will also be macroscopically assessed for the fluorescence signal of the IMP and this signal will be correlated with the anatomopathological findings. However, this is only a secondary endpoint since peritoneal lesions are the trademark of advanced stage EOC. For these non-peritoneal lesions preoperative imaging will also be correlated, especially their topographic relationship.

Epithelial ovarian cancer accounts for 90% of ovarian cancers knows five histological subtypes: high-grade serous carcinoma, low-grade serous carcinoma, endometrioid carcinoma (subdivided in high-grade and low-grade), clear-cell carcinoma and mucinous carcinoma [15]. Each of these histological subtypes have their own characteristics. Of these epithelial ovarian cancer subtypes, high-grade serous carcinoma comprised the majority of tumors. As such, we aim in this exploratory Trial to only include high-grade serous epithelial ovarian carcinoma.

Objectives

In this therapeutic exploratory Trial, we explore the diagnostic usage of ICG (an already registered IMP with Marketing Authorisation) in the diagnosis of peritoneal lesions of EOC. In this Phase II Trial the aim is to replicate previous studies where ICG had been used with the same dosing intravenously to visualize peritoneal lesions in EOC [8]. However, we expand the potential usage of the IMP by exploring the entire abdominal cavity and explore the retroperitoneum and its lymph nodes. Furthermore, we correlate preoperative imaging with the surgical findings and the influence of the IMP on these findings.

The primary research question is if ICG is capable to correctly visualize peritoneal lesions of EOC *in vivo* in both primary and interval debulking surgery. We hypothese the ICG will adequately visualise malignant peritoneal implants of EOC. Furthermore, we hypothesized that fibrotic lesions would retain less or no ICG and therefore emit a different fluorescence signal than the malignant implants.

Study Design and Methodology

Study Design

This Trial is an open label trial exploring the diagnostic capabilities of an already approved drug, thus exploring the capability of an application unrelated to original approved use. The IMP (Indocyanine green, Verdye®) will be used off-label as a diagnostic tool. Since the IMP is only utilized as a diagnostic tool, no blinding could be performed.

Each participant will be identified within the Trial by a unique Trial-specific participant identifier. The true identity of the participant will be recorded in the Trial Master File, however after inclusion of the participant, only the PI can access the personal identifiers of this participant.

The following flowchart condenses the Trial design (Figure 1):

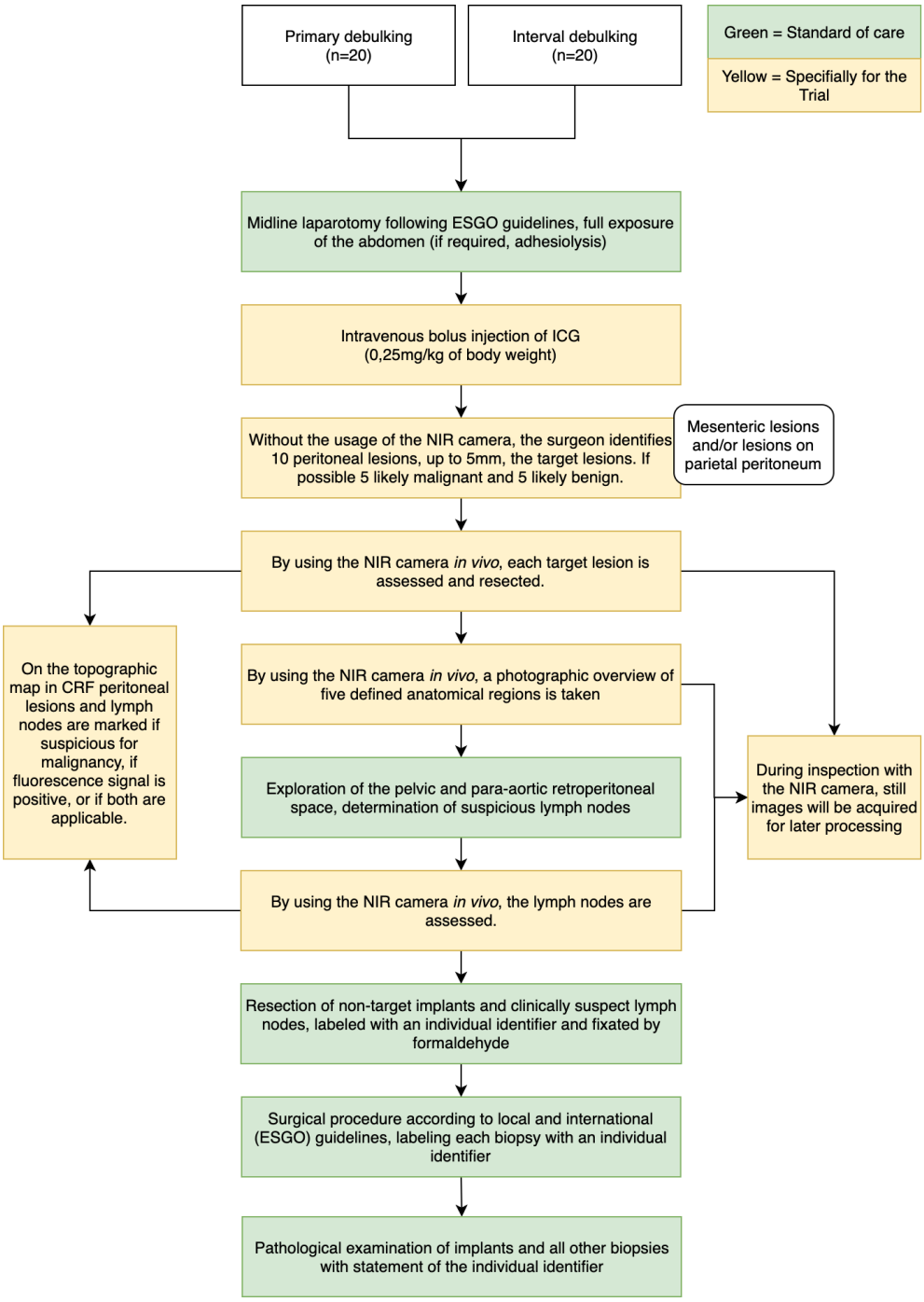

Figure 1

All relevant preoperative imaging (including but not limited to CT, PET-CT and/or MRI) will be included in the CRF. These preoperative staging is a part of the standard of care and as such is not an additional examination for this Trial. Patient history including allergies and current medication will be noted in the CRF. Additionally, information from the screening visit will be included in the CRF: demographics, physical examination, weight, height, Eastern Cooperative Oncology Group (ECOG) performance status and vital signs (Appendix **Fout! Verwijzingsbron niet gevonden.**) [16]. Any relevant and recent lab tests – in particular renal function and biomarker CA-125 – will be included in the CRF.

During the procedure, a paper CRF will be provided including the flowchart condensing the Trial design (Appendix **Fout! Verwijzingsbron niet gevonden.**). In this paper CRF the surgeon will be given a step-by-step guide to fully collect all necessary peroperative data. After the procedure, this paper CRF will be digitalized in the CRF. During surgery, the surgeon can utilize pre-operative imaging available to correctly identify the preoperative lesions and abnormal masses to obtain R0 resection. The procedure will be performed under general anesthesia, this is standard of care for a debulking surgery. Possibly, additional neuraxial anesthesia can be utilized within the standard of care, if indicated.

First, the surgeon will perform a midline laparotomy according to ESGO guidelines, as a standard of care. If necessary, dissection of adhesions can be performed in order to obtain adequate exposure of the abdominal cavity. Should this dissection be technically impossible, or should the surgeon deem the exposure of the abdominal cavity insufficient for optimal visualization, the participant will not be further participate in the Trial. This drop out remains in the database of patients and will be subject of the intention to treat analysis.

After adequate exposure of the abdominal cavity, the IMP will be administered as an intravenous bolus injection (0,25mg/kg of body weight) via the intravenous access already established. For the rationale of dosing and timing of administration, please see section **Fout! Verwijzingsbron niet gevonden.**. An exact timeframe between injection and visualization is difficult to obtain from literature. ICG can be visualized as soon as 2 minutes for lymph nodes and 5 minutes for peritoneal lesions [8,14]. As such, since the injection is prior of identification of the lesions, adequate time will be obtained between injection and identification of lesions. A maximum time between injection and visualization is also very different in literature, a maximum timeframe of 24 hours has been reported for peritoneal lesions [14]. Therefore, the maximum time after injection is not an issue in this Trial since debulking surgeries do not require 24 hours to perform.

Before utilization of the NIR fluorescence camera, the surgeon identifies 10 peritoneal lesions, the so-called target lesions: 5 lesions deemed to be malignant, and 5 lesions deemed to be benign. Should the surgeon be unable to ascertain 10 macroscopic peritoneal lesions, the maximum number of resectable lesions should be identified; this must be noted in the CRF. These lesions must be located on the mesentery and/or on the parietal peritoneum. These locations have been specially selected due to its ease of resection and the minimal risk of resection for the patient in comparison with other anatomic locations such as the bowel surface or diaphragm. If possible, these lesions should be maximum 5mm, in order to maximize the clinical relevance (cf. supra). Should such small lesion(s) not be available, larger lesion(s) are accepted, but this will be noted in the CRF. Each lesion will be scored on a six-point scale: likely malignant or likely benign. For each assessment, the surgeon has to attribute a grade of certainty: Certain, Probably or Uncertain. As such, each lesion is given a grade on a six-point scale.

In the next step the NIR fluorescence camera is used to visualize each peritoneal target lesion *in vivo*. This camera is fitted with a sterile protective cover and is placed on a holding arm. The camera used in this Trial is a Karl Storz Image1 S TH 121 4K camera capable of NIR fluorescence. This camera is mounted on a holding arm. During NIR fluorescence images procurement, a 760 nm excitation light will be utilized. The head of the camera is positioned about 30cm from the surgical field [9]. By

preserving the 30cm distance, all images obtained for quantitative calculation are comparable. Each of the 10 pervious selected peritoneal lesions (=target lesions) are labelled fluoresce positive or fluorescence negative. For every lesion, the results are noted in the CRF and in the pathological report. A structure is deemed fluorescence positive when it captures the ICG fluorescence signal and the brightness of the signal is at least two times as strong as the surrounding tissue [14]. During this identification phase of the Trial, ample still images will be procured with the NIR fluorescence camera, with an emphasis on the target lesions. A quantitative calculation of the brightness is not essential during surgery, in accordance with literature [14]. This quantitative calculation of the tumor-to-background ratio (TBR) will be performed on the acquired still images after surgery. Once again, for each target lesion, the surgeon will give the assessment on the six-point scale. Dissection of the target lesions is at the discretion of the performing surgeon, in accordance with ESGO guidance [3]. In the pathology report, each lesion location, fluorescence signal and clinical assessment (i.e., the six-point scale) will be noted and copied in the CRF. The resected lesion is fixated in formaldehyde, as standard of care, unless the surgeon wishes to perform a frozen section examination. Furthermore, each target lesion will be indicated on the topographic map provided in the CRF. The number of each lesion will be noted on this map (Figure 2).

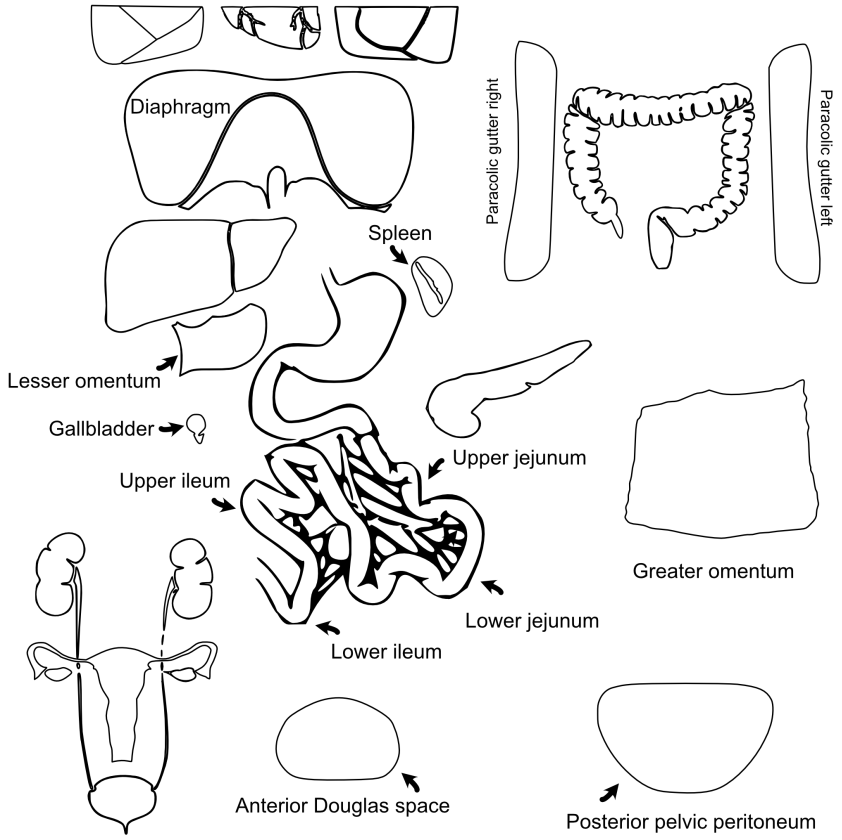

Figure 2

After resection of the target lesions, the entire abdominal cavity is systematically assessed. The surgeon will take two photographs of five defined anatomically regions. Of each region a photograph without NIR fluorescence camera will be taken. Afterwards a second photograph will be taken using the NIR fluorescence camera. These five anatomical regions are: pelvis, omentum, mesentery, right paracolic gutter and right-sided diaphragm. The procured photographs will be noted in the CRF. Dissection of the non-target lesions is at the discretion of the performing surgeon, in accordance with ESGO guidance [3].

After complete assessment of the abdominal cavity, the surgeon states an estimation (in percents) of the number of peritoneal lesions who are fluorescence positive.
As standard of care, the retroperitoneal lymph nodes in the pelvic and obturator spaces are explored. Additionally, the para-aortic and caval lymph nodes are also assessed macroscopically. If a lymph node is macroscopically suspicious for malignancy, it must be resected according to standard of care. Furthermore, if preoperative imaging reported enlarged and/or suspicious lymph node(s), these nodes should also be resected according to standard of care. However, prior to resection the lymph nodes in the exposed retroperitoneal spaces should be assessed by the NIR fluorescence camera. The fluorescence status (i.e., positive or negative) of each pre- or interoperative suspicious lymph node must be obtained and noted in the CRF. Additionally, all fluorescence positive lymph nodes must be reported in the CRF, however these lymph nodes should not be resected as this is not standard of care and the resection of these additional lymph nodes are out of the scope of this Trial. During assessment with the NIR fluorescence camera, still images will be taken. Should the lymph node be resected, the location, fluorescence signal and clinical assessment (i.e., the six-point scale) will be noted in the pathology report and copied in the CRF. The surgeon should indicate these lymph nodes on the provided topographic map in the CRF (Figure 3). The surgeon must indicate suspicious lymph nodes by an X on the second topographic map. Should an area be fluorescence positive without a clear lymph node, an O will be drawn on the map. If both are applicable, an X with a circle drawn around it will be noted. The lymph node is fixated in formaldehyde, as standard-of-care of send for frozen section examination. Should the lymph node not be resected, then a description of the location, fluorescence signal and clinical assessment (i.e., the six-point scale) will be noted in the CRF and drawn on the topographic map.

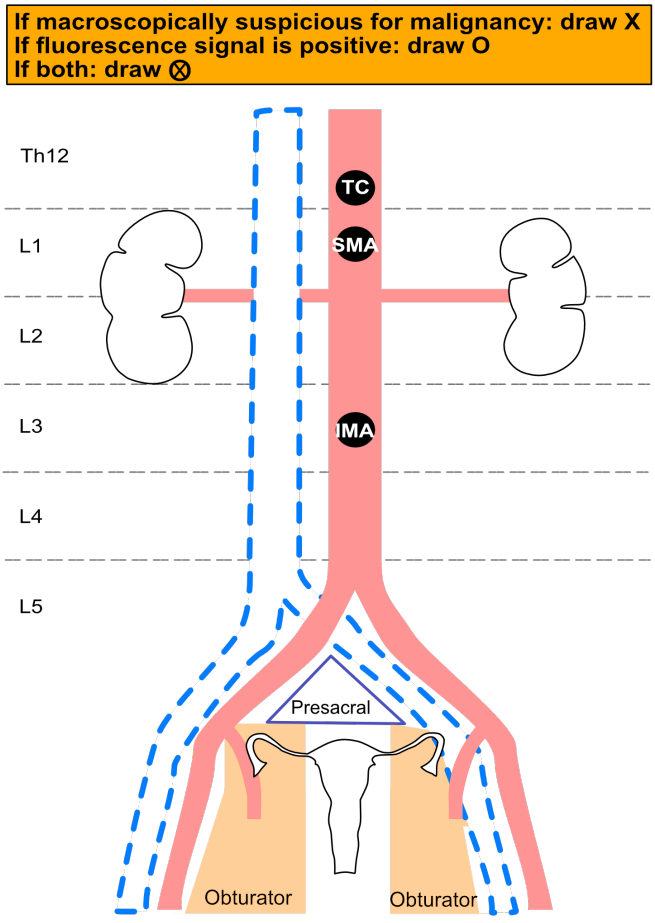

Figure 3

If feasible, the surgeon furthermore correlates the mapped structures with the pathological report in order to further optimize topographic relations. The peritoneal lesion chart is adapted from Hoogstins *et al.* and Jacquet & Sugarbaker [17,18].
Further surgical procedure is as standard of care, according to local and international guidelines, mainly ESGO guidelines [4]. After the initial visualization and documentation of the fluorescence signal in the abdominal cavity, no further fluorescence signals will be obtained within the Trial due to the risk for contamination of the tissues with the IMP and as such reducing specificity of ICG. However, all biopsies should be identified by an individual identifier and this identifier including the topographic location must be noted in the CRF.
In each of the previous steps, a timestamp is provided in the CRF in order to obtain the required time for each step and for the entire IMP-guided procedure.
The surgical report should follow ESGO guidelines and be as complete as possible [4]. This pseudonymized validated surgery report will be included in the CRF.
The pathology report of all resected biopsies will be included in the CRF after pseudonymization. This report should state all identifiers and additional information previously noted in the CRF.
Image processing to determine the TBR will be conducted in ImageJ, an open-source application developed by the National Institutes of Health (available from https://imagej.nih.gov/ij). Two zones will be identified in the still images: a zone of fluorescent uptake and a non-fluorescent background area (at least 2cm apart from the fluorescent zone) [9]. TBR will be calculated to take the ratio (expressed as mean arbitrary units) of the two areas of interest. Furthermore, contrast-to-noise ratio could be utilized if sensitivity using TBR seems inadequate [19]. If applicable, machine learning will be enabled to further enhance image processing and reduce selection and/or confirmation bias, including – but not limited to – calculation of tumor-to-background ratio.

Study Population

Inclusion criteria

Participants eligible for inclusion in this Trial must meet **all** of the following criteria:

1. Voluntary written informed consent of the participant or their legally authorized representative has been obtained prior to any screening procedures. (Appendix **Fout! Verwijzingsbron niet gevonden.**)
2. At least 18 years of age.
3. Advanced stage epithelial ovarian cancer: FIGO stage IIIb, IIIc or IV. (For FIGO staging classification, please refer to Appendix **Fout! Verwijzingsbron niet gevonden.**).
4. A biopsy or cytology confirming the presence of high-grade serous epithelial ovarian carcinoma
5. Preoperative imaging (CT and/or MRI), describing metastatic implants, as standard of care.

All participants that are considered for Trial participation, per the above criteria will be documented on the Screening Log, including Screen Failures.

Exclusion criteria

Participants eligible for this Trial must **not** meet any of the following criteria:

1. Participant has a history of following diseases:
    a. Hyperthyroidism
    b. Autonomously functioning thyroid adenoma
2. Participant has an allergy or hypersensitivity for one or more of the following components:
    a. Iodine (including potassium iodine)
    b. Indocyanine green

3. Any disorder, which in the Investigator's opinion might jeopardize the participant's safety or compliance with the protocol.
4. Any prior or concomitant treatment(s) that might jeopardize the participant's safety or that would compromise the integrity of the Trial.
5. Participation in an interventional Trial with an investigational medicinal product (IMP) or device during the surgery itself.
6. Participant has a severe renal impairment (classified as eGFR<30 ml/min/1,73m^2 according to CKD-EPI).
7. Participant utilizes sodium bisulfite-containing heparin preparations during the day before surgery. For Belgian registered drugs, this contains:
    a. Danaparoïde (Orgaran®)
    b. Other low-molecular weight heparins registered in Belgium do not contain sodium bisulfite and are not an exclusion criterion.
8. Participants requires thyroid scintigraphy utilizing radioactive iodine one week after surgery.
9. A previous history of major intra-abdominal surgery with potentially major adhesions and/or distorted anatomy.
10. Participants utilizes one of the interacting drugs listed in section 5.3.

Participants who meet one or more of the above exclusion criteria **must not proceed** to be enrolled/randomized in the Trial and will be identified on the Screening Log as Screen Failure.
NB Since the explicit intent of cytoreductive debulking surgery is to remove the ovaries, the participant cannot become pregnant. As such, the usage of contraceptive methods is futile and is not discussed within the inclusion and exclusion criteria.

Investigational Medicinal Product and Dosing Regimen

Generic Drug Name (& company brand name)	**IMP or non-IMP**	**Used within Indication?**	**Route of administration**	**Dose/dosage and units**
Indocyanine green (Verdye®)	IMP	No, off-label	Intravenous bolus injection	0,25mg/kg of body weight

The IMP in this Trial is Verdye®, manufactured and licensed for the Belgian market by Diagnostic Green GmbH (Otto-Hahn-Str. 20, 85609 Aschheim-Dornach, Germany). The Summary of Product Characteristics is provided in Appendix **Fout! Verwijzingsbron niet gevonden.**. Standard vials with the IMP obtained from the hospital pharmacy will be provided, either containing 25mg of powder, or containing 50mg of powder, depending on the required dosing. The IMP will be dispensed by a licensed hospital pharmacist. The legally required label indicating "clinical trial use only" will be attached (Appendix **Fout! Verwijzingsbron niet gevonden.**). No additional labelling or packaging of the IMP vials will be provided, since the labelling of the vial and the exterior packaging are described within the Summary of Product Characteristics of Verdye®. Verdye® is stored in an amber glass injection vial (type 1), closed by a grey rubber lid (broombutyl), which is attached by an aluminum hood. A blue polypropylene protective cap encloses the top of the vial [10].
The IMP will be dissolved with sterile water suitable for intravenous injection, obtaining a concentration of 5 mg/ml [10]. This suspension will be dissolved in the vial while retaining all sterility. Should a precipitate be present in the suspension, the vial must be discarded according to local guidance and protocols and this vial of IMP cannot be used for injection [10]. As such, each vial and each syringe containing the dissolved IMP must be visually inspected for any precipitation. With a sterile syringe the required volume of the dissolved IMP will be aspired on a sterile manner. This syringe will be administered intravenously as explained in the following paragraph within a short timeframe. Attention should be made this timeframe must be kept as short as possible, allowing for immediate intravenous injection, in order to minimize potential influence of light or other contaminants. Should

the IMP be dissolved, and immediate intravenous injection is not possible, the syringe must be kept in a dark place or must be shielded from light. A maximum timeframe of 1 hour is obtained between dissolving the IMP and injection, well within the maximal range of the 6 hours stated in the Summary of Product Characteristics [7]. If this timeframe should exceed 1 hour, the syringe and the remaining IMP in the vial must be discarded according to local guidance and protocols.
According to the Summary of Product Characteristics of Verdye®, administration should occur as a bolus injection, see Appendix **Fout! Verwijzingsbron niet gevonden.** [10]. Dosing ranges between 0,1 to 0,5 mg/kg of body weight as a single dose in adults, seniors and children. Total daily dose should not exceed 5 mg/kg of body weight [10].
In their practical guide, van Manen *et al.* advises administration of 0,25mg/kg of body weight for the visualization of peritoneal metastases [12]. Hence, we adhere to this dosing, which is within the range of Summary of Product Characteristics. When reviewing literature about the optimal dosing for the visualization of lymph nodes, no consensus could be obtained. For the visualization of sentinel lymph nodes doses range from 100µg to 25mg, with a recommended dose of 2,5mg [12]. Since the injection is intravenously, we cannot compare the dosage for the visualization of sentinel lymph nodes, in which the injection is locally. Since our primary objective is the visualization of peritoneal lesions, we retain the aforementioned dose.
Intravenous access is standard of care in all surgeries under general anesthesia, therefore the bolus administration of ICG can be performed without an additional intravenous puncture or intravenous line. The IMP will be administered by a licensed physician or operation theatre nurse with the utmost care to work in sterile environments with the IMP.
ICG will be administered after complete exposition of the abdomen, allowing for an optimal timeframe between injection of ICG and visualization. Time between injection and visualization of peritoneal lesions is minimum 5 minutes [12]. Optimal time of visualization knows a very broad range in literature, ranging between immediately up to 24 hours after injection [12,13,20]. Therefore, we pragmatically opted for a 10-minute wait time between intravenous injection of the IMP and visualization of the lesions using the NIR fluorescence camera. Other studies have explored preoperative administration of ICG, however this resulted in the absence of fluorescence signal during surgery [12,13]. Therefore, we opt for intraoperative administration of ICG. The added benefit of an intraoperative administration if the presence of a qualified anesthesiologist in the operation theatre. Should a rare anaphylactic reaction occur, specialized care is already present for the resuscitation of the patient, further minimizing patent risk.

Concomitant / Prohibited Medication / Treatment

Following drugs could possibly interact with indocyanine green and therefore are not compatible with the administration of the IMP:

Generic drug	Brand name in Belgium (as on 14th January 2021)
Anticonvulsants	- Brivaracetam (Briviact®) - Carbamazepine (Tegretol®) - Ethosuximide (Zarontin®) - Felbamate (Taloxa®) - Gabapentin (Gabapentine EG®; Gabapentine Mylan®; Gabapentine Sandoz®; Gabapentin Sandoz®; Neurontin®) - Lacosamide (Vimpat®) - Lamotrigine (Lambipol®; Lamictal®; Lamotrigine EG®) - Levetiracetam (Keppra®; Levetiracetam Sandoz®) - Oxacarbazepine (Oxacarbazepine Mylan®; Trileptal®) - Perampanel (Fycompa®) - Phenobarbital (Gardenal®; Phenobarbital Sodium Sterop®; Phenobarbital Sterop®) - Phenytoin (Diphantoine®)

	- Pregabalin (Lyrica®; Pregabaline Apotex®; Pregabaline EG®; Pregabaline Krka®; Pregabaline Mylan®; Pregabaline Teva®; Pregabaline Sandoz®) - Primidone (Mysoline®) - Rufinamide (Inovelon®) - Stiripentol (Diacomit®) - Tiagabine (Gabitril®) - Topiramate (Topamax®; Topiramate EG®; Topiramate Sandoz®) - Valproate (Depakine®; Valproate EG®; Valproate Mylan®; Valproate Sandoz®) - Vigabatrin (Sabril®) - Zonisamide (Zonegran®)
Bisulfite-containing compounds	- Danaparoïde (Orgaran®)
Cyclopropane	N/A
Fenobarbital	Gardenal®; Phenobarbital Sodium Sterop®; Phenobarbital Sterop®
Haloperidol	Haldol®
Heroin	N/A
Metamizol	Novalgine®
Methadone	Mephenon®
Morphine	MS Direct®; Morphine Teva®; MS Contin®; Morphine HCL Sterop®
Nitrofurantoine	Furadantine MC®
Opioid alkaloids	- Buprenorphine (Buphrenorphine Teva®; Temgesic®; Transtec®) - Fentanyl (Durogesic®; Fentanyl EG®; Fentanyl Sandoz®; Matrifen®) - Hydromorphone (Palladone®) - Oxycodone (Oxycodone Teva®; Oxycodon Sandoz®; OxyContin®; OxyNorm®; Targinact®) - Piritramide (Dipidolor®) - Tapentadol (Palexia®) - Tramadol (Contramal®; Dolzam®; Tradonal®, Tramadol EG®; Tramadol Krka®; Tramadol Sandoz®; Tramium®; Skudexa®; Algotra®; Pontalsic®; Tramadol / Paracetamol EG®; Tramadol / Paracetamol Krka®; Tramadol / Paracetamol Sandoz®; Tramadol / Paracetamol Teva®; Zaldiar®)
Pethidine	Pethisom®
Phenylbutazone	N/A
Probenecid	N/A
Rifampicin	Rifadine®

Study Procedures

Schedule of Events

Trial specific Procedures / Assessments

Procedures/ Assessment	Screening	Treatment Period	
Visits / Contacts	Visit 1	Surgery	Unscheduled Visit
Timing (weeks)		0	
Visit Window (days)	-28 Days to -1		
Informed consent	X [1]		
Inclusion / Exclusion criteria	X	X	
Demographics	X		
Medical, Surgical history	X		(X)
Physical examination	X		(X)
Weight / Height	X		(X)
Vital Signs	X		(X)
ECOG performance status	X		(X)
Haematology sampling	X		(X)
Coagulation sampling	X		(X)
Chemistry sampling	X		(X)
Urinalysis			(X)
Trial drug treatment (intravenous IMP)		X	
Trial drug dispensation (intravenous IMP)		X	
Trial drug accountability (intravenous IMP)		X	
Radiological Assessment: CT scan	(X)		(X)
Radiological Assessment: MRI scan	(X)		

Radiological Assessment: PET-CT scan	(X)		
Biomarker: CA-125	X		
Biopsy		X[2]	
Reason for discontinuation		X	
(Serious) Adverse event (S)(AE) assessment	X	X	X
Concomitant Medication (CM)	X	X	X

1 : Informed Consent be obtained prior to performing any other Trial-related procedures
2: Biopsies of the macroscopically visable peritoneal lesions is standard of care, the only difference will be the in vivo assessment of the flurorescense signal prior to resection.

Green = Standard of Care	Yellow = Specifically for the Trial

Expected Duration of the Trial

The expected duration of the Trial for a single participant will be one day since administration of the IMP will only occur during surgery and will not be repeated. If the participant does not show any allergic reaction, the Trial is concluded for this patient. Should an allergic reaction occur, the patient will be observed within the trial for the duration of the symptoms.
Since images will be taken during the procedure with the NIR fluorescence camera and this camera will be draped before incision, the total duration of the surgery will be a little bit longer than standard-of-care. However, we expect this delay will be minimal, since a thorough and careful examination of the entire abdomen is standard of care.
The expected duration of the Trial of one case will be until the definitive pathological report is finished, then the CRF will be closed. No long-term follow-up of the patient will be conducted for the patient within this trial. Results of the pathological examination resected during surgery will be included, however biopsies of a later date will not be included.
The duration of the entire Trial is expected to be two years after the start of inclusion of participants.

Participant consent and withdrawal of consent

The Trial will be conducted only on the basis of prior informed consent by the Trial participants and/or their legally authorized representative(s). As such, no Trial-related procedures will be conducted prior to obtaining written informed consent from potential Trial participants.
The process for obtaining and documenting initial and continued informed consent from potential Trial participants will be conducted in accordance with ICH-GCP E6(R2), applicable regulatory requirements and internal Standard Operating Procedures (SOPs).
All originally signed obtained Informed Consent Forms (ICFs) must be retained/archived in the Investigator Site File (ISF) at the Participating Site and must not be destroyed (even when a scanned copy is available) before expiration of the legal archiving term as defined in the protocol section entitled “Archiving”.
Participants may voluntarily withdraw consent to participate in the Trial for any reason at any time. The participant’s request to withdraw from the Trial must always be respected without prejudice or consequence to further treatment. Consent withdrawal will be documented in the participant’s medical record.
Trial data and samples collected before withdrawal can be used in the trial. No new trial data or samples will be collected after withdrawal of the participant.

Selection of Participants / Recruitment

Patients will be identified when booked for primary or interval debulking after multidisciplinary board review. All patients receiving this surgery are applicable for recruitment. Recruitment will happen by the gynaecological oncology department (GNC) of UZ Leuven.
Patients will be asked if they are willing to participate in this Trial and receive all required information. The patient can sign the ICF between the moment of requitement and just before surgery. When a participant is asked for participation, she will be screened for eligibility to participate in the Trial.
If a patient refuses participation, all patient data will be removed from the Trial. However, a failed recruitment statement without any patient identifiers will be kept.
No advertising materials nor patient brochures will be used in this Trial.

Randomization Procedure / Blinding

No randomization will be performed, all patients will receive identical therapy.
Since this is an open label Trial with a one-step surgical procedure, blinding is not applicable.

Unblinding

Since this is an open label Trial with a one-step surgical procedure, blinding is not used and as such unblinding is not applicable.

Premature discontinuation of Trial treatment

Participants may voluntarily discontinue from Trial treatment and/or prematurely end their participation in the Trial for any reason at any time. In such case the Investigator must make a reasonable effort to contact the participant (e.g., via telephone, e-mail, letter) in order to document the primary reason for this decision.
The Investigator may also decide at any time during the course of the Trial, to temporarily interrupt or permanently discontinue the Trial treatment if it is deemed that continuation would be detrimental to, or not in the best interest of the participant.
Similarly, the Sponsor, Ethics Committee or authorized regulatory authority can decide to halt or prematurely terminate the Trial when new information becomes available whereby the rights, safety and well-being of Trial participants can no longer be assured, when de integrity of the Trial has been compromised, or when the scientific value of the Trial becomes obsolete and/or unjustifiable.
Circumstances requiring premature treatment interruption or discontinuation of the Trial, include but are not limited to:

- Safety concerns related to IMP or unacceptable intolerability
- Trial participation while in violation of the inclusion and/or exclusion criteria
- Cancellation of surgery, either by the patient, by the surgeon or due to unforeseen problems.

In any such case of early Trial termination and/or treatment interruption/discontinuation, the Investigator will continue to closely monitor the participant's condition and ensure adequate medical care and follow-up. It is recommended that follow-up information will be collected as follows:

- Regular follow-up visits on the gynaecological oncology unit.
- No specific examinations are required to be done at End of Trial or during follow-up

For participants whose status is unclear because they fail to appear for Trial visits without stating an intention to discontinue or withdraw, the Investigator must make every effort to demonstrate "due diligence" by documenting in the source documents which steps have been taken to contact the participant to clarify their willingness and ability to continue their participation in the Trial (e.g., dates of telephone calls, registered letters, etc.).
A participant should not be considered lost to follow-up until due diligence has been completed.

Endpoints

Primary Endpoints

The primary objective of this Trial is to determine the diagnostic accuracy of ICG in visualizing peritoneal lesions of EOC *in vivo*. By using the NIR fluorescence camera, peritoneal malignant implants should be fluorescent after intravenous injection of ICG. Benign lesions should not be fluorescent after intravenous injection of ICG.

Secondary Endpoints

Secondary endpoints of this Trial are:

- Obtaining the false positive and false negative rate of *in vivo* ICG fluorescence signal by correlating these results with the pathological report.
- Determine the difference of estimated ICG uptake *in vivo* of peritoneal lesions between primary debulking and interval debulking.
- Correlation between the pre-operative radiographic examination(s) and the ICG signal *in vivo* and the pathological examination.
- Determination of the tumor-to-background ratio of fluorescence in peritoneal lesions, lymph nodes and other anatomical structures. Correlation of this ratio with the pathological examination.
- Assessment of the number and type of adverse effects, severe adverse effects and adverse reactions with the trial dose of the IMP.

Statistical Methods

Statistical analysis will be performed in accordance with ICH E9; a detailed description of the analysis is provided in the Trial-specific Statistical Analysis Plan (SAP). ICH E3 and E8 will guide the structure and content of the clinical trial report.

In this open-label Trial, classical methods to minimize bias such as randomization, blinding and compliance determination are not applicable. No active comparator is utilized in this Trial; therefore, randomization is not achievable. The surgeon cannot be blinded during this surgical procedure due to the intrinsic nature of the Trial. However, the surgeon must identify the target lesions before the usage of the NIR fluorescence camera, therefore selection bias will be minimized. Since the administration of the IMP is a single event and the administration of the IMP will occur intravenously by a licensed practitioner, compliance determination is futile.

However, for the secondary endpoint concerning the TBR, selection and/or confirmation bias is likely since the area of interest (i.e., tumor and background area's) must be determined manually. To minimize this risk, machine learning will be utilized if technically feasible. Trainable Weka Segmentation is an ImageJ plugin capable of machine learning, allowing to produce pixel-based segmentations of unknown data (i.e., the fluorescence images captured during surgery), available from https://imagej.net/Trainable_Segmentation. We will aim to produce a new learning algorithm for this plugin in order to allow the tool to select tumor and background rather than the investigator. This should greatly reduce bias.

Sample Size Determination

Approximately 60 patients will be screened for this Trial. In total, 40 patients will be assigned to Trial treatment. The Trial exists of 2 arms, each with 20 patients. These two arms are the primary debulking group and the interval debulking group. Approximately 40 participants will be evaluable to complete the Trial.

Based on the previous report by Veys *et al.*, a power calculation has been conducted [13]. Values were determined from the fluorescence positive peritoneal nodules: 72,6% for malignant nodules, 45,7% for benign nodules [13]. The Fisher's Exact test for an a priori power analysis for two independent

groups was utilized, with an alpha of 0,05 with a power of 95% and a two-tail analysis and a 1:1 allocation. A minimum of 184 peritoneal lesions must be included to achieve statistically significant results in each arm. In each arm of the Trial, we will aim to include 200 (10 lesions in 20 patients) peritoneal lesions. Since the study has two arms with potentially significant different rates of ICG positivity, we aim to obtain statistical power in each separate arm. As such we aim to include 400 (10 lesions in 2 times 20 patients) peritoneal lesions in this Trial. Should the number of usable lesions be less than expected, we can still obtain statistical significance when lowering power to 90% with an alpha of 0,05. As such, the minimum number of peritoneal lesions to achieve statistical significance is 148 in each arm.

Although clustering in participants could theoretically occur, we did not correct for this due to negligible clinical relevance. The location of the peritoneal lesion is more important than patient characteristics. Vascularization – and as such the uptake and retention of the IMP – is mainly determined by the anatomical location and the tumor characteristics. These tumor characteristics also vary very little between patients with HGSOC. Therefore, we do not expect clustering in 1 participant nor in 1 specific group of participants.

Statistical Analysis

The main object of statistical analysis will be to determine the diagnostic accuracy of ICG. Therefore, we will use simple descriptive statistical methods to determine sensitivity, specificity, positive predictive value, negative predictive value, accuracy and diagnostic odds ratio. To determine statistical significance, confidence intervals will be used. Sensitivity and specificity will be plotted on a receiver operating characteristic curve to further explore diagnostic accuracy. Since participants will only receive one administration of the IMP during surgery and afterward the Trial is ended for the participant, no longitudinal data will be analyzed.

For secondary endpoints, similar descriptive statistical analysis will be utilized, mainly contingency table related statistical tests to determine statistical significance for these unpaired categorical data points.

Interim analysis will be discussed below.

For all statistical tests, the significance level will be 0.05. Should a participant drop out due to inoperability, determination of inadequate abdominal visualization, or any other permissible reason, this participant will be accounted for in the statistical analysis with an intention-to-treat analysis.

Efficacy Analysis

Endpoint	Statistical Analysis Methods
Primary	Calculation of sensitivity, specificity, positive predictive value, negative predictive value, accuracy and diagnostic odds ratio.
Secondary	Contingency tables and their associated statistical test (e.g., Chi-squared test, Fisher's Exact test) will be utilized.
Exploratory	Not applicable

Other Analysis

Pharmacokinetic and pharmacodynamic analyses are not a part of this Trial since the IMP is a registered drugs and these properties are already known [7,10].

Interim Analysis and Final Database Lock

Although utilizing ICG in the detection of peritoneal lesions is still a very early technique and sensitivity for this technique varies greatly in literature (72%-100%), we wish not to perform an interim analysis [13,14]. Since the number of participants included in each Trial arm in total will be only 20 participants, an interim analysis with for example 10 participants will be too uncertain to indicate futility. Therefore, statistical analysis will be performed on each arm of the Trial when completed.

Final database lock will occur when both Trial arms have included 20 participants and each individual participant has fully completed follow-up (i.e., definitive pathological report has been obtained, and no adverse events have been registered).

Changes in Study Design or Conduct

None

Study Subjects

Disposition of Subjects

N°	Arm	Screened	Enrolled	Treated	Reason Exclusion
1	2	Yes	Yes	Yes	
2	2	Yes	Yes	Yes	
3	1	Yes	Yes	Yes	
4	2	Yes	Yes	Yes	
5	2	Yes	Yes	Yes	
6	2	Yes	Yes	Yes	
7	2	Yes	Yes	Yes	
8	2	Yes	Yes	Yes	
9	2	Yes	Yes	Yes	
10	1	Yes	Yes	Yes	
11	2	Yes	No	No	Participant utilizes one of the interacting drugs listed in the protocol
12	2	Yes	Yes	Yes	
13	2	Yes	Yes	Yes	
14	2	Yes	Yes	Yes	

Arm 1 = Primary Debulking; Arm 2 = Interval Debulking

Demographics

	Primary Debulking (n=2)	Interval Debulking (n= 11)
Age (mean)	72.5	56.4
Body Mass Index (kg/m2) (mean)	31.7	26.1
FIGO stage of ovarian cancer		
IIIc (n,%)	1 (50.0%)	3 (27.3%)
IV (n,%)	1 (50.0%)	8 (72.7%)
Most recent CA-125 (kU/L) (mean)	149.5	34.6
Preoperative chemotherapy regimen		
Paclitaxel & Carboplatin (PC) (n,%)	0	9 (81,8%)
PC + bevacizumab (n,%)	0	1 (9,1%)
PC + pembrolizumab (n,%)	0	1 (9,1%)
Reason for Interval Debulking		
High intra-abdominal tumor load (n,%)	0	5 (45.5%)
Extra-abdominal tumor load (n,%)	0	6 (54.6%)
Unresectable lesions (n,%)	0	3 (27.3%)

Protocol Deviations

None

Efficacy Results

Primary Efficacy Results

Since in the Primary Debulking group only one patient had lesions assessed, we opted to not calculate any efficacy results since this cannot truly reflect a population. As such, both primary as secondary efficacy results depict only the group with an interval debulking.

	Primary Debulking (n=2)	Interval Debulking (n= 11)
Final pathology shows HGSOC (n,%)	2 (100.0%)	9 (81,8%)
Number of assessed lesions per participant (n,%)		
0	1 (50.0%)	1 (9,1%)
5	0	1 (9,1%)
6	0	1 (9,1%)
7	0	1 (9,1%)
8	1 (50.0%)	2 (18,2%)
10	0	5 (45.5%)
Sensitivity (95%CI)	Not calculated	70.7% (54.5 - 83.9%)
Specificity (95%CI)	Not calculated	34.9% (21.0 - 50.9%)
Positive Predictive Value (95%CI)	Not calculated	50.9% (43.6 - 58.2%)
Negative Predictive Value (95%CI)	Not calculated	55.6% (40.0 - 70.1%)
Accuracy (95%CI)	Not calculated	52.4% (41.2 - 63.4%)
Diagnostic odds ratio (95%CI)	Not calculated	1.30 (0.52 - 3.25)

Secondary Efficacy Results

False positive and false negative rate of *in vivo* ICG fluorescence signal by correlating these results with the pathological report

	Primary Debulking (n=2)	Interval Debulking (n= 11)
False positive rate	Not calculated	65.1%
False negative rate	Not calculated	29.3%

Difference of estimated ICG uptake *in vivo* of peritoneal lesions between primary debulking and interval debulking

This was not calculated due to the insignificant number of peritoneal lesions in the primary debulking group.

Correlation between the pre-operative radiographic examination(s) and the ICG signal *in vivo* and the pathological examination.

This was not calculated due to the futility of the technique.

Determination of the tumor-to-background ratio of fluorescence in peritoneal lesions, lymph nodes and other anatomical structures. Correlation of this ratio with the pathological examination.

This was not calculated due to the futility of the technique.

Assessment of the number and type of adverse effects, severe adverse effects and adverse reactions with the trial dose of the IMP.

Please see “Safety Results” on page 26.

Safety Results

Duration of exposure to the IMP

	Primary Debulking (n=2)	Interval Debulking (n= 11)
Duration of exposure to the IMP	1 day	1 day
Unscheduled visits before EoT	0	0

Adverse Events

	Primary Debulking (n=2)	Interval Debulking (n= 11)
No Adverse Events	1	9 participants
Hypertension	1 instance	
Ileus	1 instance	
Pleural effusion	1 instance	

Hypertension

Participant 1

Surgical Complication	No
Clavien-Dindo classification	/
"d" suffix applicable	/
CTCAE term	Hypertension
CTCAE grade	3
MedDRA LLT	Hypertension worsened
Outcome	Recovered
Action taken	- Medication: Additional antihypertensive drugs
Action taken regarding study treatment	No action taken
Severity	Mild
Causality to IMP	Unlikely
Causality to study procedure	No

Ileus

Participant 1

Surgical Complication	Yes
Clavien-Dindo classification	I
"d" suffix applicable	No
CTCAE term	Ileus
CTCAE grade	3
MedDRA LLT	Ileus
Outcome	Recovered
Action taken	- Medication: IV rehydratation - Non-drug therapy: Tube placement
Action taken regarding study treatment	No action taken
Severity	Moderate
Causality to IMP	Not Related
Causality to study procedure	No

Pleural effusion

Participant 1

Surgical Complication	No
Clavien-Dindo classification	/
"d" suffix applicable	/
CTCAE term	Pleural effusion
CTCAE grade	3
MedDRA LLT	Malignant pleural effusion
Outcome	Recovered
Action taken	- Non-drug therapy: Pleurodesis - Further investigations performed
Action taken regarding study treatment	No action taken
Severity	Moderate
Causality to IMP	Unlikely
Causality to study procedure	No

Serious Adverse Events

	Primary Debulking (n=2)	Interval Debulking (n= 11)
No Serious Adverse Events	1 participant	9 participants
Acute kidney injury		1 instance
Gastrointestinal anastomotic leak		1 instance
Lung infection		1 instance
Respiratory failure		2 instances

Acute kidney injury

Participant 1

Surgical Complication	Yes
Clavien-Dindo classification	IVa
"d" suffix applicable	Yes
CTCAE term	Acute kidney injury
CTCAE grade	4
MedDRA LLT	Stage 3 acute kidney injury
Outcome	Not yet recovered
Action taken	- Non-drug therapy: Dialysis - Further investigation performed
Action taken regarding study treatment	No action taken
Reason for Serious Adverse Event	- Is life-threatening - Results in persistent or significant disability/incapacity - Requires or prolongs in patient hospitalization - Is considered as an important medical event
Severity	Severe
Causality to IMP	Unlikely
Causality to study procedure	No

Gastrointestinal anastomotic leak

Participant 1

Surgical Complication	Yes
Clavien-Dindo classification	V
"d" suffix applicable	Yes
CTCAE term	Gastrointestinal anastomotic leak
CTCAE grade	5
MedDRA LLT	Anastomotic leak
Outcome	Fatal
Action taken	- Non-drug therapy: Surgery
Action taken regarding study treatment	No action taken
Reason for Serious Adverse Event	- Resulted in death - Is life-threatening - Results in persistent or significant disability/incapacity - Requires or prolongs in patient hospitalization - Is considered as an important medical event
Severity	Severe
Causality to IMP	Not Related
Causality to study procedure	No

Lung infection

Participant 1

Surgical Complication	No
Clavien-Dindo classification	/
"d" suffix applicable	/
CTCAE term	Lung infection
CTCAE grade	5
MedDRA LLT	Pneumonia necrotizing
Outcome	Fatal
Action taken	- Medication: Antibiotics - Non-drug therapy: Intubation
Action taken regarding study treatment	No action taken
Reason for Serious Adverse Event	- Resulted in death - Is life-threatening - Results in persistent or significant disability/incapacity - Requires or prolongs in patient hospitalization - Is considered as an important medical event
Severity	Severe
Causality to IMP	Unlikely
Causality to study procedure	No

Respiratory failure

Participant 1

Surgical Complication	No

Clavien-Dindo classification	/
"d" suffix applicable	/
CTCAE term	Respiratory failure
CTCAE grade	5
MedDRA LLT	Respiratory failure
Outcome	Fatal
Action taken	- Medication: Antibiotics - Non-drug therapy: Intubation
Action taken regarding study treatment	No action taken
Reason for Serious Adverse Event	- Resulted in death - Is life-threatening - Results in persistent or significant disability/incapacity - Requires or prolongs in patient hospitalization - Is considered as an important medical event
Severity	Severe
Causality to IMP	Unlikely
Causality to study procedure	No

Participant 2

Surgical Complication	No
Clavien-Dindo classification	/
"d" suffix applicable	/
CTCAE term	Respiratory failure
CTCAE grade	4
MedDRA LLT	Respiratory failure
Outcome	Recovered
Action taken	- Non-drug therapy: Intubation
Action taken regarding study treatment	No action taken
Reason for Serious Adverse Event	- Is life-threatening - Results in persistent or significant disability/incapacity - Requires or prolongs in patient hospitalization - Is considered as an important medical event
Severity	Severe
Causality to IMP	Unlikely
Causality to study procedure	No

Deaths or Suspected Unexpected Serious Adverse Reactions

	Primary Debulking (n=2)	Interval Debulking (n= 11)
Deaths		1 participant
Suspected Unexpected Serious Adverse Reactions		0

Death

Participant 1

Cause of death	- Respiratory failure - Lung infection - Gastrointestinal anastomotic leak
Causality to IMP	Unlikely
Causality to study procedure	No

Safety Conclusions

No Adverse Events, Serious Adverse Events, Deaths or Suspected Unexpected Serious Adverse Reactions could be linked to the IMP or the study procedure with a probability higher than “unlikely”.

Pharmacokinetics/Pharmacodynamics

Not applicable

Discussion and Overall Conclusions

Summary of Key Findings

The study aimed to evaluate the diagnostic accuracy of Indocyanine Green (ICG) [the IMP] in visualizing peritoneal lesions of epithelial ovarian cancer (EOC) during primary and interval debulking surgeries. The primary endpoint was to determine the sensitivity and specificity of ICG in identifying malignant peritoneal implants. The study aimed to include 40 patients, divided into two arms: primary debulking and interval debulking. However, due to futility, the study was terminated prematurely with only 2 participants inclued in the primary debulking arm and 11 in the interval debulking arm.
Key findings indicated a sensitivity of 70.7% and a specificity of 34.9% for ICG in the interval debulking group. The positive predictive value was 50.9%, and the negative predictive value was 55.6%.

Interpretation of Results

The results demonstrate that ICG, when used with near-infrared (NIR) fluorescence imaging, has moderate sensitivity but low specificity in detecting malignant peritoneal lesions during interval debulking surgery. The high false positive rate suggests that while ICG can identify malignant lesions, it also highlights benign lesions, which could lead to unnecessary resections and therefore makes this additional step in the surgical proces futile. This finding is consistent with previous studies that reported variability in the diagnostic accuracy of ICG fluorescence imaging.

Strengths and Limitations of the Study

Strengths

- The study design included a well-defined patient population with advanced-stage EOC, ensuring relevance to clinical practice.
- The use of a standardized protocol for ICG administration and NIR fluorescence imaging provided consistency in data collection.
- The correlation of fluorescence signals with pathological findings allowed for a robust assessment of diagnostic accuracy.

Limitations

- The small sample size, particularly in the primary debulking group, limited the statistical power and generalizability of the findings.
- The open-label design may have introduced selection bias, as surgeons identified target lesions before using the NIR fluorescence camera.
- The low specificity and high false positive rate indicate a need for further refinement of the technique or additional imaging modalities to improve diagnostic accuracy.

Benefit-Risk Assessment

The use of ICG for intraoperative imaging in EOC surgeries presents a moderate benefit in terms of sensitivity but poses a risk of unnecessary resections due to low specificity. The overall benefit-risk profile suggests that while ICG can aid in identifying malignant lesions, its use should be complemented with other diagnostic tools to minimize false positives and improve surgical outcomes.

Conclusions

The study concludes that ICG fluorescence imaging has potential as an adjunctive tool for visualizing malignant peritoneal lesions in EOC surgeries. However, its diagnostic accuracy is limited by a high false positive rate and therefore without any clear added value during the surgical proces.

Future research should focus on optimizing the technique, possibly by combining ICG with other imaging modalities, to enhance specificity and overall diagnostic performance. The findings underscore the importance of a multimodal approach to improve the precision of surgical interventions in advanced-stage EOC.

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Appendices

1. Documentation of Ethical Review Board/Independent Ethics Committee (ERB/IEC) approvals.
2. Study Protocol Including Data Management Plan (DM
3. Sample Case Report Form (CRF)

UZ LEUVEN

Coronavirus - COVID-19

Check altijd eerst de meest recente richtlijnen voor raadplegingen, functiemetingen, (dag)opnames, bezoek of vaccinaties.

Bekijk de richtlijnen

Ethische commissie onderzoek

Ledenlijst EC onderzoek

Ledenlijst en openbare belangenverklaringen

- Prof. Minne Casteels (voorzitter)
- Prof. Dominique Bullens (ondervoorzitter)
- Prof. Ariel Alonso Abad (plaatsvervanger)
- Prof. Pascal Borry
- Prof. Guy Bosmans
- Prof. Xavier Bossuyt
- Prof. Simon Brumagne
- Ms. Michèle Dekervel (plaatsvervanger)
- Mr. Jean-Jacques Derèze
- Dr. Lut De Groote
- Ms. Theresia De Fraye
- Prof. Jan de Hoon

- Mr. Aernout De Raemaeker (plaatsvervanger)
- Ms. Lia De Wilde (plaatsvervanger)
- Pharm. Erwin Dreesen (plaatsvervanger)
- Prof. André Loeckx (plaatsvervanger)
- Prof. Koen Luyckx (plaatsvervanger)
- Prof. Ben Nemery
- Dr. Marleen Renard
- Ms. Angélique Rézer (plaatsvervanger)
- Prof. Maria Schetz
- Prof. Karin Sipido
- Prof. Anne Smits
- Mr. Mathijs Swaak
- Pharm. Josse R. Thomas
- Prof. Anne Uyttebroeck (plaatsvervanger)
- Ms. Liliane Vandergeeten (plaatsvervanger)
- Ms. Annick Vanclooster
- Ms. Marilien Vandeputte
- Pharm .Veerle Vanparys
- Prof. Ben Van Calster
- Dr. Kristel Van Landuyt
- Ms. Katelijne Van Overwalle (plaatsvervanger)
- Prof. Jan Verhaegen
- Prof. Gregor Verhoef

Laatste aanpassing: 17 februari 2021

contact
Nancy Trolin
Nancy.trolin@uzleuven.be
tel. +32 16 344634
fax +32 16 344629

campus Gasthuisberg

To whom it may concern

Uw bericht van	Uw kenmerk	Ons kenmerk SD/TVG	Leuven June 30th, 2021

Subject: Visualisation of Indocyanine Green in Primary and Interval Debulking for Ovarian Cancer / VIPIDO
Cover Letter - EudraCT number: 2021-002449-13

Dear Madam,
Dear Sir,

We wish to submit this monocentric academic therapeutic exploratory Trial. We wish to explore the diagnostic usage of indocyanine green (ICG) (an already registered IMP with Marketing Authorisation) in the diagnosis of peritoneal lesions of epithelial ovarian cancer. In this Phase II Trial the aim is to replicate previous studies where ICG had been used with the same dosing intravenously to visualize peritoneal lesions in epithelial ovarian cancer [1]. However, we expand the potential usage of the IMP by exploring the entire abdominal cavity and explore the retroperitoneum and its lymph nodes. Furthermore, we correlate preoperative imaging with the surgical findings and the influence of the IMP on these findings. We wish to visualise peritoneal lesions of epithelial ovarian cancer in both primary and interval debulking surgery by using intravascular ICG) and near-infrared light. The primary research question is if ICG is capable to correctly visualize peritoneal lesions of epithelial ovarian cancer *in vivo* in both primary and interval debulking surgery. We hypothesize the ICG will adequately visualise malignant peritoneal implants of epithelial ovarian cancer. Furthermore, we hypothesized that fibrotic lesions would retain less or no ICG and therefore emit a different fluorescence signal than the malignant implants.
We summarised all required datapoints in the table below. In the CTA folder the protocol with the required appendices is provided.

The IMP utilised in this Trial is ICG, registered in Belgium under Verdye®. Verdye® is manufactured and licensed for the Belgian market by Diagnostic Green GmbH (Otto-Hahn-Str. 20, 85609 Aschheim-Dornach, Germany). The Summary of Product Characteristics is provided within this CTA folder. Indocyanine green has already been utilised an approved for decades in diagnostics. However, in this Trial we wish to utilise the IMP as an off-label drugs, allowing to visualise peritoneal lesions and retroperitoneal lymph nodes during surgery for high-grade serous ovarian cancer.
We will not utilise any NIMP in this Trial.

Since this Trial is a non-commercial monocentric study, utilising an IMP with MA in Belgium, we did not provide an Investigator's Brochure. However, the usage of the IMP is off label, since intra-operative intra-abdominal visualisation of peritoneal lesions and lymph nodes is not a part of the MA. Therefore, we wish to complement the SmPC with a summary of relevant clinical data to comply with the Directive. In abdominal surgery, the off label ICG has been extensively utilised in the mapping of sentinel lymph nodes and visualisation of tumours [1–3]. Sentinel lymph nodes has been identifies using the IMP in oesophageal, gastric, colorectal, bladder, prostate, cervical, and endometrial cancer. Even in ovarian cancer, ICG has been successfully utilised to identify the sentinel lymph node [4]. Studies of liver tumours, peritoneal carcinomatosis and adrenal tumours have proven to be effective in visualising tumour tissue while maintaining save results for participants, even in higher doses than utilised in this Trial (up to 0,5mg/kg) [2]. A similar Belgian study as the Trial here presented demonstrated clinical effectiveness of visualising peritoneal metastases in locally advanced ovarian cancer, reporting an *ex* vivo sensitivity of 72.6% [5]. This study utilised the same dose of the IMP that we propose (0,25mg/kg) and did not report any serious adverse events [5]. Tummers *et al.* even reported an *in vivo* sensitivity of 100% in patients with ovarian cancer [6]. In a systematic review, the sensitivity of ICG in the detection of peritoneal carcinomatosis of various cancers, proved to range between 72.5 to 100% [7]. Of great clinical relevance, the utilisation of ICG changed the planned intervention in 25-29% of patients in the trials who reported these events [7]. As such, the utilisation of the IMP has been proven to be clinically effective in numerous studies and patients, even in patients with ovarian cancer.

Since this Trial is a non-commercial monocentric study, utilising an IMP with MA in Belgium, we did not provide an Investigational Medicinal Product Dossier. However, the SmPC is provided in the CTA folder. Furthermore, we did not request Scientific Advice since the IMP has a MA and has been utilised both in clinical practice and clinical trials for decades, as such most properties are well known.

The Reference Safety Information of this IMP can be found in the SmPC on page 5.
We wish to request waiver for the labeling of the IMP. This IMP has MA and will be utilised in its unchanged form and packaging as per MA. The IMP will be administered on site only. The participants cannot handle the product at any phase. The clinical team understands the nation language(s) used on the label and the SmPC attached. Furthermore, administration of the IMP is unblinded. The protocol fully complies with dosing, handling, processing, and discarding the IMP as stated in the SmPC, as such we wish to request a waiver for the labeling of the IMP.

In this Trial, only standard of care tissue and blood samples will be taken, no additional samples must be procured within the context of the Trial. As such, all samples will be following normal per protocol clinical workflow of the laboratories of University Hospitals Leuven (UZ Leuven). These laboratories adhere to Good Laboratory Practice. Both the anatomopathological laboratory as the general laboratories comply with RIZIV and ISO standards.

This Trial has simultaneously been submitted to the Ethic Committee of University Hospitals Leuven (UZ Leuven). When approval has been granted, this file will be submitted as soon as available.

We would like to thank Your consideration and efforts made towards approval of our Trial.

Yours Sincerely,

Toon VAN GORP, MD, PhD
Department of Gynaecological Oncology
University Hospitals Leuven (UZ Leuven)
Herestraat 49, B-3000 Leuven, Belgium
E-mail: toon.vangorp@uzleuven.be
Telephone number: +32 16 34 47 50

OVERVIEW

General information	
Title of clinical Trial («Trial»)	Visualisation of Indocyanine Green in Primary and Interval Debulking for Ovarian Cancer
Protocol Short Title Acronym	VIPIDO
Version number and date	1-2 / 30-06-2021
Trial Phase (I, II, III, IV)	Phase II
Sponsor name	University Hospitals Leuven (UZ Leuven)
Coordinating Investigator	Toon VAN GORP, MD, PhD
Contact Address CI	Herestraat 49, B-3000 Leuven, Belgium
Contact Email CI	toon.vangorp@uzleuven.be
Contact Phone CI	+32 16 34 47 50
UZ Leuven number	S65525
EudraCT number	2021-002449-13
ClinicalTrials.gov number	NCT04891185
Additional information	
Specific features of the Trial	None
Clinical trial with special population	Not applicable
First-in-man administration of a new active substance	Not applicable
Scientific advice related to the IMP	Not applicable
Part of a Paediatric Investigation Plan	No
Usage of narcotic or psychotropic substance	No
Re-submission	Not applicable, first submission
Manufacturing sites in Belgium of the IMP	None
NIMP	None
Exploratory trial	No
Radiopharmaceuticals	None
Additional documents	
Manufacturing authorization	Please see SmPC, manufacturing authorisation granted to Diagnostic Green GmbH (Otto-Hahn-Str. 20, 85609 Aschheim-Dornach, Germany).
Declaration of the Qualified Person	Not applicable, IMP with MA
GMP certificate	Not applicable, IMP with MA
Import authorization	Not applicable, IMP with MA
Viral safety studies	Not applicable, IMP with MA
TSE certificates	Not applicable, IMP with MA

LIST OF ABBREVIATIONS

Abbreviation	Definition
CTA	Clinical Trial Application
IB	Investigator's Brochure
ICG	Indocyanine green
IMP	Investigational Medicinal Product
MA	Market Authorisation
MA	Market Authorisation
NIMP	Non-Investigational Medicinal Product
SmPC	Summary of Product Characteristics

REFERENCES

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[2] van Manen L, Handgraaf HJM, Diana M, Dijkstra J, Ishizawa T, Vahrmeijer AL, et al. A practical guide for the use of indocyanine green and methylene blue in fluorescence-guided abdominal surgery. J Surg Oncol 2018;118:283–300. https://doi.org/10.1002/jso.25105.

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[6] Tummers QRJG, Hoogstins CES, Peters AAW, de Kroon CD, Trimbos JBMZ, van de Velde CJH, et al. The Value of Intraoperative Near-Infrared Fluorescence Imaging Based on Enhanced Permeability and Retention of Indocyanine Green: Feasibility and False-Positives in Ovarian Cancer. PLoS One 2015;10:e0129766. https://doi.org/10.1371/journal.pone.0129766.

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Leuven, 30 Jul 2021

Ethics Committee
Research UZ/KU Leuven
Herestraat 49
B 3000 Leuven (Belgium)
Tel +32 16 34 86 00
Email : ec@uzleuven.be

prof. dr. Toon Van Gorp
GYNAECOLOGIE-VERLOSKUNDE

Our reference:	EudraCT-nr:	Belg. Regnr:
S65525	2021-002449-13	

Visualisation of Indocyanine Green in Primary and Interval Debulking for Ovarian Cancer.

Positive advice in accordance with the law of 7 May 2004 on experiments on the human person

Dear colleague

The Ethics Committee Research (EC Research) of University Hospitals Leuven (UZ Leuven) has examined and discussed the above mentioned dossier at its meeting of 12 Jul 2021.

After having consulted the additional information and/or adapted documents relating to this dossier, EC Research considers that the proposed study, as described in the protocol, is scientifically relevant and ethically justified. It therefore gives on 30 Jul 2021 a favourable opinion of this study.

EC Research emphasizes the responsibility of the PI/promotor of this study concerning the privacy of the person/patient data in contacts with patients, or when viewing patient data, including the correct implementation thereof by coworkers and students. The PI/promotor is responsible for the implementation of the project proposal in accordance with applicable laws and regulations including, but not limited to, the EU regulation 2016/679 (General Data Protection Regulation), the Belgian Law on patients' rights of 22/8/2002, and the policy of the institution where the research will be carried out.

EC Research refers to the ICH/GCP guidelines on its website, and confirms that a GCP-training is required from each investigator. It is the responsibility of the principal investigator that each member of the study team has a valid GCP-certificate.

For the assessment of this dossier, documents/answers submitted on 01 Jul 2021 have

been taken into account.

The favourable advice concerns:

Protocol:
Version 1-3 dd 28Jul2021
Informed Consent Form:
ICF version I-3 dd 28Jul2021 Nl
Investigator's brochure/scientific leaflet:
SmPC Verdye version Feb2016
Proof of "no-fault" insurance cover:
Policy period: 01Jan2021 - 31Dec2021
GDPR questionnaire:
Submitted on 23Jul2021

EC Research confirms working in accordance with the ICH-GCP principles (International Conference on Harmonization Guidelines on Good Clinical Practice), the latest version of the Declaration of Helsinki, the Oviedo Convention on Human Rights and Biomedicine and applicable laws and regulations.

EC Research confirms that - in case of conflict of interest - involved members do not take part in the vote concerning the study.

List of members: see appendix.

Points of concern: (if applicable)

The conformity of translated documents compared to the Dutch documents, is the responsibility of the sponsor.

We would like to draw your attention to the fact that EC Research expects her initial comments to be taken into account ab initio at the next submission by the same sponsor.

*Provided that there is a **Clinical Trial Agreement**, the study can only start when the Clinical Trial Agreement has been approved and signed by the CEO of UZ Leuven (and/or by an authorized representative of KU Leuven R&D).*

Studies with investigational medicinal products and certain studies with "medical devices" should be submitted by the client (PI or sponsor) to the FAMHP (Federal Agency for Medicines and Health Products).

Studies with investigational medicinal products are only allowed to be conducted, provided that the minister (FAMHP) does not state objections within legal deadlines as described in art. 13 of the Belgian law of 7/5/2004 concerning experiments on human people.

Certain studies using medical devices are also covered by legal deadlines (KB of 17/3/2009). Please consult the FAMHP website for more information: www.fagg-afmps.be.

Research on embryos in vitro is covered by the law of May 11, 2003. Before the research project can start, such research also requires a positive advice of the Federal Committee for medical and scientific research on embryos in vitro.

Please take into account the regulations of the hospital concerning tissue management and the regulations of the law of December 19, 2008.
This favourable advice of EC Research does not imply that it will assume responsibility for the planned study. You will remain responsible for the study. In addition, you should ensure that your opinion as an involved researcher is reproduced in publications, reports for the government, etc. which are the result of this study. You are reminded that concerning clinical studies, any observed serious event needs to be reported immediately to the sponsor and the ethics committee, even if the causal relationship with the study is unclear.

The EC approval given for a specific project, is valid for one year. We request you to inform us if the study will not be initiated or if the study does not start within 1 year after approval.

If the study will not be terminated within a year, the ICH-GCP demands that an ***annual progress report*** *will be provided to EC Research.*

Finally, we request you to report the termination (early or planned) of the study within the legal deadlines and provide the ***Clinical Study Report*** *(CSR) to EC Research.*

In case of a clinical trial (EudraCT), please be informed that the results must be published in the European Clinical Trial Register. The report of these results can be sent to the EC Research as the CSR.

Yours sincerely,

Prof. Dr. Minne Casteels
Chair
Ethics Committee Research UZ Leuven

Cc:
FAMHP (Federal Agency for Medicines and Health Products)

CTC (Clinical Trial Center UZ Leuven)

List of members EC Research UZ/KU Leuven

Chair	prof. dr. Maria-Reinhilde Casteels	Clinical Pharmacology
Vice chair	prof. dr. Dominique Bullens	Paediatrics
	De heer Aernout De Raemaeker	Medical Legislation alternate
	De heer Jean-Jacques Derèze	Medical Legislation alternate
	De heer Mathijs Swaak	Healthy volunteer repres.
	Mevr. Angélique Rézer	Medical Legislation alternate
	Mevr. Annick Vanclooster	Nurse
	Mevr. Katelijne Van Overwalle	Pt representative (alternate)
	Mevr. Lia De Wilde	Pt representative (alternate)
	Mevr. Liliane Vandergeeten	Pt representative (alternate)
	Mevr. Marilien Vandeputte	Nurse
	Mevr. Michèle Dekervel	Medical Legislation alternate
	Mevr. Teresia De Fraye	Pt representative
	Mevr. Veerle Vanparys	Pharmacist (alternate)
	apr. Josse R. Thomas	Clinical Pharmacology
	dr. Erwin Dreesen	Pharmacist (alternate)
	dr. Kristel Van Landuyt	Reumatology
	dr. Lut De Groote	General Practitioner
	dr. Marleen Renard	Paediatrics
	prof. André Loeckx	Pt representative (alternate)
	prof. Ben Van Calster	Statistics
	prof. Guy Bosmans	Clinical Psycology (alternate)
	prof. Pascal Borry	Ethics
	prof. dr. Anne Smits	Paediatrics
	prof. dr. Anne Uyttebroeck	Paediatrics
	prof. dr. Ariel Alonso	Statistics (alternate)
	prof. dr. Benoit Nemery	Pneumology
	prof. dr. Gregor Verhoef	Haematology
	prof. dr. Jan Verhaegen	Laboratory Medicine
	prof. dr. Jan de Hoon	Clinical Pharmacology
	prof. dr. Karin Sipido	Experimental Cardiology
	prof. dr. Koen Luyckx	Clinical Psycology (alternate)
	prof. dr. Maria Schetz	Intensive care
	prof. dr. Simon Brumagne	Physiotherapy
	prof. dr. Xavier Bossuyt	Immunology

contact
Nancy Trolin
Nancy.trolin@uzleuven.be
tel. +32 16 344634
fax +32 16 344629

campus Gasthuisberg

To whom it may concern

Uw bericht van	Uw kenmerk	Ons kenmerk SD/TVG	Leuven June the 30th, 2021

Subject: Visualisation of Indocyanine Green in Primary and Interval Debulking for Ovarian Cancer / VIPIDO
Cover Letter - S-number: S65525

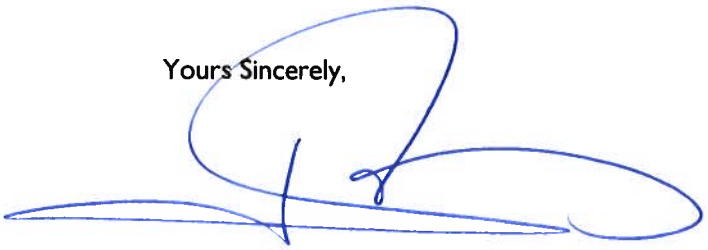
Dear Chair of the Ethics Committee Research,

We wish to submit this monocentric academic therapeutic exploratory Trial for your review. We wish to explore the diagnostic usage of indocyanine green (ICG) (an already registered IMP with Marketing Authorisation) in the diagnosis of peritoneal lesions of epithelial ovarian cancer. In this Phase II Trial the aim is to replicate previous studies where ICG had been used with the same dosing intravenously to visualize peritoneal lesions in epithelial ovarian cancer. However, we expand the potential usage of the IMP by exploring the entire abdominal cavity and explore the retroperitoneum and its lymph nodes. Furthermore, we correlate preoperative imaging with the surgical findings and the influence of the IMP on these findings. We wish to visualise peritoneal lesions of epithelial ovarian cancer in both primary and interval debulking surgery by using intravascular ICG) and near-infrared light. The primary research question is if ICG is capable to correctly visualize peritoneal lesions of epithelial ovarian cancer *in vivo* in both primary and interval debulking surgery. We hypothesize the ICG will adequately visualise malignant peritoneal implants of epithelial ovarian cancer. Furthermore, we hypothesized that fibrotic lesions would retain less or no ICG and therefore emit a different fluorescence signal than the malignant implants.

This Trial will be conducted monocentric in University Hospitals Leuven (UZ Leuven). The surgeons participating in the Trials are clinical staff members of the department of Gynaecological Oncology. The coordinating investigator is prof. dr. Toon Van Gorp. Attached you will find a Table of Contents, numbering all required documents. Where applicable, the necessary files were separately uploaded in your online submission form. We do not report any conflicts of interest.

We would like to thank Your consideration and efforts made towards approval of our Trial.

Yours Sincerely,



Toon VAN GORP, MD, PhD
Department of Gynaecological Oncology
University Hospitals Leuven (UZ Leuven)
Herestraat 49, B-3000 Leuven, Belgium
E-mail: toon.vangorp@uzleuven.be
Telephone number: +32 16 34 47 50

UZ LEUVEN

KU LEUVEN

CLINICAL TRIAL PROTOCOL

Visualisation of Indocyanine Green in Primary and Interval Debulking for Ovarian Cancer

Acronym: VIPIDO

Version number: 1-3 – **Date** 28/07/2021

Internal ref. Nbr: S65525

EudraCT Nbr: 2021-002449-13

ClinicalTrials.gov Nbr: NCT04891185

Sponsor

University Hospitals Leuven (UZ Leuven)

Herestraat 49, B-3000 Leuven, Belgium

Coordinating Investigator

Toon VAN GORP, MD, PhD

LIST OF PARTICIPATING SITES

List Of Participating Sites	Principal Investigator
University Hospitals Leuven (UZ Leuven) Herestraat 49, B-3000 Leuven, Belgium	Toon VAN GORP, MD, PhD

SIGNATURES

Title: Visualisation of Indocyanine Green in Primary and Interval Debulking for Ovarian Cancer

Acronym: VIPIDO

The undersigned confirm that the above referenced protocol has been acknowledged and accepted, and agree to conduct the Trial in compliance with the approved protocol, and will adhere to: the principles outlined in the requirements for the conduct of clinical trials in the EU as provided for in Directive 2001/20/EC or the EU Clinical Trial Regulation 536/2014 (as soon as in effect) and any subsequent amendments thereto, the ICH guidelines, the most recent version of the Declaration of Helsinki, the Belgian law of May 7th 2004 regarding experiments on the human person (as amended) or the Belgian law of May 7th 2017 related to clinical trials on medicinal products for human use (as soon as in effect), the EU General Data Protection Regulation 2016/679 (GDPR), relevant Belgian laws implementing the GDPR, the Belgian Law of August 22nd 2002 on patient rights, and any other regulatory requirements and Standard Operating Procedures (SOPs), as applicable.

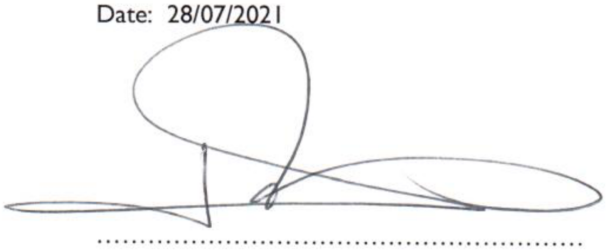
The undersigned agree not to disclose the confidential information contained in this document for any purpose other than the evaluation or conduct of the Trial, without prior written consent of the Sponsor.

The undersigned also commit to making the findings of the Trial publicly available through publication and/or other dissemination tools, in accordance with this protocol and applicable regulations, without any unnecessary delay and to provide an honest, accurate and transparent account of the Trial; and to explain any discrepancies or deviations from the approved Trial protocol.

Coordinating Investigator/Principal Investigator

prof. dr. VAN GORP Toon

Date: 28/07/2021



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Signature

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
APR	Annual Progress Report
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Coordinating Investigator
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CM	Concomitant Medication
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
DMP	Data Management Plan
DPA	Data Processing Annex
DSMB	Data Safety Monitoring Board
DSUR	Development Safety Update Report
DTA	Data Transfer Agreement
EC	Ethics Committee
ECG	Electrocardiogram
(e)CRF	(electronic) Case Report Form
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOC	Epithelial ovarian cancer
EoT	End of Trial
EPR	Enhanced permeability and retention
ESGO	European Society of Gynaecological Oncology
EU	European Union
FIGO	International Federation of Gynaecology and Obstetrics
FPFV	First Patient First Visit
GCP	Good Clinical Practice (latest version of ICH E6)
GDPR	General Data Protection Regulation
IB	Investigator's Brochure
ICF	Informed Consent Form
ICG	Indocyanine green
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ISF	Investigator Site File
JCI	Joint Commission International
LPLV	Last Patient Last Visit
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MP	Monitoring Plan
MRI	Magnetic resonance imaging
NIR	Near-infrared
PET-CT	Positron emission tomography–computed tomography
PI	Principal Investigator (Participating Site)
PRO	Patient Reported Outcome
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBR	Tumour-to-background ratio
TMF	Trial Master File

FUNDING AND SUPPORT

No funding was received for this Trial.

Financing for the IMP will be provided by the funds of the Principle Investigator.

No reimbursement isprovided for participants. Since no additional travels are required of the participants for this Trial, travel expenses are not reimbursed.

ROLES AND RESPONSIBILITIES

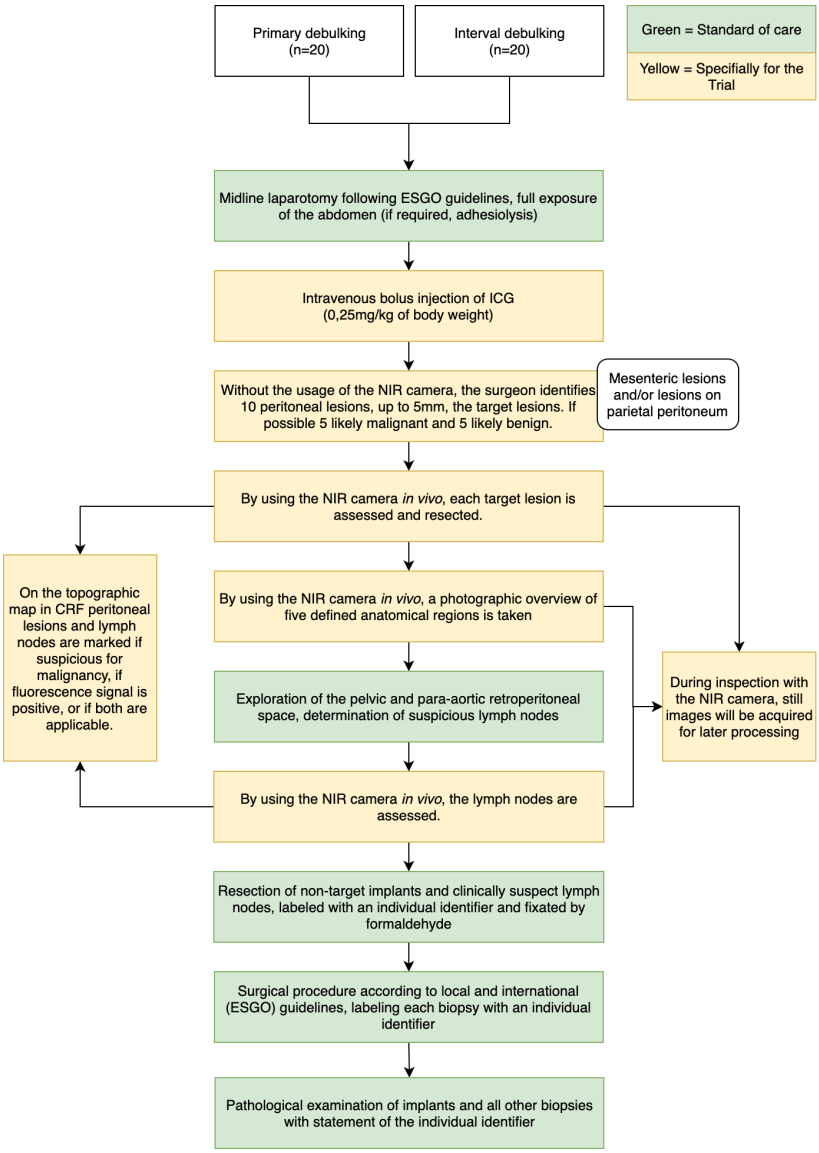
The Principle Investigator (PI) is responsible for the conduct of the Trial at his/her Participating Site, and for protecting the rights, safety and well-being of the Trial participants. As such the PI must ensure adequate supervision of the Trial conduct at the Participating Site. If any tasks are delegated, the PI will maintain a log of appropriately qualified persons to whom he/she has delegated specified Trial-related duties. The PI will ensure that adequate training is provided and documented for all Trial staff, prior to conducting assigned Trial-related activities.

It is the Coordinating Investigator's (CI's) responsibility to supervise the general conduct (e.g. Trial progress, communication, protocol training and support of the participating sites, annual reporting to the Ethics Committee (EC), end of Trial notification(s) and results reporting) of the Trial. The CI fulfils both Investigator and Sponsor responsibilities, as outlined in International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) E6(R2) and applicable regulations.

PI and CI shall each be referred to as «Investigator(s)».

TRIAL SYNOPSIS

Title of clinical Trial («Trial»)	Visualisation of Indocyanine Green in Primary and Interval Debulking for Ovarian Cancer
Protocol Short Title Acronym	VIPIDO
Trial Phase (I, II, III, IV)	Phase II
Sponsor name	University Hospitals Leuven (UZ Leuven)
Coordinating Investigator	Toon VAN GORP, MD, PhD
Contact Address CI	Herestraat 49, B-3000 Leuven, Belgium
Contact Email CI	toon.vangorp@uzleuven.be
Contact Phone CI	+32 16 34 47 50
EudraCT number	2021-002449-13
ClinicalTrials.gov number	NCT04891185
Principal Investigators and Participating Sites	Toon VAN GORP, MD, PhD University Hospitals Leuven (UZ Leuven)
Medical condition or disease under investigation	Advanced stage high-grade serous epithelial ovarian cancer: FIGO stage IIIb, IIIc and IV
Trial rationale	Visualise peritoneal lesions of EOC in both primary and interval debulking surgery by using intravascular ICG and NIR light. We want to investigate whether ICG can increase the visibility of peritoneal lesions and can differentiate between peritoneal implants and fibrosis.
Primary objective	Determine the diagnostic accuracy of ICG in visualising peritoneal lesions of EOC *in vivo*.
Secondary objective(s)	- Obtaining the false positive and false negative rate of *in vivo* ICG fluorescence signal. - Determine the difference of estimated ICG uptake *in vivo* of peritoneal lesions between primary debulking and interval debulking. - Correlation between the pre-operative radiographic examination(s) and the ICG signal *in vivo* and the pathological examination. - Determination of the tumour-to-background ratio of fluorescence in peritoneal lesions, lymph nodes and other anatomical structures. - Assessment of the number and type of adverse effects, severe adverse effects and adverse reactions with the trial dose of the IMP.
Trial Design	Open label trial exploring the diagnostic capabilities of an already approved drug, thus exploring the capability of an application unrelated

	to original approved use. The IMP (Indocyanine green, Verdye®) will be used off-label as a diagnostic tool. Flowchart condensing the Trial Design: 
Endpoints	- Determination of diagnostic accuracy of ICG in visualising peritoneal lesions of EOC in vivo. - Correlation between pre-operative radiographic examination(s) and the ICG signal in vivo and the pathological examination. - Determination of the tumour-to-background ratio of fluorescence in peritoneal lesions, lymph nodes and other anatomical structures. - Assessment of the number and type of adverse effects, severe adverse effects and adverse reactions with the trial dose of the IMP.
Sample Size	In total, 40 patients will be assigned to Trial treatment. The Trial exists of 2 arms, each with 20 patients. These two arms are the primary debulking group and the interval debulking group.

IMP, dosage and route of administration	Indocyanine green (Verdye®), 0,25mg/kg of body weight, intravenous bolus injection
Active comparator product(s)	None
Maximum duration of treatment and Follow Up of a Participant	Maximum duration of treatment: one day Maximum duration of Follow Up: until final results of pathological examination (variable length, typically less then 2 weeks)
Maximum duration of entire Trial	Two years after start of recruitment
Date anticipated First Patient First Visit (FPFV)	As soon as possible
Date anticipated Last Patient Last Visit (LPLV)	12-18 months after start of recruitment
Third parties	None

TRIAL FLOWCHART

Schedule of Events – Trial specific Procedures / Assessments

Procedures/ Assessment	Screening	Treatment Period	
Visits / Contacts	Visit 1	Surgery	Unscheduled Visit
Timing (weeks)		0	
Visit Window (days)	-28 Days to -1		
Informed consent	X [1]		
Inclusion / Exclusion criteria	X	X	
Demographics	X		
Medical, Surgical history	X		(X)
Physical examination	X		(X)
Weight / Height	X		(X)
Vital Signs	X		(X)
ECOG performance status	X		(X)
Haematology sampling	X		(X)
Coagulation sampling	X		(X)
Chemistry sampling	X		(X)
Urinalysis			(X)
Trial drug treatment (intravenous IMP)		X	
Trial drug dispensation (intravenous IMP)		X	
Trial drug accountability (intravenous IMP)		X	
Radiological Assessment: CT scan	(X)		(X)
Radiological Assessment: MRI scan	(X)		
Radiological Assessment: PET-CT scan	(X)		
Biomarker: CA-125	X		
Biopsy		X[2]	
Reason for discontinuation		X	
(Serious) Adverse event (S)(AE) assessment	X	X	X
Concomitant Medication (CM)	X	X	X

1 : Informed Consent be obtained prior to performing any other Trial-related procedures
2: Biopsies of the macroscopically visable peritoneal lesions is standard of care, the only difference will be the in vivo assessment of the flurorescense signal prior to resection.

Green = Standard of Care	Yellow = Specifically for the Trial

1 Background, Rationale and Risk Assessment

1.1 Background

Epithelial ovarian cancer (EOC) is the most lethal gynaecological cancer and the fifth largest cause of cancer-related death in women in Europe [1]. Two thirds of diagnoses are made in an advanced stage (International Federation of Gynaecology and Obstetrics (FIGO) stage III and IV), adding to the mortality [2]. The main goal for surgery in these advanced cases is to optimally resect all macroscopically visible tumour deposits, in order to optimize patient prognosis [3]. However, this optimal and complete (R0) resection is not always an option. Peritoneal involvement is a typical aspect from advanced disease, possible leading to large spread disease with bowel involvement or involvement into the portal vessels. This renders primary surgery ("debulking") not feasible. The European Society of Gynaecological Oncology (ESGO) guidelines advice to administer neoadjuvant chemotherapy in unresectable disease or unfit patients [4]. If the disease is less extensive after this neoadjuvant treatment and the patient is deemed fit for surgery, interval debulking surgery is advisable to achieve an R0 resection and to increase overall survival.

However, during interval debulking surgery, the clinician often encounters residual peritoneal lesions. Macroscopically, the surgeon cannot always differentiate these masses between active peritoneal disease or inactive and harmless fibrotic tissue, deprived from tumour cells due to the neoadjuvant therapy. If such a deposit exists on the parietal peritoneal surface, resection is no issue. Nonetheless, if such a deposit is situated next to the portal vein or on the serosa of the bowel, resection could cause significant morbidity and R0 resection could be compromised. Pre-operative imaging such as positron emission tomography–computed tomography (PET-CT) or magnetic resonance imaging (MRI) could aid the surgeon to differentiate active versus non-active lesions, however sensitivity for smaller lesions remains low and localisation of the exact lesion is cumbersome [5]. Especially lesions smaller then 5mm are hard to differentiate preoperatively (due to resolution restraints of both PET-CT and MRI) and intra-operatively, mainly during interval debulking surgery, due to less obvious macroscopic aspect and the possible missing very small lesions during debulking surgery [6].

Indocyanine green is an amphiphilic tricarbocyanine iodine dye that rapidly binds to plasma protein, mainly albumin, which maintains the ICG intravascular [7,8]. This allows for easy visualisation of the arteriovenous and lymphatic system, including lymph nodes. Furthermore, by bonding to plasma proteins, ICG behaves as a macromolecule. These macromolecules are accumulated in tumour tissues due to increased permeability and reduced drainage [9]. This effect is called the "enhanced permeability and retention" (EPR) effect, allowing to visualize the tumour tissue by using ICG. ICG is visualized by exciting the molecule with near-infrared (NIR) light. Typically, ICG is excited by a wavelength between 750 and 800nm and viewed at 830nm which is the peak emission level [8,10]. This wavelength is an optimal range to visualize *in vivo* tissues, since it is situated between the isobestic point (around 700nm) of tissues containing haemoglobin and myoglobin and between the wavelengths (above 900nm) absorbed by water and lipids [8,11]. Furthermore, the NIR light can penetrate the tissue deeper than visible light, up to 10mm of tissue [12].

1.2 Rationale

The rationale of this Trial is to adequately visualise peritoneal lesions of EOC in both primary and interval debulking surgery by using intravascular ICG and NIR light. Without ICG, macroscopic lesions in primary surgery are easily visible, however in interval debulking adequate visualisation of active peritoneal lesions is challenging. Active peritoneal implants could be mistaken for fibrosis, leading to suboptimal debulking surgery (i.e., not a true R0 resection) with higher rates of recurrence. We want to investigate whether ICG can increase the visibility of peritoneal lesions and can differentiate between peritoneal implants and fibrosis. In previous studies with a limited number of patients, this concept has already been proved feasible [8,12–14]. In this Trial we aim to further optimize this technique with a larger number of patients and in both primary and interval debulking surgery. Furthermore, we will associate operative findings with preoperative imaging, allowing to correlate the visualisation of lesions by the IMP with these examinations.

In this Trial patients that undergo either primary or interval debulking surgery are included. The aim of the Trial is to identify active peritoneal implants; in primary debulking surgery we expect that all macroscopic peritoneal lesions will be fluorescence positive, as such this could be considered our positive control arm of the IMP efficacity. However, in interval debulking surgery, the possibility exists that some macroscopic peritoneal lesions are mere fibrotic tissue and as such we would expect the fluorescence signal to be less

intense or absent. If such a difference would exist between active (fluorescence positive) peritoneal implants, this could aid in the visualisation and selective resection of peritoneal disease in EOC, ultimately reducing the risk for hazardous resections.

Non-peritoneal lesions and in particular lymph nodes will also be macroscopically assessed for the fluorescence signal of the IMP and this signal will be correlated with the anatomopathological findings. However, this is only a secondary endpoint since peritoneal lesions are the trademark of advanced stage EOC. For these non-peritoneal lesions preoperative imaging will also be correlated, especially their topographic relationship.

Epithelial ovarian cancer accounts for 90% of ovarian cancers knows five histological subtypes: high-grade serous carcinoma, low-grade serous carcinoma, endometrioid carcinoma (subdivided in high-grade and low-grade), clear-cell carcinoma and mucinous carcinoma [15]. Each of these histological subtypes have their own characteristics. Of these epithelial ovarian cancer subtypes, high-grade serous carcinoma comprised the majority of tumours. As such, we aim in this exploratory Trial to only include high-grade serous epithelial ovarian carcinoma.

1.3 Risk Assessment

By utilising an already licenced IMP off-label we aim to minimalize potential risk for the patients. ICG has already been licensed in Belgium for diagnostic purposes (cardiac, cerebral, liver and choroidal perfusion), see also Appendix 3 [10]. It also has been licenced by the American Food and Drug Administration since 1956 for retinal angiography and in the years 2000 for cardiac vessel angiography, neurosurgical research and for surgical microscopes [8]. Off-label usage of ICG has been extensively explored in abdominal and plastic surgery, including oncological indications such as sentinel lymph node mapping [8,11].

The lethal dose (LD_{50}) of ICG is 50-80 mg/kg of body weight, allowing for a virtually nontoxic administration when utilizing normal doses (in this Trial 0,25mg/kg of body weight) [8]. Adverse effects have been reported in less than 1 in 40000 patients, mainly hypersensitivity reactions and iodine-based allergies [8,12]. Compared to other dyes such as methylene blue, this risk for adverse reactions is significantly lower [12].

As such, the safety profile and the extensive positive experience with ICG allows for a positive benefit/risk balance. By utilising this promising diagnostic tool, the benefit can be increased by the higher chance for adequate R0 resection.

In this trial, preoperative radiologic examinations such as CT, PET-CT and MRI will be included in the dataset. However, these examinations will only be a part of the standard of care preoperative assessments. Which examination will be performed and which not, are not determined by the Trial, these are standard of care and only the treating physician chooses the suitable examinations. MRI whole body is considered standard of care in University Hospitals Leuven (UZ Leuven) and will be performed therefore in most to all participants before surgery. Other examinations depend on the specific clinical situation of the participant. Since these examinations are standard of care, no additional irradiation risk exists within the Trial.

The macroscopic lesions identified by the IMP and subsequently resected must be located on either the parietal peritoneum or superficially on the mesentery. These localisations are chosen to minimize potential risk for the participant. Since no vital structures lie superficially on the mesentery or on the parietal peritoneum, these lesions can be resected without potentially damaging bowels, vessels, nerves or other vital structures. Furthermore, excellent surgical exposure can be obtained in these anatomical regions, optimising surgical approach leading to an additional decreased risk.

2 Trial Objectives and Design

2.1 Trial objectives

In this therapeutic exploratory Trial, we explore the diagnostic usage of ICG (an already registered IMP with Marketing Authorisation) in the diagnosis of peritoneal lesions of EOC. In this Phase II Trial the aim is to replicate previous studies where ICG had been used with the same dosing intravenously to visualize peritoneal lesions in EOC [8]. However, we expand the potential usage of the IMP by exploring the entire abdominal cavity and explore the retroperitoneum and its lymph nodes. Furthermore, we correlate preoperative imaging with the surgical findings and the influence of the IMP on these findings.

The primary research question is if ICG is capable to correctly visualize peritoneal lesions of EOC *in vivo* in both primary and interval debulking surgery. We hypothese the ICG will adequately visualise malignant peritoneal implants of EOC. Furthermore, we hypothesized that fibrotic lesions would retain less or no ICG and therefore emit a different fluorescence signal than the malignant implants.

2.2 Primary Endpoints

The primary objective of this Trial is to determine the diagnostic accuracy of ICG in visualising peritoneal lesions of EOC *in vivo*. By using the NIR fluorescence camera, peritoneal malignant implants should be fluorescent after intravenous injection of ICG. Benign lesions should not be fluorescent after intravenous injection of ICG.

2.3 Secondary Endpoints

Secondary endpoints of this Trial are:

- Obtaining the false positive and false negative rate of *in vivo* ICG fluorescence signal by correlating these results with the pathological report.
- Determine the difference of estimated ICG uptake *in vivo* of peritoneal lesions between primary debulking and interval debulking.
- Correlation between the pre-operative radiographic examination(s) and the ICG signal *in vivo* and the pathological examination.
- Determination of the tumour-to-background ratio of fluorescence in peritoneal lesions, lymph nodes and other anatomical structures. Correlation of this ratio with the pathological examination.
- Assessment of the number and type of adverse effects, severe adverse effects and adverse reactions with the trial dose of the IMP.

2.4 Trial Design

This Trial is an open label trial exploring the diagnostic capabilities of an already approved drug, thus exploring the capability of an application unrelated to original approved use. The IMP (Indocyanine green, Verdye®) will be used off-label as a diagnostic tool. Since the IMP is only utilised as a diagnostic tool, no blinding could be performed.

Each participant will be identified within the Trial by a unique Trial-specific participant identifier. The true identity of the participant will be recorded in the Trial Master File, however after inclusion of the participant, only the PI can access the personal identifiers of this participant.

The following flowchart condenses the Trial design (Figure 1):

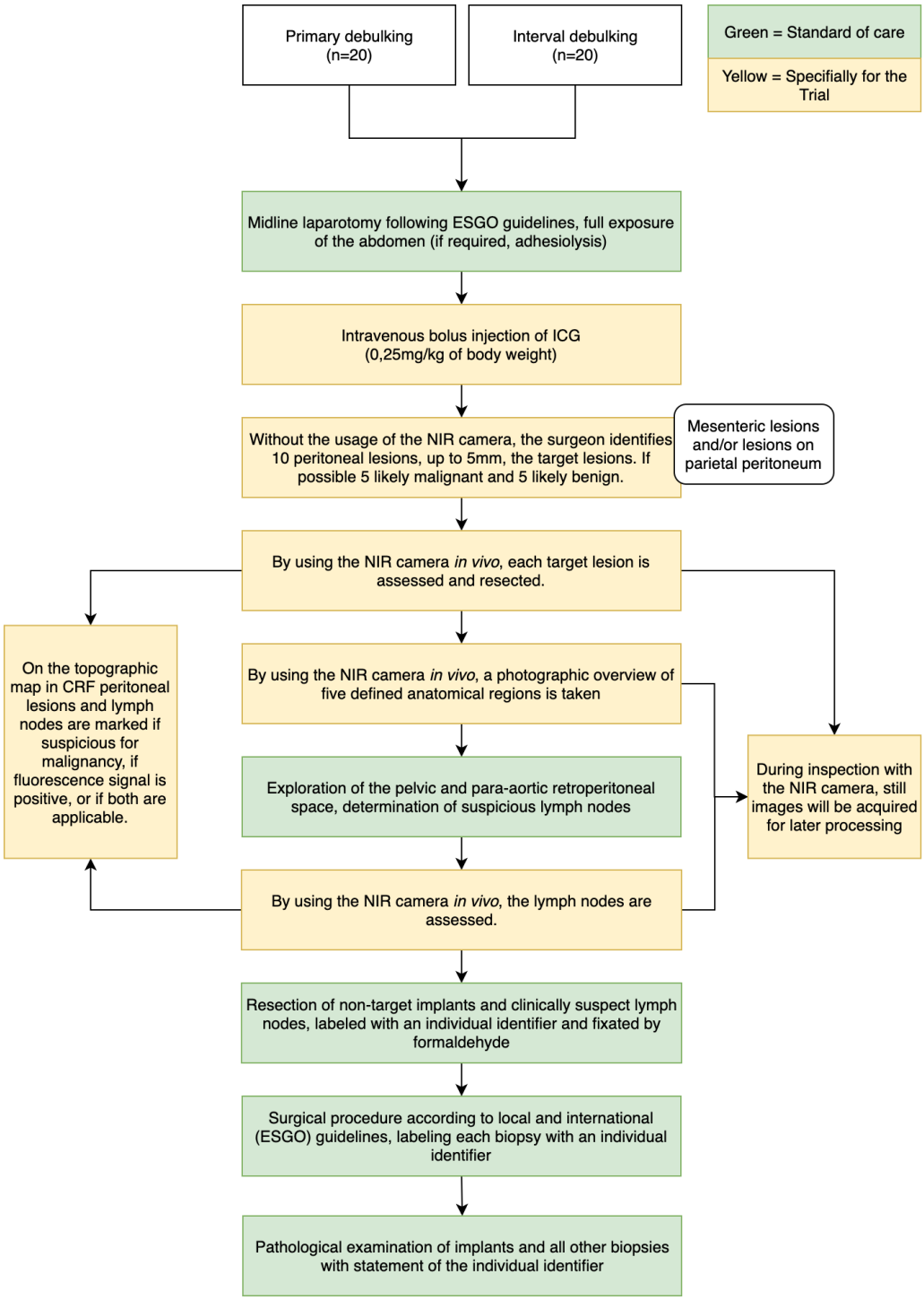


Figure 1

All relevant preoperative imaging (including but not limited to CT, PET-CT and/or MRI) will be included in the CRF. These preoperative staging is a part of the standard of care and as such is not an additional examination for this Trial. Patient history including allergies and current medication will be noted in the CRF. Additionally, information from the screening visit will be included in the CRF: demographics, physical examination, weight, height, Eastern Cooperative Oncology Group (ECOG) performance status and vital signs (Appendix 4) [16]. Any relevant and recent lab tests – in particular renal function and biomarker CA-125 – will be included in the CRF.

During the procedure, a paper CRF will be provided including the flowchart condensing the Trial design (Appendix 5). In this paper CRF the surgeon will be given a step by step guide to fully collect all nessisary peroperative data. After the procedure, this paper CRF will be digitalised in the CRF. During surgery, the

surgeon can utilise pre-operative imaging available to correctly identify the preoperative lesions and abnormal masses to obtain R0 resection. The procedure will be performed under general anaesthesia, this is standard of care for a debulking surgery. Possibly, additional neuraxial anaesthesia can be utilised within the standard of care, if indicated.

First, the surgeon will perform a midline laparotomy according to ESGO guidelines, as a standard of care. If necessary, dissection of adhesions can be performed in order to obtain adequate exposure of the abdominal cavity. Should this dissection be technically impossible, or should the surgeon deem the exposure of the abdominal cavity insufficient for optimal visualisation, the participant will not be further participate in the Trial. This drop out remains in the database of patients and will be subject of the intention to treat analysis.

After adequate exposure of the abdominal cavity, the IMP will be administered as an intravenous bolus injection (0,25mg/kg of body weight) via the intravenous access already established. For the rationale of dosing and timing of administration, please see section 0. An exact timeframe between injection and visualisation is difficult to obtain from literature. ICG can be visualised as soon as 2 minutes for lymph nodes and 5 minutes for peritoneal lesions [8,14]. As such, since the injection is prior of identification of the lesions, adequate time will be obtained between injection and identification of lesions. A maximum time between injection and visualisation is also very different in literature, a maximum timeframe of 24 hours has been reported for peritoneal lesions [14]. Therefore, the maximum time after injection is not an issue in this Trial since debulking surgeries do not require 24 hours to perform.

Before utilisation of the NIR fluorescence camera, the surgeon identifies 10 peritoneal lesions, the so-called target lesions: 5 lesions deemed to be malignant, and 5 lesions deemed to be benign. Should the surgeon be unable to ascertain 10 macroscopic peritoneal lesions, the maximum number of resectable lesions should be identified; this must be noted in the CRF. These lesions must be located on the mesentery and/or on the parietal peritoneum. These locations have been specially selected due to its ease of resection and the minimal risk of resection for the patient in comparison with other anatomic locations such as the bowel surface or diaphragm. If possible, these lesions should be maximum 5mm, in order to maximize the clinical relevance (cf. supra). Should such small lesion(s) not be available, larger lesion(s) are accepted, but this will be noted in the CRF. Each lesion will be scored on a six-point scale: likely malignant or likely benign. For each assesement, the surgeon has to attribute a grade of certainty: Certain, Probably or Uncertain. As such, each lesion is given a grade on a six-point scale.

In the next step the NIR fluorescence camera is used to visualise each peritoneal target lesion *in vivo*. This camera is fitted with a sterile protective cover and is placed on a holding arm. The camera used in this Trial is a Karl Storz Image1 S TH 121 4K camera capable of NIR fluorescence. This camera is mounted on a holding arm. During NIR fluorescence images procurement, a 760 nm excitation light will be utilised. The head of the camera is positioned about 30cm from the surgical field [9]. By preserving the 30cm distance, all images obtained for quantitative calculation are comparable. Each of the 10 pervious selected peritoneal lesions (=target lesions) are labelled fluoresce positive or fluorescence negative. For every lesion, the results are noted in the CRF and in the pathological report. A structure is deemed fluorescence positive when it captures the ICG fluorescence signal and the brightness of the signal is at least two times as strong as the surrounding tissue [14]. During this identification phase of the Trial, ample still images will be procured with the NIR fluorescence camera, with an emphasis on the target lesions. A quantitative calculation of the brightness is not essential during surgery, in accordance with literature [14]. This quantitative calculation of the tumour-to-background ratio (TBR) will be performed on the acquired still images after surgery. Once again, for each target lesion, the surgeon will give the assesement on the six-point scale. Dissection of the target lesions is at the discretion of the performing surgeon, in accordance with ESGO guidance [3]. In the pathology report, each lesion location, fluorescence signal and clinical assessment (i.e., the six-point scale) will be noted and copied in the CRF. The resected lesion is fixated in formaldehyde, as standard of care, unless the surgeon whises to perform a frozen section examination. Furthermore, each target lesion will be indicated on the topographic map provided in the CRF. The number of each lesion will be noted on this map (Figure 2).

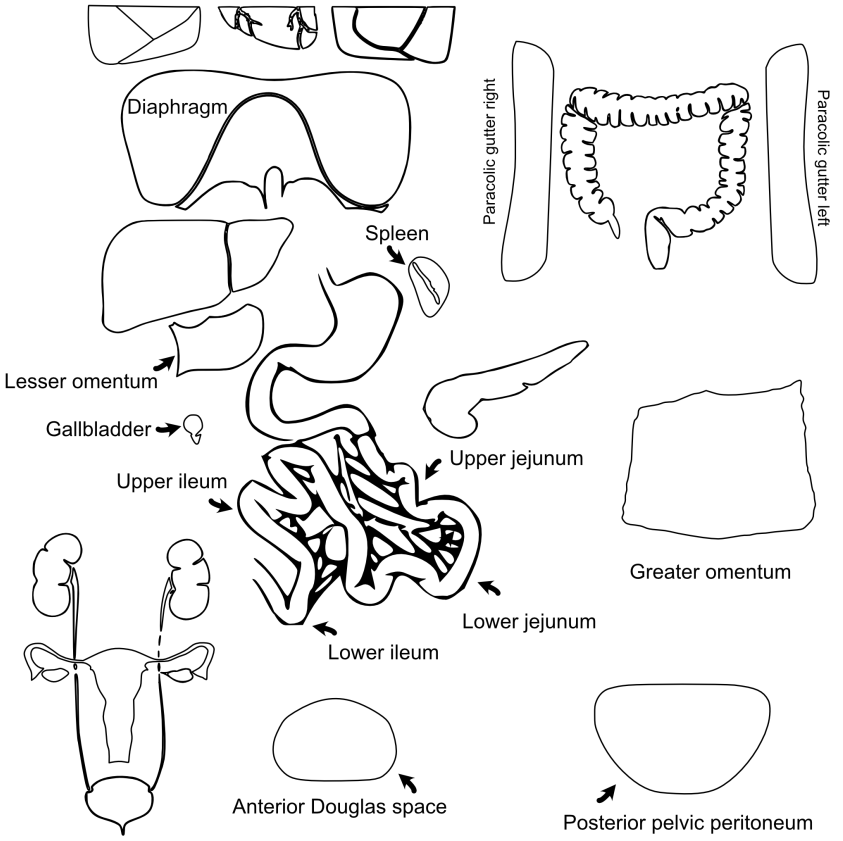


Figure 2

After resection of the target lesions, the entire abdominal cavity is systematically assessed. The surgeon will take two photographs of five defined anatomically regions. Of each region a photograph without NIR fluorescence camera will be taken. Afterwards a second photograph will be taken using the NIR fluorescence camera. These five anatomical regions are: pelvis, omentum, mesentery, right paracolic gutter and right-sided diaphragm. The procured photographs will be noted in the CRF. Dissection of the non-target lesions is at the discretion of the performing surgeon, in accordance with ESGO guidance [3].

After complete assesement of the abdominal cavity, the surgeon states an estimation (in percents) of the number of peritoneal lesions who are fluorescence positive.

As standard of care, the retroperitoneal lymph nodes in the pelvic and obturator spaces are explored. Additionally, the para-aortic and caval lymph nodes are also assessed macroscopically. If a lymph node is macroscopically suspicious for malignancy, it must be resected according to standard of care. Furthermore, if preoperative imaging reported enlarged and/or suspicious lymph node(s), these nodes should also be resected according to standard of care. However, prior to resection the lymph nodes in the exposed retroperitoneal spaces should be assessed by the NIR fluorescence camera. The fluorescence status (i.e., positive or negative) of each pre- or interoperative suspicious lymph node must be obtained and noted in the CRF. Additionally, all fluorescence positive lymph nodes must be reported in the CRF, however these lymph nodes should not be resected as this is not standard of care and the resection of these additional lymph nodes are out of the scope of this Trial. During assessment with the NIR fluorescence camera, still images will be taken. Should the lymph node be resected, the location, fluorescence signal and clinical assessment (i.e., the six-point scale) will be noted in the pathology report and copied in the CRF. The surgeon should indicate these lymph nodes on the provided topographic map in the CRF (Figure 3). The surgeon must indicate suspicious lymph nodes by an X on the second topographic map. Should an area be fluorescence positive without a clear lymph node, an O will be drawn on the map. If both are applicable, an X with a circle drawn around it will be noted. The lymph node is fixated in formaldehyde, as standard-of-care of send for frozen section examination. Should the lymph node not be resected, then a description of the location, fluorescence signal and clinical assessment (i.e., the six-point scale) will be noted in the CRF and drawn on the topographic map.

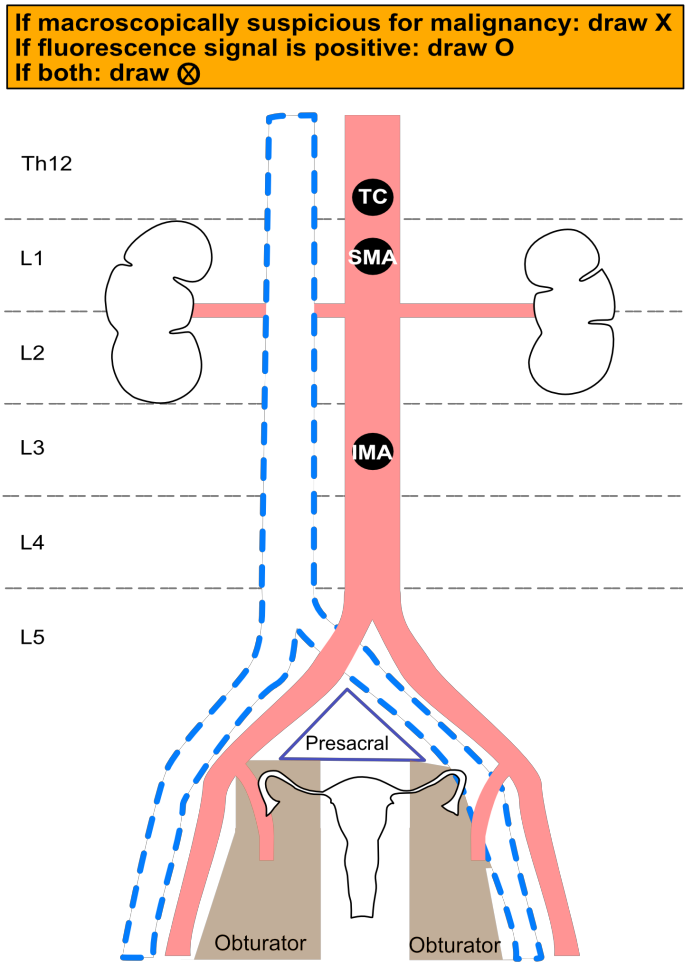


Figure 3

If feasible, the surgeon furthermore correlates the mapped structures with the pathological report in order to further optimise topographic relations. The peritoneal lesion chart is adapted from Hoogstins *et al.* and Jacquet & Sugarbaker [17,18].

Further surgical procedure is as standard of care, according to local and international guidelines, mainly ESGO guidelines [4]. After the initial visualisation and documentation of the fluorescence signal in the abdominal cavity, no further fluorescence signals will be obtained within the Trial due to the risk for contamination of the tissues with the IMP and as such reducing specificity of ICG. However, all biopsies should be identified by an individual identifier and this identifier including the topographic location must be noted in the CRF.

In each of the previous steps, a timestamp is provided in the CRF in order to obtain the required time for each step and for the entire IMP-guided procedure.

The surgical report should follow ESGO guidelines and be as complete as possible [4]. This pseudonymised validated surgery report will be included in the CRF.

The pathology report of all resected biopsies will be included in the CRF after pseudonymisation. This report should state all identifiers and additional information previously noted in the CRF.

Image processing to determine the TBR will be conducted in ImageJ, an open-source application developed by the National Institutes of Health (available from https://imagej.nih.gov/ij). Two zones will be identified in the still images: a zone of fluorescent uptake and a non-fluorescent background area (at least 2cm apart from the fluorescent zone) [9]. TBR will be calculated to take the ratio (expressed as mean arbitrary units) of the two areas of interest. Furthermore, contrast-to-noise ratio could be utilised if sensitivity using TBR seems inadequate [19]. If applicable, machine learning will be enabled to further enhance image processing

and reduce selection and/or confirmation bias, including – but not limited to – calculation of tumour-to-background ratio.

2.5 Expected Duration of the Trial

The expected duration of the Trial for a single participant will be one day since administration of the IMP will only occur during surgery and will not be repeated. If the participant does not show any allergic reaction, the Trial is concluded for this patient. Should an allergic reaction occur, the patient will be observed within the trial for the duration of the symptoms.

Since images will be taken during the procedure with the NIR fluorescence camera and this camera will be draped before incision, the total duration of the surgery will be a little bit longer than standard-of-care. However, we expect this delay will be minimal, since a thorough and carefull examination of the entire abdomen is standard of care.

The expected duration of the Trial of one case will be until the definitive pathological report is finished, then the CRF will be closed. No long-term follow-up of the patient will be conducted for the patient within this trial. Results of the pathological examination resected during surgery will be included, however biopsies of a later date will not be included.

The duration of the entire Trial is expected to be two years after the start of inclusion of participants.

3 Trial Population / Eligibility Criteria

3.1 Inclusion criteria

Participants eligible for inclusion in this Trial must meet **all** of the following criteria:

1. Voluntary written informed consent of the participant or their legally authorized representative has been obtained prior to any screening procedures. (Appendix 6)
2. At least 18 years of age.
3. Advanced stage epithelial ovarian cancer: FIGO stage IIIb, IIIc or IV. (For FIGO staging classification, please refer to Appendix 7).
4. A biopsy or cytology confirming the presence of high-grade serous epithelial ovarian carcinoma
5. Preoperative imaging (CT and/or MRI), describing metastatic implants, as standard of care.

All participants that are considered for Trial participation, per the above criteria will be documented on the Screening Log, including Screen Failures.

3.2 Exclusion criteria

Participants eligible for this Trial must **not** meet any of the following criteria:

1. Participant has a history of following diseases:
    a. Hyperthyroidism
    b. Autonomously functioning thyroid adenoma
2. Participant has an allergy or hypersensitivity for one or more of the following components:
    a. Iodine (including potassium iodine)
    b. Indocyanine green
3. Any disorder, which in the Investigator's opinion might jeopardise the participant's safety or compliance with the protocol.
4. Any prior or concomitant treatment(s) that might jeopardise the participant's safety or that would compromise the integrity of the Trial.
5. Participation in an interventional Trial with an investigational medicinal product (IMP) or device during the surgery itself.
6. Participant has a severe renal impairment (classified as eGFR<30 ml/min/1,73m^2 according to CKD-EPI).
7. Participant utilises sodium bisulfite-containing heparin preparations during the day before surgery. For Belgian registered drugs, this contains:
    a. Danaparoïde (Orgaran®)

   b. Other low-molecular weight heparins registered in Belgium do not contain sodium bisulfite and are not an exclusion criterion.
8. Participants requires thyroid scintigraphy utilising radioactive iodine one week after surgery.
9. A previous history of major intra-abdominal surgery with potentially major adhesions and/or distorted anatomy.
10. Participants utilises one of the interacting drugs listed in section 5.3.

Participants who meet one or more of the above exclusion criteria **must not proceed** to be enrolled/randomized in the Trial and will be identified on the Screening Log as Screen Failure.

NB Since the explicit intent of cytoreductive debulking surgery is to remove the ovaries, the participant cannot become pregnant. As such, the usage of contraceptive methods is futile and is not discussed within the inclusion and exclusion criteria.

4 Trial Procedures

4.1 Participant consent and withdrawal of consent

The Trial will be conducted only on the basis of prior informed consent by the Trial participants and/or their legally authorized representative(s). As such, no Trial-related procedures will be conducted prior to obtaining written informed consent from potential Trial participants.

The process for obtaining and documenting initial and continued informed consent from potential Trial participants will be conducted in accordance with ICH-GCP E6(R2), applicable regulatory requirements and internal Standard Operating Procedures (SOPs).

All originally signed obtained Informed Consent Forms (ICFs) must be retained/archived in the Investigator Site File (ISF) at the Participating Site and must not be destroyed (even when a scanned copy is available) before expiration of the legal archiving term as defined in the protocol section entitled "Archiving".

Participants may voluntarily withdraw consent to participate in the Trial for any reason at any time. The participant's request to withdraw from the Trial must always be respected without prejudice or consequence to further treatment. Consent withdrawal will be documented in the participant's medical record.

Trial data and samples collected before withdrawal can be used in the trial. No new trial data or samples will be collected after withdrawal of the participant.

4.2 Selection of Participants / Recruitment

Patients will be identified when booked for primary or interval debulking after multidisciplinary board review. All patients receiving this surgery are applicable for recruitment. Recruitment will happen by the gynaecological oncology department (GNC) of UZ Leuven.

Patients will be asked if they are willing to participate in this Trial and receive all required information. The patient can sign the ICF between the moment of requitement and just before surgery. When a participant is asked for participation, she will be screened for eligibility to participate in the Trial.

If a patient refuses participation, all patient data will be removed from the Trial. However, a failed recruitment statement without any patient identifiers will be kept.

No advertising materials nor patient brochures will be used in this Trial.

4.3 Randomization Procedure / Blinding

No randomization will be performed, all patients will receive identical therapy.

Since this is an open label Trial with a one-step surgical procedure, blinding is not applicable.

4.4 Unblinding

Since this is an open label Trial with a one-step surgical procedure, blinding is not used and as such unblinding is not applicable.

4.5 Premature discontinuation of Trial treatment

Participants may voluntarily discontinue from Trial treatment and/or prematurely end their participation in the Trial for any reason at any time. In such case the Investigator must make a reasonable effort to contact the participant (e.g., via telephone, e-mail, letter) in order to document the primary reason for this decision.

The Investigator may also decide at any time during the course of the Trial, to temporarily interrupt or permanently discontinue the Trial treatment if it is deemed that continuation would be detrimental to, or not in the best interest of the participant.

Similarly, the Sponsor, Ethics Committee or authorized regulatory authority can decide to halt or prematurely terminate the Trial when new information becomes available whereby the rights, safety and well-being of Trial participants can no longer be assured, when de integrity of the Trial has been compromised, or when the scientific value of the Trial becomes obsolete and/or unjustifiable.

Circumstances requiring premature treatment interruption or discontinuation of the Trial, include but are not limited to:

- Safety concerns related to IMP or unacceptable intolerability
- Trial participation while in violation of the inclusion and/or exclusion criteria
- Cancellation of surgery, either by the patient, by the surgeon or due to unforeseen problems.

In any such case of early Trial termination and/or treatment interruption/discontinuation, the Investigator will continue to closely monitor the participant's condition and ensure adequate medical care and follow-up. It is recommended that follow-up information will be collected as follows:

- Regular follow-up visits on the gynaecological oncology unit.
- No specific examinations are required to be done at End of Trial or during follow-up

For participants whose status is unclear because they fail to appear for Trial visits without stating an intention to discontinue or withdraw, the Investigator must make every effort to demonstrate "due diligence" by documenting in the source documents which steps have been taken to contact the participant to clarify their willingness and ability to continue their participation in the Trial (e.g., dates of telephone calls, registered letters, etc.).

A participant should not be considered lost to follow-up until due diligence has been completed.

5 Trial Medication / Drug

Generic Drug Name (& company brand name)	**IMP or non-IMP**	**Used within Indication?**	**Route of administration**	**Dose/dosage and units**
Indocyanine green (Verdye®)	IMP	No, off-label	Intravenous bolus injection	0,25mg/kg of body weight

5.1 Investigational Medicinal Product and Dosing Regimen

The IMP in this Trial is Verdye®, manufactured and licensed for the Belgian market by Diagnostic Green GmbH (Otto-Hahn-Str. 20, 85609 Aschheim-Dornach, Germany). The Summary of Product Characteristics is provided in Appendix 3. Standard vials with the IMP obtained from the hospital pharmacy will be provided, either containing 25mg of powder, or containing 50mg of powder, depending on the required dosing. The IMP will be dispensed by a licensed hospital pharmacist. The legally required label indicating "clinical trial use only" will be attached (Appendix 8). No additional labelling or packaging of the IMP vials will be provided, since the labelling of the vial and the exterior packaging are described within the Summary of Product Characteristics of Verdye®. Verdye® is stored in an amber glass injection vial (type 1), closed by a grey rubber lid (broombutyl), which is attached by an aluminium hood. A blue polypropylene protective cap encloses the top of the vial [10].

The IMP will be dissolved with sterile water suitable for intravenous injection, obtaining a concentration of 5 mg/ml [10]. This suspension will be dissolved in the vial while retaining all sterility. Should a precipitate be present in the suspension, the vial must be discarded according to local guidance and protocols and this vial of IMP cannot be used for injection [10]. As such, each vial and each syringe containing the dissolved IMP must be visually inspected for any precipitation. With a sterile syringe the required volume of the dissolved IMP will be aspired on a sterile manner. This syringe will be administered intravenously as explained in the following paragraph within a short timeframe. Attention should be made this timeframe must be kept as short as possible, allowing for immediate intravenous injection, in order to minimize potential influence of light or other contaminants. Should the IMP be dissolved, and immediate intravenous injection is not possible, the syringe must be kept in a dark place or must be shielded from light. A maximum timeframe of 1 hour is obtained between dissolving the IMP and injection, well within the maximal range of the 6 hours stated in the Summary of Product Characteristics [7]. If this timeframe should exceed 1 hour, the syringe and the remaining IMP in the vial must be discarded according to local guidance and protocols.

According to the Summary of Product Characteristics of Verdye®, administration should occur as a bolus injection, see Appendix 3 [10]. Dosing ranges between 0,1 to 0,5 mg/kg of body weight as a single dose in adults, seniors and children. Total daily dose should not exceed 5 mg/kg of body weight [10].

In their practical guide, van Manen *et al.* advises administration of 0,25mg/kg of body weight for the visualisation of peritoneal metastases [12]. Hence, we adhere to this dosing, which is within the range of Summary of Product Characteristics. When reviewing literature about the optimal dosing for the visualisation of lymph nodes, no consensus could be obtained. For the visualisation of sentinel lymph nodes doses range from 100µg to 25mg, with a recommended dose of 2,5mg [12]. Since the injection is intravenously, we cannot compare the dosage for the visualisation of sentinel lymph nodes, in which the injection is locally. Since our primary objective is the visualisation of peritoneal lesions, we retain the aforementioned dose.

Intravenous access is standard of care in all surgeries under general anaesthesia, therefore the bolus administration of ICG can be performed without an additional intravenous puncture or intravenous line. The IMP will be administered by a licensed physician or operation theatre nurse with the utmost care to work in sterile environments with the IMP.

ICG will be administered after complete exposition of the abdomen, allowing for an optimal timeframe between injection of ICG and visualisation. Time between injection and visualisation of peritoneal lesions is minimum 5 minutes [12]. Optimal time of visualisation knows a very broad range in literature, ranging between immediately up to 24 hours after injection [12,13,20]. Therefore, we pragmatically opted for a 10 minute wait time between intravenous injection of the IMP and visualisation of the lesions using the NIR fluorescence camera. Other studies have explored preoperative administration of ICG, however this resulted in the absence of fluorescence signal during surgery [12,13]. Therefore, we opt for intraoperative administration of ICG. The added benefit of an intraoperative administration if the presence of a qualified anaesthesiologist in the operation theatre. Should a rare anaphylactic reaction occur, specialised care is already present for the resuscitation of the patient, further minimizing patent risk.

5.2 Drug Accountability

The IMP utilised in this Trial will be used only as directed in the study protocol. The IMP will be obtained from the hospital pharmacy according to local guidance for shipping, supplying, handling and storing of the vials. The all pre-operative phases of drug accountability of the IMP are standard of care since the IMP has been registered and used within UZ Leuven for other indications and the IMP is readily available.

The IMP will be prepared for sterile injection (as explained before) in the operation room. No prior manipulation of the IMP will be necessary. The hospital pharmacy will as standard of care ensure optimal temperature (below 30°C), environmental and shipping environments for the IMP. Unused vials of the IMP must be returned to the hospital pharmacy. Opened vials of the IMP or unused prepared IMP must be discarded according to local guidance and protocols. No opened vials will be returned to the hospital pharmacy nor will they be used in another participant of the Trial.

Any irregularities occurring before, during or after administration of the IMP concerning the preparing, handling, storing or destruction of the IMP must be noted in the CRF.

5.3 Concomitant / Prohibited Medication / Treatment

Following drugs could possibly interact with indocyanine green and therefore are not compatible with the administration of the IMP:

Generic drug	Brand name in Belgium (as on 14th January 2021)
Anticonvulsants	- Brivaracetam (Briviact®) - Carbamazepine (Tegretol®) - Ethosuximide (Zarontin®) - Felbamate (Taloxa®) - Gabapentin (Gabapentine EG®; Gabapentine Mylan®; Gabapentine Sandoz®; Gabapentin Sandoz®; Neurontin®) - Lacosamide (Vimpat®) - Lamotrigine (Lambipol®; Lamictal®; Lamotrigine EG®) - Levetiracetam (Keppra®; Levetiracetam Sandoz®) - Oxacarbazepine (Oxacarbazepine Mylan®; Trileptal®) - Perampanel (Fycompa®) - Phenobarbital (Gardenal®; Phenobarbital Sodium Sterop®; Phenobarbital Sterop®) - Phenytoin (Diphantoine®) - Pregabalin (Lyrica®; Pregabaline Apotex®; Pregabaline EG®; Pregabaline Krka®; Pregabaline Mylan®; Pregabaline Teva®; Pregabaline Sandoz®) - Primidone (Mysoline®) - Rufinamide (Inovelon®) - Stiripentol (Diacomit®) - Tiagabine (Gabitril®) - Topiramate (Topamax®; Topiramate EG®; Topiramate Sandoz®) - Valproate (Depakine®; Valproate EG®; Valproate Mylan®; Valproate Sandoz®) - Vigabatrin (Sabril®) - Zonisamide (Zonegran®)
Bisulfite-containing compounds	- Danaparoïde (Orgaran®)
Cyclopropane	N/A
Fenobarbital	Gardenal®; Phenobarbital Sodium Sterop®; Phenobarbital Sterop®
Haloperidol	Haldol®
Heroin	N/A
Metamizol	Novalgine®
Methadone	Mephenon®
Morphine	MS Direct®; Morphine Teva®; MS Contin®; Morphine HCL Sterop®
Nitrofurantoine	Furadantine MC®
Opioid alkaloids	- Buprenorphine (Buphrenorphine Teva®; Temgesic®; Transtec®) - Fentanyl (Durogesic®; Fentanyl EG®; Fentanyl Sandoz®; Matrifen®) - Hydromorphone (Palladone®) - Oxycodone (Oxycodone Teva®; Oxycodon Sandoz®; OxyContin®; OxyNorm®; Targinact®) - Piritramide (Dipidolor®) - Tapentadol (Palexia®) - Tramadol (Contramal®; Dolzam®; Tradonal®, Tramadol EG®; Tramadol Krka®; Tramadol Sandoz®; Tramium®; Skudexa®; Algotra®; Pontalsic®; Tramadol / Paracetamol EG®; Tramadol / Paracetamol Krka®; Tramadol / Paracetamol Sandoz®; Tramadol / Paracetamol Teva®; Zaldiar®)
Pethidine	Pethisom®
Phenylbutazone	N/A
Probenecid	N/A
Rifampicin	Rifadine®

5.4 Rescue Medication

Not applicable.

Should an anaphylactic shock occur, follow advanced life support guidelines. 100-300mg hydrocortisone or equally active compound would be administered by swift intravenous injection. An isotonic electrolytes solution should be administered intravenously.

6 Safety

Definitions[1,2]

[1] Guideline for good clinical practice E6(R2) Step 5 EMA/CHMP/ICH/135/1995 dated 1 December 2016
[2] Belgian law of May 7th, 2004 regarding experiments on the human person (as amended) or the Belgian law of May 7th, 2017 related to clinical trials on medicinal products for human use (as soon as in effect).

6.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient, clinical investigation participant or participant of the treated group during an experiment who had been administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered to be related to the product. Any worsening (i.e., any clinically significant adverse change) in the frequency or intensity of a pre-existing condition, should be considered an AE.

6.2 Adverse Reaction (AR)

An AR is any untoward and unintended response to an investigational medicinal product or to an experiment and, when an investigational product is concerned, related to any dose administered. 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.

6.3 Serious Adverse Event (SAE)

A SAE is any untoward medical occurrence that at any dose, results in any of the following:

- Death
- A life-threatening[a] experience
- In-patient hospitalisation or prolongation of existing hospitalisation
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- Important medical events that may be considered an SAE when - based on appropriate medical judgement - they could jeopardise the participant's safety and may require medical or surgical intervention to prevent one of the above outcomes[b]

[a] The term "life threatening" in the definition of SAE refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.
[b] ICH E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting CPMP/ICH/377/95 dated Jun 1995

6.4 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is an AR, the nature or severity of which is not consistent with the information on the experiment, and, when a clinical Trial is concerned, with the applicable product information (e.g., Investigator's brochure (IB) for an unauthorised investigational product or the patient leaflet joined to the summary of product characteristics for an authorised product).

6.5 Adverse Events of Special Interest (AESI)

The following events should always be reported within the same timelines as SAEs:

- Overdose
- Misuse/abuse
- Medication error

6.6 Safety Events that do not require reporting

In general, the following should not be reported as AEs:

- Pre-existing conditions, including those found as a result of screening (these should be reported as medical history or concomitant illness), unless the condition worsens during Trial treatment

- Pre-planned procedures unless the condition for which the procedure was planned has worsened from the first Trial-related activity after the participant has signed the informed consent

The following AEs are commonly observed and expected, and/or are part of the well-known safety profile of Verdye® as documented in the Summary of Product Characteristics (SmPC) when used within the approved indication, and are therefore not considered adverse events for the purpose of the Trial [10]:

- Skin reaction including wheals

Although these events should not be reported to the Sponsor, these should be recorded in the participant's medical notes according to routine practice.

The following events are not to be considered as SAEs:

- Pre-planned hospitalisations unless the condition for which the hospitalisation was planned has worsened from the first Trial-related activity after the participant has signed the informed consent
- Hospitalisation as part of the standard procedure for protocol therapy administration However, hospitalisation or prolonged hospitalisation for a complication of therapy administration will be reported as an SAE
- Hospitalisation or prolongation of hospitalisation for technical, practical, or social reasons, in absence of an AE

6.7 Recording and Reporting of Safety Events

Investigators will seek information on the occurrence of safety events at each participant contact. All events, whether reported by the participant or noted by Trial staff, will be recorded in a timely manner in the participant's medical record and in the (e)CRF and this within 7 days after becoming aware. If available, the *diagnosis* should be reported on the appropriate (S)AE page in the (e)CRF, rather than the individual signs or symptoms. If no diagnosis is available, the Investigator should record each sign and symptom as individual safety events.

The following minimum information should be recorded for each event:

- event description
- start and stop date of the event
- severity
- seriousness
- causality assessment to the IMP and/or Trial procedures
- outcome

6.7.1 Assessment

All safety events must be evaluated by an Investigator with regards to:

- Seriousness**:** determine whether the AE is an SAE. See above for the seriousness criteria.
- Severity:
  - Severity must be evaluated by the Investigator according to the following definitions:
    - *Mild* – no or transient symptoms, no interference with the participant's daily activities
    - *Moderate* – marked symptoms, moderate interference with the participant's daily activities
    - *Severe* – considerable interference with the participant's daily activities, unacceptable
  - The severity of the AE will additionally be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, ranging from grade 1 till 5 [21]. Grading is provided in Appendix 9.
- Causality:
  - *None* – The AE is not related to the IMP or participation in the experiment
  - *Unlikely* – It is unlikely that the AE is related to the IMP or participation in the experiment; an alternative explanation is more likely (e.g., concomitant medication(s), concomitant disease(s)), and/or the relationship in time suggests that a causal relationship is unlikely

- *Possible* – The AE might be due to the use of the IMP or participation in the experiment. An alternative explanation is inconclusive. The relationship in time is reasonable; therefore, the causal relationship cannot be ruled out
- *Probable* - The AE might be due to the use of the IMP or participation in the experiment. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely
- *Definitely* – The AE is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation. The relationship in time is very suggestive (e.g., it is confirmed by dechallenge and rechallenge)

- System Organ Class: The AE will be identified utilising an System Organ Class, the highest level of the Medical Dictionary for Regulatory Activities (MedDRA) hierarchy [21,22]. This identifiers indicates the applicable anatomical or physiological system, aetiology, or purpose (e.g., Investigations for laboratory test results) [21]. Additionally, a further identifier according to the appropriate CTCAE term will be noted for each AE.
- Should a complication arise due to surgery, this must be noted as an AE as indicated above. However, an additional Clavien-Dindo grade will be attributed to the AE [23]. Grading is provided in Appendix 10.

6.7.2 Timelines for reporting

After obtaining informed consent and prior to initiation of Trial treatment, only (serious) adverse events caused by a Trial specific procedure should be reported in the (e)CRF.

After initiation of Trial treatment, safety events will be reported as follows:

- All AEs, SAEs and AESIs occurring during Trial treatment or within 30 days after last Trial treatment administration, or last follow-up visit (whichever occurs first) will be reported.
- All SAEs and AESIs as defined in the protocol must be reported to the Sponsor within 24 hours of the Trial staff becoming aware of the event. The initial report shall be followed by detailed, written reports. Both the initial and follow-up reports shall identify participants only by their Trial-specific identification.
- SAE details will be reported by the Investigator to the Sponsor by completing the SAE form in the (e)CRF.

- If an authorised Investigator from the reporting site is unavailable, initial reports without causality and expectedness assessment should be submitted to the Sponsor by a healthcare professional within 24 hours of becoming aware of the SAE, but must be followed-up by a medical assessment performed by an authorised Investigator, as soon as possible thereafter.

6.7.3 Follow-up

The Investigator must record follow-up information by updating the participant's medical records and the appropriate form(s) in the (e)CRF.

SAE follow-up information should only include new information (e.g. corrections or additions) and must be reported within 24 hours of the Investigator's first awareness of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- All **SAEs** must be followed until the outcome of the event is 'recovered', 'recovered with sequelae', 'not recovered' (in case of death due to another cause than the SAE) and until all related queries have been resolved, or until the end of the Trial (whichever occurs first)
- **Non-serious AEs** must be followed until the participant's last Trial visit, and until all related queries have been resolved

SAEs after the end of the Trial: If the Investigator or Trial team becomes aware of an SAE with suspected causal relationship to the IMP or experiment, after the participant has ended the Trial, than this SAE must be reported within the same timelines as for SAEs occurring during the Trial.

6.7.4 Pregnancy

Since the intrinsic nature of debulking surgery is to remove the ovaries, the patient cannot be pregnant. As such pregnancy is not in issue within this Trial.

6.7.5 Technical Complaints

Technical complaints should be reported to the Marketing Authorisation Holder (eg. change in color, unequal sizes, broken vials/pills, sedimentation, …).

6.7.6 Death

All deaths (except those defined under section 6.6) will be reported without delay to the Sponsor (irrespective of whether the death is related to disease progression, the IMP, participation in the experiment or an unrelated event). The Sponsor will notify all deaths as soon as possible after becoming aware to the central EC and the local EC of the concerned research site (via the contact person of the local research site, as applicable) and provide additional information if requested.

6.8 Reporting requirements to Ethics Committees (ECs) and Competent Authorities (CAs)

The Investigator is responsible for ensuring that all safety events are recorded in the (e)CRF and reported to the Sponsor in accordance with instructions provided in the protocol.

The Sponsor will promptly evaluate all SAEs and AESIs against medical experience to identify and expeditiously communicate possible new safety findings to Investigators, EC(s) and applicable CA(s) and participants as appropriate, in accordance with applicable legislation.

6.8.1 Sponsor's reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

After receiving the SAE report form from the Investigator, the Sponsor must perform a causality (relationship) assessment. The term Serious Adverse Drug Reaction (SADR) is to be used whenever either the Investigator or the Sponsor deems the SAE is possibly or probably related to the IMP.

The Sponsor must evaluate (and document the evaluation of) the expectedness for each SADR against the Reference Safety Information, e.g. the Investigator's Brochure or applicable product information. In case the event is Unexpected (i.e. a SUSAR) it must be reported by the Sponsor to the EC(s), CA(s) (through the EudraVigilance database or other local process) and other participating Investigators using the Council for International Organizations of Medical Sciences (CIOMS) form within the following timelines:

- **7 calendar days** if the event is fatal or life-threatening (follow-up information to be provided within an additional 8 calendar days)
- **15 calendar days** if non-fatal or non-life-threatening event (follow-up information be provided as soon as possible)

6.8.2 Annual reporting

he Sponsor has the obligation to, once a year throughout the clinical trial (or on request), submit a progress report to the EC's and CA's containing an overview of all SARs occurred during the reporting period and taking into account all new available safety information received during the reporting period.

6.8.3 Overview reporting requirements

WHO	WHAT	HOW	TO	TIMELINES
Investigator	AE	AE form	Sponsor	as defined in protocol
	SAE	SAE form	Sponsor	Initial & follow-up information: Immediately (within 24 hours of becoming aware of the event) Exceptions: as defined in protocol
	Death	SAE form	Sponsor	asap
Sponsor	SUSAR	CIOMS form: EC-reporting: according to EC process	**Unblinded report:** - EC - CA	For fatal or life-threatening SUSAR: asap, but no later than:

		- Reporting to CA(s): through EudraVigilance or local CA process	- MAH **Blinded report to:** PI's of participating sites	- 7 calendar days (initial report) - 8 calendar days (follow-up report) For non-fatal and non-life-threatening SUSAR: 15 calendar days (initial report) asap (follow-up report)
	Death	SAE form + narrative	EC(s)	asap
	Annual Progress/ Safety Report	DSUR or APR/ASR template	EC(s)	annually

6.9 Data Safety Monitoring Board (DSMB)

In accordance with EMA guideline on Data Monitoring Commitees (Doc. Ref. EMEA/CHMP/EWP/5872/03 Corr), this study does not require a DSMB. This study is a clinical study in a non-critical indication with a very short (one day) treatement time. Furthermore, the IMP is well characterised and known for not harming patients.

7 Statistics and Data Analysis

Statistical analysis will be performed in accordance with ICH E9; a detailed description of the analysis is provided in the Trial-specific Statistical Analysis Plan (SAP). ICH E3 and E8 will guide the structure and content of the clinical trial report.

In this open-label Trial, classical methods to minimize bias such as randomisation, blinding and compliance determination are not applicable. No active comparator is utilized in this Trial; therefore, randomisation is not achievable. The surgeon cannot be blinded during this surgical procedure due to the intrinsic nature of the Trial. However, the surgeon must identify the target lesions before the usage of the NIR fluorescence camera, therefore selection bias will be minimized. Since the administration of the IMP is a single event and the administration of the IMP will occur intravenously by a licensed practitioner, compliance determination is futile.

However, for the secondary endpoint concerning the TBR, selection and/or confirmation bias is likely since the area of interest (i.e., tumour and background area's) must be determined manually. To minimize this risk, machine learning will be utilised if technically feasible. Trainable Weka Segmentation is an ImageJ plugin capable of machine learning, allowing to produce pixel-based segmentations of unknown data (i.e., the fluorescence images captured during surgery), available from https://imagej.net/Trainable_Segmentation. We will aim to produce a new learning algorithm for this plugin in order to allow the tool to select tumour and background rather than the investigator. This should greatly reduce bias.

7.1 Sample Size Determination

Approximately 60 patients will be screened for this Trial. In total, 40 patients will be assigned to Trial treatment. The Trial exists of 2 arms, each with 20 patients. These two arms are the primary debulking group and the interval debulking group. Approximately 40 participants will be evaluable to complete the Trial.

Based on the previous report by Veys *et al.*, a power calculation has been conducted [13]. Values were determined from the fluorescence positive peritoneal nodules: 72,6% for malignant nodules, 45,7% for benign nodules [13]. The Fisher's Exact test for an a priori power analysis for two independent groups was utlised, with an alpha of 0,05 with a power of 95% and a two tail analysis and a 1:1 allocation. A minimum of 184 peritoneal lesions must be included to achieve statistically significant results in each arm. In each arm of the Trial, we will aim to include 200 (10 lesions in 20 patients) peritoneal lesions. Since the study has two arms with potentially significant different rates of ICG positivity, we aim to obtain statistical power

in each separate arm. As such we aim to include 400 (10 lesions in 2 times 20 patients) peritoneal lesions in this Trial. Should the number of usable lesions be less than expected, we can still obtain statistical significance when lowering power to 90% with an alpha of 0,05. As such, the minimum number of peritoneal lesions to achieve statistical significance is 148 in each arm.

Although clustering in participants could theoretically occur, we did not correct for this due to negligible clinical relevance. The location of the peritoneal lesion is more important than patient characteristics. Vascularisation – and as such the uptake and retention of the IMP – is mainly determined by the anatomical location and the tumour characteristics. These tumour characteristics also vary very little between patients with HGSOC. Therefore, we do not expect clustering in 1 participant nor in 1 specific group of participants.

7.2 Statistical Analysis

The main object of statistical analysis will be to determine the diagnostic accuracy of ICG. Therefore, we will use simple descriptive statistical methods to determine sensitivity, specificity, positive predictive value, negative predictive value, accuracy and diagnostic odds ratio. To determine statistical significance, confidence intervals will be used. Sensitivity and specivicity will be plotted on a receiver operating characteristic curve to further explore diagnostic accuracy. Since participants will only receive one administration of the IMP during surgery and afterward the Trial is ended for the participant, no longitudinal data will be analysed.

For secondary endpoints, similar descriptive statistical analysis will be utilised, mainly contingency table related statistical tests to determine statistical significance for these unpaired categorical data points.

Interim analysis will be discussed below.

For all statistical tests, the significance level will be 0,05. Should a participant drop out due to inoperability, determination of inadequate abdominal visualisation, or any other permissible reason, this participant will be accounted for in the statistical analysis with an intention-to-treat analysis.

7.2.1 Efficacy Analysis

Endpoint	Statistical Analysis Methods
Primary	Calculation of sensitivity, specificity, positive predictive value, negative predictive value, accuracy and diagnostic odds ratio
Secondary	Contingency tables and their associated statistical test (e.g., Chi-squared test, Fisher's Exact test) will be utilised
Exploratory	Not applicable

7.2.2 Other Analysis

Pharmacokinetic and pharmacodynamic analyses are not a part of this Trial since the IMP is a registered drugs and these properties are already known [7,10].

7.3 Interim Analysis and Final Database Lock

Altough utilising ICG in the detection of peritoneal lesions is still a very early technique and sensitivity for this technique varies greatly in literature (72%-100%), we wish not to perform an interim analysis [13,14]. Since the number of participants included in each Trial arm in total will be only 20 participants, an interim analysis with for example 10 participants will be too uncertain to indicate futility. Therefore, statistical analysis will be performed on each arm of the Trial when completed.

Final database lock will occur when both Trial arms have included 20 participants and each individual participant has fully completed follow-up (i.e., definitive pathological report has been obtained and no adverse events have been registered).

8 Data handling

Data handling and data flows for the Trial are summarized below and will be described in more detail in the Trial-specific Data Management Plan (DMP), see Appendix 11. An electronic CRF will be utilised. In this Trial, CRF will be provided by REDCap™ software, hosted on KU Leuven data servers (further details are provided in the DMP).

Data will be pseudonymised. The participant's name or other identifiers should be stored separately from the Trial data and replaced with a unique code to create a new identity for the participant, for the purpose of the Trial. In such case data are encoded (pseudonymised) and solely the Investigator and his/her Trial staff shall be able to link the data to an identifiable person. The code list will be retained on site, in a secured place with restricted access and can under no circumstances leave the site or be accessed by unauthorized persons.

As already discussed, all adverse events and reactions will be classified in the CRF using the CTCAE v5.0 and MedDRA terminology [21,22]. Clavien-Dindo classification will be utilised to classify surgical complications in the CRF [23].

Data flow of this Trial is condensed in the Data Flow Diagram (DFD), depicted in Figure 4.

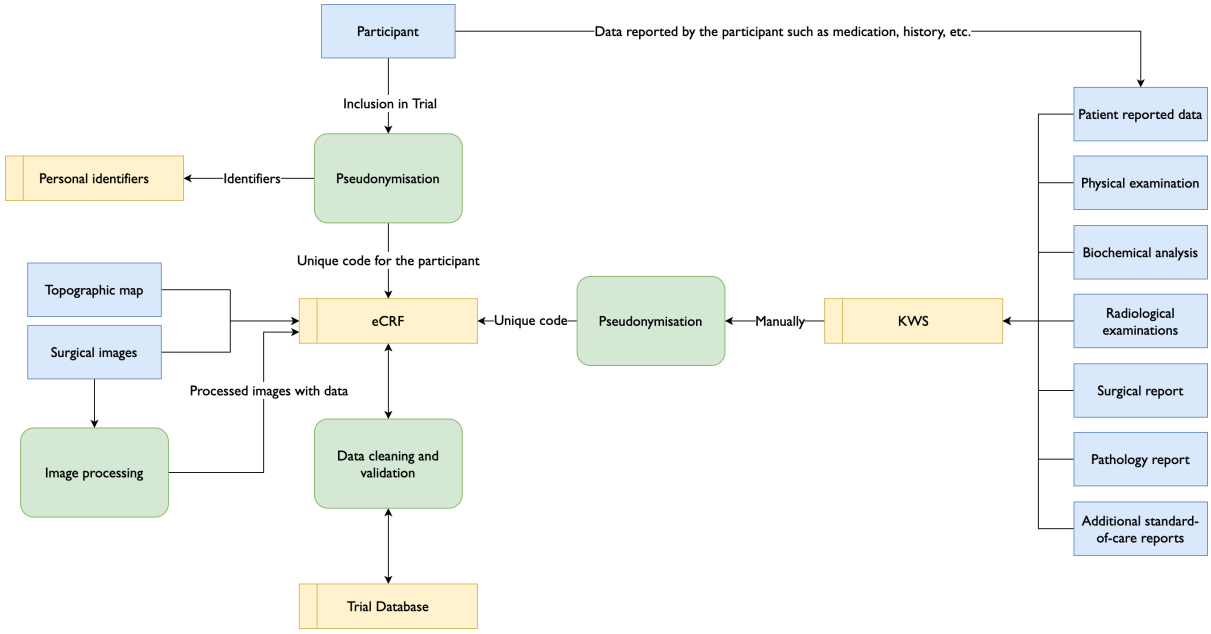


Figure 4

8.1 Data Collection Tools and Source Document Identification

8.1.1 Operational aspects

Data collection, handling, processing and transfer for the purpose of this Trial will be performed in compliance with applicable regulations, guidelines for clinical trials and internal procedures, as follows:

8.1.1.1 Data collection

Source Data will be collected and recorded in the Trial participant's files/medical records.

If applicable, worksheets may be used for capturing some specific data in order to facilitate completion of the (e)CRF. Any such worksheets will become part of the Trial participant's source documentation and will be filed together with or as part of the medical records (during but also following completion of the Trial).

It remains the responsibility of the Investigator to check that all data relating to the Trial, as specified in the Trial protocol, are entered into the (e)CRF in accordance with the instructions provided and that the forms are filled out accurately, completely and in a timely manner.

(e)CRFs are provided by the Sponsor for each participant. The Trial data will be transcribed from the source records (i.e. participant's medical file or Trial-specific source data worksheets) into an (e)CRF by Trial Staff. Transcription to the (e)CRF will be done as soon as possible after a participant visit and in a pseudonymized manner using a unique identifier assigned by the Sponsor.

The (e)CRFs will be available for review at the next scheduled monitoring visit (as applicable) and shall under no circumstances capture personal data such as but not limited to the participant or their relative(s) name, home address, contact details, full date of birth medical record number (e.g. UZ Leuven EAD number), social security number etc.

8.1.1.2 Data Validation

All data relating to the Trial must be prepared and validated by the Investigator. Any (e)CRF entries, corrections and alterations must be made by the Investigator or other authorized Trial staff.

Proper audit trails must be available to demonstrate the validity of the Trial data collected. This includes historical records of original data entries, by whom and when the data was entered, as well as detailed records of any corrections or additions made to the original data entry (i.e. who made the correction/addition, when and why), without obliterating the original data entry information.

8.1.1.3 Data Management

The Trial Data Manager will perform extensive consistency checks on the received data. Queries will be issued in case of inconsistencies in accordance with internal procedures. A Data Management Plan (DMP) will be developed to map data flows, data validation measures that will be taken, how (interim) database lock(s) will be managed and, as applicable, the role and responsibilities of the Data Safety Monitoring Committee (DSMB)

8.1.1.4 Data Transfer

Any participant records or datasets that are transferred to the Sponsor or any partners of the Sponsor will contain the Trial-specific participant identifier only; participant names or any information which would make the participant identifiable will not be transferred. All pseudonymized data relating to the Trial must be transmitted in a secure manner to the Sponsor or any partners of the Sponsor(see 8.1.2. legal requirements).

8.1.2 Legal requirements

All source data will be kept at a secured location with restricted access at all times. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data protection laws and regulations and more in particular the EU General Data Protection Regulation 2016/679 (GDPR) and relevant national laws implementing the GDPR. Appropriate technical and organizational measures to protect the data against unauthorized disclosure or access, accidental or unlawful destruction, or accidental loss or alteration must be established. Trial staff whose responsibilities require access to personal data agree to keep the data confidential.

The Investigator and the Participating Site(s) (as applicable) shall treat all information and data relating to the Trial disclosed to them as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the objectives of the Trial as described in this protocol. The collection, processing and disclosure of personal data, such as participant health and medical information is subject to compliance with applicable laws and regulations regarding personal data protection and the processing of personal data.

The Investigator will maintain all source documents and completed (e)CRFs that support the data collected from each Trial participant, and will maintain a Trial Master File (TMF)/Investigator Site File (ISF) containing all Trial documents as specified in ICH-GCP E6(R2) Chapter 8 entitled "Essential Documents for the Conduct of a Clinical Trial", and as specified by applicable regulatory requirement(s). The Investigator will take appropriate measures to prevent accidental or premature destruction of these documents.

Transfer of the pseudonymized data will be performed via a secured method of transfer taking into account all applicable security arrangements and regulations (such as the European General Data Protection Regulation). The receiving party will be bound by contractual agreement to keep the transferred data confidential at all times and to only process the data for the purpose of the Trial. To this end, appropriate Data Transfer Agreements (DTAs) will be established.

8.2 Audits and Inspections

The Investigator will permit direct access to Trial data and documents for the purpose of monitoring, audits and/or inspections by authorized entities such as but not limited to: the Sponsor or its designees and competent regulatory or health authorities. As such (e)CRFs, source records and other Trial related documentation (e.g. Investigator Site File, the Trial Master File, pharmacy records, etc.) must be kept current, complete and accurate at all times.

8.3 Monitoring

The purpose of clinical investigation monitoring is to verify that the conduct of the clinical investigation complies with the approved Clinical Investigational Plan (CIP), subsequent amendment(s), the ISO 14155:2011, and the applicable regulatory requirement(s).

UZ Leuven Clinical Trial Center (CTC) performs a risk analysis to determine the monitoring strategy. Based on this risk assessment, the clinical trial was classified as 'intermediate risk' as the potential risks associated to study procedures and protocol design are slightly higher to that of standard medical care since the IMP is used off-label.

However:

- Visualisation with Indocyanine Green will not influence patients treatment i.e. total resection will always be performed in this patient group
- Safety risks associated with trial participation are lower or equal to standard of care
- No medical decisions are taken solely based on the output of the visualisation with ICG.
- Any possible medical intervention that would occur as a result of comparing visualisation methods would not defer from how the treatment would be realised in routine medical practice
- The duration of trial participation for each subject is extremely short and very little data will be collected

Based on the above risk assessment and as permitted by ICH-GCP (r2) section 5.0.4, the Sponsor of the trial accepts the minimal risks associated with this trial and determines that monitoring activities (as defined by ICH-GCP E6(r2) §1.38) by a qualified individual, independent of the study team, is not necessary as it will provide little or no added value in protecting the safety of trial participants and assuring the integrity of collected trial data.

Nonetheless, the UZ Leuven study team will take all possible measures to assure the quality and integrity of trial data and to safeguard the safety and wellbeing of trial participants, in accordance with the requirements set out in ICH-GCP(r2) and ISO:14155

8.4 Archiving

As specified in ICH-GCP E6(R2) section 8.1 Addendum, the Sponsor and Investigator/Participating Site will maintain a record of the location(s) of all respective Essential Trial Documents (including but not limited to Source Documents, completed and final (e)CRF and ISF/TMF). The Sponsor should ensure that the Investigator has control of and continuous access to the (e)CRF data reported to the Sponsor during the Trial.

The Investigator/Participating Site should have control of all Essential Documents and records generated by the Investigator/Participating Site before, during and following termination of the Trial.

The Sponsor is responsible for archiving Trial specific documentation (such as but not limited to the Trial protocol, any amendments thereto, the final Clinical Study Report (CSR) and the Trial database) according to ICH-GCP E6(R2). Source data and site-specific Trial documents (such as but not limited to the original signed ICFs) will be archived by the participating site(s) according to local practice, and for at least 25 years following termination of the Trial. Archived data may be held on electronic record, provided that media back-up exists, hard copies can be obtained, if required and measures are taken to prevent accidental or premature loss or destruction of data. Destruction of Essential Documents prior to, during or upon completion of the required archival period, will require written authorisation from the Sponsor.

9 Ethical and Regulatory Considerations

9.1 Ethics Committee (EC) review & reports

Before the start of the Trial, this protocol and other related documents (e.g. ICF, advertisements, IB, etc.) will be submitted for review to the EC and to the relevant CA for Trial authorization. The Trial shall not commence until such approvals have been obtained.

It is the responsibility of the CI to produce the Annual Progress Report (APR) and submit to the EC/CA within 30 days of the anniversary date on which favourable opinion to start the Trial was given, and annually until the Trial is declared ended.

The CI shall notify the EC/CA of the end of the Trial. Should the Trial be temporarily suspended or, ended prematurely, the CI will notify the EC/CA and include the reasons for suspension/premature termination within 15 days of the decision. The CI will submit a final report with the results of the study, including any publications/abstracts, to the EC/CA within 1 year of trial termination or within 6 months for paediatric Trials.

9.2 Peer review

This Trial protocol was peer reviewed by the surgeons of the department of gynaecological oncology of UZ Leuven, each experts to the professional and scientific standards expected for clinical studies. Some aspects of the protocol were reviewed by prof. dr. Vandecaveye Vincent and prof. dr. Dresen Elleke, department of radiology, UZ Leuven.

9.3 Regulatory Compliance

The Trial will be conducted in compliance with the principles outlined in the requirements for the conduct of clinical Trials in the EU as provided for in Directive 2001/20/EC or EU Regulation 536/2014, as applicable, and any subsequent amendments, as well as in compliance with ICH-GCP E6(R2) guidelines, other GxP guidelines, the most recent version of the Declaration of Helsinki, the Belgian law of May 7th 2004 regarding experiments on the human person (as amended) or the Belgian law of May 7th 2017 on clinical Trials with medicinal products for human use, as applicable, and with the EU General Data Protection Regulation 2016/679 (GDPR), the relevant Belgian laws implementing the GDPR, the Belgian Law of August 22nd 2002 on patient rights and all other applicable legal and regulatory requirements.

9.4 Protocol / GCP compliance

The Trial must be performed in accordance with the protocol, current ICH and ICH-GCP guidelines, and applicable regulatory and country-specific requirements. ICH guidelines are an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of Trial participants are protected, consistent with the principles that originated in the most recent version of the Declaration of Helsinki, and that the Trial data are credible, reliable and reproducible.

The Investigator and Trial team acknowledge and agree that prospective, planned deviations or waivers to the protocol are not permitted under applicable regulations on clinical studies. However, should there be an accidental protocol deviation, such deviation shall be adequately documented in the source documents and on the relevant forms and reported to the CI and Sponsor. Deviations should also be reported to the EC as part of the EC's continued review of the Trial (e.g. through the ASR, APR, etc.). Protocol deviations which are found to frequently recur, will require (immediate) action. The Investigator acknowledges that such recurring protocol deviations could potentially be classified as a serious violation of ICH and/or the protocol.

It is understood that "a serious violation" is likely to affect to a significant degree:

- the safety or physical or mental integrity of the Trial participants; or
- the scientific validity of the Trial

The Investigator is expected to take any immediate action required to protect the safety of any participant included in the Trial, even if this action represents a deviation from the protocol. In such cases, the Sponsor

should be notified of this action and the EC at the Trial site should be informed according to local procedures and regulations.

9.5 Data protection and participant confidentiality

The Trial will be conducted in compliance with the requirements of the EU General Data Protection Regulation 2016/679 (GDPR), the relevant Belgian laws implementing the GDPR including the Belgian Privacy Act of 30 July 2018 on the protection of privacy in relation to the processing of personal data. Any collection, processing and disclosure of personal data, such as participant health and medical information is subject to compliance with the aforementioned personal data protection laws (cfr. Data Processing Annex (DPA) in Appendix 2). In case personal data is transferred outside the European Economic Area, safeguards will be taken to ensure that appropriate protection travels with the data in accordance with the GDPR.(https://ec.europa.eu/info/law/law-topic/data-protection/international-dimension-data-protection/rules-international-data-transfers_en#documents)

Any personal data shall be treated as confidential at all times including during collection, handling and use or processing, and the personal data (including in any electronic format) shall be stored securely at all times and with all technical and organizational security measures that would be necessary for compliance with EU and national data protection legislation (whichever is more stringent). The Sponsor shall take appropriate measures to ensure the security of all personal data and guard against unauthorized access thereto or disclosure thereof or loss or destruction while in its custody.

9.6 Insurance

The Participating Site, the Investigator and Sponsor shall have and maintain in full force and effect during the term of this Trial, and for a reasonable period following termination of the Trial, adequate insurance coverage for: (i) medical professional and/or medical malpractice liability, and (ii) general liability.

Art 29 of the Belgian Law relating to experiments on human persons dated May 7th, 2004 applies.

Prior to the start of the Trial, the Sponsor shall enter into an insurance contract in order to adequately cover Trial participants from Belgian sites in accordance with art. 29 of the said law.

9.7 Amendments

Unless for urgent reasons as specified in ICH-GCP E6(R2) section 4.5.4, amendments must not be implemented prior to EC and/or CA review and/or approval, as applicable.
In accordance with the Belgian law of May 7th 2004 regarding experiments on humans, the Sponsor may develop a non-substantial amendment at any time during the Trial. If a substantial amendment to the clinical Trial agreement or the documents that supported the original application for the clinical Trial authorisation is needed, the Sponsor must submit a valid substantial amendment to the Competent Authority (CA) for consideration, and to the EC for review and approval. The CA and/or EC will provide a response in accordance with timelines defined by applicable regulations. It is the Sponsor's responsibility to assess whether an amendment is substantial or non-substantial for the purpose of submission to the CA and/or EC.

Amendments to the Trial are regarded as 'substantial' when they are likely to have a significant impact on the safety or physical or mental integrity of the clinical Trial participants, or the scientific value of the Trial.

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2010_c82_01/2010_c82_01_en.pdf

9.8 Post-Trial activities

Since this study is a proof of concept study without direct therapeutic implications and the IMP will only be administered as a diagnostic tool, post Trial access is not applicable. Optimal debulking surgery will also be performed out of the scope of the Trial, as such patients who chose not to participate in this Trial will not receive any disadvangages of doing so.

10 Research Registration, Dissemination of Results and Publication Policy

The Declaration of Helsinki (latest version) and European and Belgian regulations require that every research Trial involving human participants be registered in a publicly accessible database before recruitment of the first participant. The CI is responsible for registering the Trial.

In addition, the CI will fulfil their ethical obligation to disseminate and make the research results publicly available. As such the CI is accountable for the timeliness, completeness and accuracy of the reports. Researchers, authors, Sponsors, editors and publishers must adhere to accepted guidelines for ethical reporting. Negative and inconclusive, as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in publication.

Publications will be coordinated by the CI. Authorship to publications will be determined in accordance with the requirements published by the International Committee of Medical Journal Editors and in accordance with the requirements of the respective medical journal.

11 Intellectual Property

Any know how, inventions, methods, developments, innovations, discoveries and therapies, whether patentable or not, arising from the Trial or made in the performance of the Trial protocol ("Inventions") shall vest in the Sponsor. The Participating Site, its employees and Investigator(s) shall promptly disclose to the Sponsor any such Inventions. Parties have expressly agreed that any and all Trial data as collected and prepared in the performance of the Trial protocol shall be the sole property of Sponsor unless otherwise agreed in the clinical trial agreement.

12 Joint Commission International (JCI)

In order to ensure the same quality and safety standards in patient care for clinical research as commonly applied by the Sponsor in its regular activities, and in accordance with JCI standards, the Sponsor shall comply with the following obligations: (a) the Sponsor will use trained and qualified employees or contractors to manage and coordinate the Trial; (b) the Sponsor will ensure that multi-center Trial reporting is reliable and valid, statistically accurate, ethical, and unbiased. (c) the Sponsor will not grant incentives, other than standard compensations and reimbursement of costs, to Trial participants or to participating site's staff that would compromise the integrity of the research; (d) the Sponsor is responsible for monitoring and evaluating the quality, safety, and ethics of the Trial and will respect the participating site's policies and processes when performing such monitoring and evaluation activities; (e) the Sponsor will protect the privacy and confidentiality of the Trial participants in accordance with all applicable laws.

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Appendices

1 Appendix 1: Clinical trial protocol history

Original CTP version:	1-0 dated 29-04-2021

Amendment #1: v1-1	07-05-2021
Modifications made / Reason for amendment:	
Added S-number and EudraCT number	Number just been available after version 1-0
Changed step 3 in the procedure	After feedback from the surgical staff, it was determined step 3 to be a clinicall assesemnt of peritoneal lesions and fluorescence signal by procuring images on specified location. This should reduce workload and improve correct analysis of the technique.
ISF files	Manditory ISF files are added.

Amendment #1: v1-2	30-06-2021
Modifications made / Reason for amendment:	
Added NCT number	Number just been available after version 1-1
2.4: Removed "*Preoperative imaging is not a prerequisite to participate in this Trial.*"	This is a faulty statement, one of the inclusion criteria.
8.3 Monitoring	Included the waiver for monitoring by UZ Leuven CTC after analysis by the CTC itself.

Amendment #2: v1-3	28/07/2021
Modifications made / Reason for amendment: (please see red text)	
1.3	Added indication that the performed examinations are not determined by the Trial, these are standard of care and only the treating physician chooses the suitable examinations.
2.5	Added indication more thime is needed for the surgery due to draping of the camera and taking of pictures.
5.1	Added indication for "Clinical-use Only" label, included a new appendix with this label. This was added after requirement from Competent Authorities.
7.1	Added additional information about power calculation, the to be performed statistical analysis and potential clustering in participants.
7.3	Interim analysis was removed due to inability to claim futility only after 10 participants could be included per arm.
Appendices	Changed numbering due to inclusion of new appendix with the label

2 Appendix 2: Data Processing Annex (DPA)

Definitions:

- "Protocol" means the document entitled "Visualisation of Indocyanine Green in Primary and Interval Debulking for Ovarian Cancer" containing the details of the academic Trial as developed by the Sponsor and approved by the relevant Ethics Committee.
- "Sponsor" means University Hospitals Leuven (UZ Leuven).
- Participating site acts as a data processor as defined under article 4, 8) of the Regulation (EU) 2016/679 ("Data Processor") for the Sponsor who acts as data controller as defined under article 4, 7) of the Regulation (EU) 2016/679 ("Data Controller").
- "Applicable Law" means any applicable data protection or privacy laws, including:
  a) the Regulation (EU) 2016/679 also referred as the General Data Protection Regulation ("GDPR");
  b) other applicable laws that are similar or equivalent to or that are intended to or implement the laws that are identified in (a) of this definition;
- "Personal Data" means any information relating to an identified or identifiable natural person ("Data Participant"), including without limitation pseudonymized information, as defined in Applicable Law and described in the Protocol.

Rights and obligations:

1. The Data Processor is instructed to process the Personal Data for the term of the Trial and only for the purposes of providing the data processing tasks set out in the Protocol. The Data Processor may not process or use Personal Data for any purpose other than a Data Participant's medical records, or other than provided in the instructions of the Trial protocol, including with regard to transfers of personal data to a third country or an international organization, unless the Data Processor is required to do so according to Union or Member State law.
2. Data Processor shall at all times maintain a record of processing of Personal Data in accordance with Applicable Law and if the Data Processor considers an instruction from the Data Controller to be in violation of the Applicable Law, the Data Processor shall promptly inform the Data Controller in writing about this.
3. The Data Processor must ensure that persons authorized to process the Personal Data have committed themselves to confidentiality or are under an appropriate statutory obligation of confidentiality.
4. The Data Processor shall implement appropriate technical and organizational measures to prevent that the Personal Data processed is:
   (i) accidentally or unlawfully destroyed, lost or altered,
   (ii) disclosed or made available without authorization, or
   (iii) otherwise processed in violation of Applicable Law.
5. The appropriate technical and organizational security measures must be determined with due regard for:
   (i) the current state of the art,
   (ii) the cost of their implementation, and
   (iii) the nature, scope, context and purposes of processing as well as the risk of varying likelihood and severity for the rights and freedoms of natural persons.
6. Taking into account the nature of the processing, the Data Processor shall assist the Data Controller, by means of appropriate technical and organizational measures, insofar as this is possible, in fulfilling its obligation to respond to requests from Data Participants pursuant to laws and regulations in the area of privacy and data protection (such as, the right of access, the right to rectification, the right to erasure, the right to restrict the processing, the right to data portability and the right to object)
7. The Data Processor shall upon request provide the Data Controller with sufficient information to enable the Data Controller to ensure that the Data Processor's obligations under this DPA are complied with, including ensuring that the appropriate technical and organizational security measures have been implemented.

8. The Data Controller is entitled to appoint at its own cost an independent expert, reasonably acceptable to the Data Processor, who shall have access to the Data Processor's data processing facilities and receive the necessary information for the sole purpose of auditing whether the Data Processor has implemented and maintained said technical and organizational security measures. The expert shall upon the Data Processor's request sign a non-disclosure agreement provided by the Data Processor, and treat all information obtained or received from the Data Processor confidentially, and may only pass on, after conferral with the Data Processor, the findings as described under 10) (ii) below to the Data Controller.
9. The Data Processor must give authorities who by Union or Member State law have a right to enter the Data Controller's or the Data Controller's processors' facilities, or representatives of the authorities, access to the Data Processor's physical facilities against proper proof of identity and mandate, during normal business hours and upon reasonable prior written notice.
10. The Data Processor must without undue delay in writing notify the Data Controller about:
    (i) any request for disclosure of Personal Data processed under the Protocol by authorities, unless expressly prohibited under Union or Member State law,
    (ii) any finding of (a) breach of security that results in accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, Personal Data transmitted, stored or otherwise processed by the Data Processor under the Protocol, or (b) other failure to comply with the Data Processor's obligations, or
    (iii) any request for access to the Personal Data (with the exception of medical records for which the Data Processor is considered data controller) received directly from the Data Participants or from third parties.
11. Such a notification from the Data Processor to the Data Controller with regard to a breach of security as meant in 10) (ii)(a) above will contain at least the following information:
    (i) the nature of the Personal Data breach, stating the categories and (by approximation) the number of Data Participants concerned, and stating the categories and (by approximation) the number of the personal data registers affected (datasets);
    (ii) the likely consequences of the Personal Data breach;
    (iii) a proposal for measures to be taken to address the Personal Data breach, including (where appropriate) measures to mitigate any possible adverse effects of such breach.
12. The Data Processor shall document (and shall keep such documentation available for the Data Controller) any Personal Data breaches, including the facts related to the Personal Data breach, its effects and the corrective measures taken. After consulting with the Data Controller, the Data Processor shall take any measures needed to limit the (possible) adverse effects of Personal Data breaches (unless such consultation cannot be awaited due to the nature of the Personal Data breach).
13. The Data Processor must promptly and reasonably assist the Data Controller (with the handling of (a) responses to any breach of security as described in 10) (ii) above and (b) any requests from Data Participants under Chapter III of the GDPR, including requests for access, rectification, blocking or deletion. The Data Processor must also reasonably assist the Data Controller by implementing appropriate technical and organizational measures for the fulfilment of the Data Controller's obligation to respond to such requests.
14. The Data Processor must reasonably assist the Data Controller with meeting the other obligations that may be incumbent on the Data Controller according to Union or Member State law where the assistance of the Data Processor is implied, and where the assistance of the Data Processor is necessary for the Data Controller to comply with its obligations. This includes, but is not limited to, at the request to provide the Data Controller with all necessary information about an incident under 10) (ii), and all necessary information for an impact assessment in accordance with Article 35 and Article 36 of the GDPR.

Subprocessor:

15. The Data Processor may only engage a subprocessor, with prior specific or general written consent from the Data Controller. The Data Processor undertakes to inform the Data Controller of any intended changes concerning the addition or replacement of a subprocessor by providing a reasonable prior written notice to the Data Controller. The Data Controller may reasonably and in a duly substantiated manner object to the use of a subprocessor. The Data Processor must inform the Data Controller in writing of the discontinued use of a subprocessor.

16. Prior to the engagement of a subprocessor, the Data Processor shall conclude a written agreement with the subprocessor, in which at least the same data protection obligations as set out in this DPA shall be imposed on the subprocessor, including obligations to implement appropriate technical and organizational measures and to ensure that the transfer of Personal Data is done in such a manner that the processing will meet the requirements of the Applicable Law.
17. The Data Controller has the right to receive a copy of the relevant provisions of Data Processor's agreement with the subprocessor related to data protection obligations. The Data Processor shall remain fully liable to the Data Controller for the performance of the subprocessor obligations under this DPA. The fact that the Data Controller has given consent to the Data Processor's use of a subprocessor is without prejudice for the Data Processor's duty to comply with this DPA.

3 Appendix 3: Summary of Product Characteristics of Verdye®

Please see separate attached file.

4 Appendix 4: Eastern Cooperative Oncology Group (ECOG) performance status

From Oken *et al.* [16]:

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

5 Appendix 5: Paper Case Report File

Please see separate attached file.

6 Appendix 6: Informed Consent Form (ICF)

Please see separate attached file.

7 Appendix 7: FIGO staging classification for cancer of the ovary, fallopian tube, and peritoneum

From Berek *et al.* [2]:

Stage I: Tumor confined to ovaries or fallopian tube(s)	T1-N0-M0
IA: Tumor limited to 1 ovary (capsule intact) or fallopian tube; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings	T1a-N0-M0
IB: Tumor limited to both ovaries (capsules intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings	T1b-N0-M0
IC: Tumor limited to 1 or both ovaries or fallopian tubes, with any of the following:	
IC1: Surgical spill	T1c1-N0-M0
IC2: Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface	T1c2-N0-M0
IC3: Malignant cells in the ascites or peritoneal washings	T1c3-N0-M0
Stage II: Tumor involves 1 or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or peritoneal cancer	T2-N0-M0
IIA: Extension and/or implants on uterus and/or fallopian tubes and/or ovaries	T2a-N0-M0

IIB: Extension to other pelvic intraperitoneal tissues	T2b-N0-M0
Stage III: Tumor involves 1 or both ovaries or fallopian tubes, or peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes	
IIIA1: Positive retroperitoneal lymph nodes only (cytologically or histologically proven):	T1/T2-N1-M0
IIIA1(i) Metastasis up to 10 mm in greatest dimension	
IIIA1(ii) Metastasis more than 10 mm in greatest dimension	
IIIA2: Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes	T3a2-N0/N1-M0
IIIB: Macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes	T3b-N0/N1-M0
IIIC: Macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)	T3c-N0/N1-M0
Stage IV: Distant metastasis excluding peritoneal metastases	Any T, any N, M1
Stage IVA: Pleural effusion with positive cytology	Any T, any N, M1
Stage IVB: Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)	Any T, any N, M1

8 Appendix 8: Clinical-use Only Label

Please see separate attached file.

9 Appendix 9: Common Terminology Criteria for Adverse Events (CTCAE) v5.0

Also please see separate attached file in ISF folder for full CTCAE criteria.

9.1 Terminology

Each AE will be classified by a System Organ Class, the highest level of the MedDRA hierarchy [21,22].

Each AE will further be classified by the applicable CTCAE term according to version 5.0 [21].

9.2 Grades

Grade	**Definition**
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 ageappropriate instrumental Activities of Daily Living (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.

* 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.

10 Appendix 10: Clavien-Dindo Classification

From Dindo *et al.* [23]:

Grade	**Definition**
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications)* requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient
Suffix "d" If the patient suffers from a complication at the time of discharge, the suffix "d" (for "disability") is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.	

*Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.

CNS, central nervous system; IC, intermediate care; ICU, intensive care unit.

11 Appendix 11: Data Management Plan (DMP)

Please see separate attached file.

1. NAAM VAN HET GENEESMIDDEL

VERDYE 25 mg, poeder voor oplossing voor injectie
VERDYE 50 mg, poeder voor oplossing voor injectie

2. KWALITATIEVE EN KWANTITATIEVE SAMENSTELLING

Iedere injectieflacon bevat 25 mg indocyanine groen (wordt gereconstitueerd met 5 ml water voor injectie) of 50 mg indocyanine groen (wordt gereconstitueerd met 10 ml water voor injectie).

1 ml gereconstitueerde oplossing voor injectie bevat 5 mg indocyanine groen.

Voor een volledige lijst van hulpstoffen, zie rubriek 6.1.

3. FARMACEUTISCHE VORM

Poeder voor oplossing voor injectie.
Donkergroen poeder.

4. KLINISCHE GEGEVENS

4.1 Therapeutische indicaties

Dit geneesmiddel is uitsluitend voor diagnostisch gebruik.

Diagnostische indicaties

Diagnostiek van hart, circulatie en microcirculatie:
- meting van het hartminuutvolume en slagvolume
- meting van circulerende bloedvolumes
- meting van de cerebrale perfusie

Diagnostiek van de leverfunctie:
- meting van de bloeddoorstroming in de lever
- meting van de excretiefunctie van de lever

Oogangiografie:
- meting van de perfusie van de choroidea

4.2 Dosering en wijze van toediening

Wijze van toediening

Voor de toediening moet het poeder worden gereconstitueerd met water voor injectie. Voor instructies over reconstitutie van het geneesmiddel, zie rubriek 6.6. De gereconstitueerde oplossing moet helder zijn en vrij van deeltjes.

Diagnostische onderzoeken met VERDYE moeten worden uitgevoerd onder supervisie van een arts.

VERDYE is bedoeld voor intraveneuze injectie via een injectienaald, een centrale of perifere katheter of hart katheter.

De toediening en de plaats van toediening van VERDYE zijn van doorslaggevend belang voor de kwaliteit van de metingen. In principe, om de optimale kwaliteit first pass indicator verdunningscurven te verkrijgen, dient de injectie zo dicht mogelijk bij het vaatbed, orgaan of te onderzoeken weefsel plaats te vinden.

Bij perifere injectie moet onmiddellijk geïnjecteerd worden na plaatsing van de tourniquet en de arm moet omhoog gehouden worden na het losmaken van de tourniquet. Dit garandeert een vlugge verplaatsing van de kleurstof van de plaats van injectie en perifere injectie is dan praktisch gelijkwaardig aan een centrale veneuze injectie.

Dosering

De enkelvoudige dosis per meting bij volwassenen, bejaarden, kinderen:

Diagnostiek van hart, circulatie, microcirculatie en weefselperfusie evenals de cerebrale doorbloeding: 0.1 tot 0.3 mg/kg lichaamsgewicht als bolusinjectie.

Leverfunctie diagnostiek: 0.25 – 0.5 mg/kg lichaamsgewicht als bolusinjectie.

Oogangiografie: 0.1 tot 0.3 mg/kg lichaamsgewicht als bolusinjectie.

Totale dagelijkse dosis:

Volwassenen, bejaarden en adolescenten van 11-18 jaar:
De totale dagelijkse dosis van VERDYE moet onder de 5 mg/kg lichaamsgewicht blijven.

Kinderen van 2 – 11 jaar:
De totale dagelijkse dosis moet onder de 2.5 mg/kg lichaamsgewicht blijven.

Kinderen van 0 – 2 jaar:
De totale dagelijkse dosis moet onder de 1.25 mg/kg lichaamsgewicht blijven.

Methodes van meting

Het absorptie- en emissie maximum van indocyanine groen zijn beide in het nabij-infrarood spectrum gelegen, het absorptiemaximum bij 800 nm en het emissiemaximum voor fluorescentiemeting bij 830 nm.
In *in-vitro*-tests blijft indocyanine groen verschillende dagen stabiel in humaan serum. Opgelost in water vertoont indocyanine groen slechts gedurende een paar uur geen opspoorbare afbraak.

Meting van hart-, circulatie-, en cerebrale doorbloeding en leverfunctie

De oppervlaktes onder de first pass curve, de passage tijd, de halfwaardetijd, de plasma-eliminatiesnelheid en de retentietijd van VERDYE kan worden bepaald:

a. niet-invasief door intermitterende kleurstof densitometrie of nabij infrarood spectroscopie.

b. invasief door optische vezel sondes/katheters in geschikte venen.
c. conventioneel door bepaling van de concentratie door ofwel continue onttrekking van bloed behandeld met heparine door een cuvette densitometer of door het nemen van bloedmonsters en het meten van de plasmaconcentratie met behulp van een fotometer.

Evaluatie van de fundus perfusie in de oogangiografie

De perfusie van de oogfundus kan door oftamologische fluorescentieangiografie worden bepaald en gemeten.

Meting van de weefselperfusie

Weefselperfusie van de oppervlakkige weefsellagen kan zichtbaar worden gemaakt en worden gemeten door nabij infrarood fluorescentie video angiografie.

4.3 Contra-indicaties

VERDYE is contra-geïndiceerd wegens veiligheidsredenen bij:

- patiënten met een overgevoeligheid voor indocyanine groen of voor natriumjodide tenzij speciale voorzorgsmaatregelen worden genomen,
- patiënten met een overgevoeligheid voor jodium,
- patiënten met hyperthyroïdie, patiënten met autonoom thyroïdaal adenoma.
- aangezien in-vitro experimenten hebben aangetoond dat indocyanine groen bilirubine verdringt van zijn eiwitbinding, mag VERDYE niet worden gebruikt bij te vroeg geboren of pasgeboren kinderen waarbij een wisseltransfusie is geïndiceerd omwille van hyperbilirubinemie,
- indien in het verleden injectie van VERDYE slecht werd verdragen, mag het niet opnieuw worden gebruikt, daar ernstige anafylactische reacties zouden kunnen optreden.

4.4 Bijzondere waarschuwingen en voorzorgen bij gebruik

- Daar ernstige anafylactische reacties zouden kunnen voorkomen na toepassing van VERDYE, mag het enkel worden toegediend onder supervisie van een arts.

- Als gevolg van een verhoogde incidentie van bijwerkingen bij patiënten met ernstige nierinsufficiëntie, mag VERDYE enkel worden toegediend na zorgvuldig afwegen van de voor- en nadelen.

- Heparine bereidingen die natriumbisulfiet bevatten verminderen de absorptiepiek van indocyanine groen in bloedplasma en bloed, en mogen daardoor niet worden gebruikt als anticoagulans bij het verzamelen van monsters voor analyse.

- Indocyanine groen is stabiel in plasma en bloed zodat monsters verkregen via discontinue monstertechnieken uren later kunnen worden gelezen. De behandeling van de kleurstofoplossing moet steeds in steriele omstandigheden gebeuren.

- De jodiuminhoud van VERDYE kan interfereren met schildkliertesten die werden uitgevoerd kort voor of kort na toediening van de kleurstof. Daardoor

mogen onderzoeken met radioactieve jodiumopname niet worden uitgevoerd tot minstens een week na toediening van VERDYE.

4.5 Interacties met andere geneesmiddelen en andere vormen van interactie

Betreffende onverenigbaarheden met oplosmiddelen voor verdunning zie rubriek 6.6.

De klaring van indocyanine groen kan worden gewijzigd door geneesmiddelen die interfereren met de leverfunctie.

Probenicid en sommige van zijn metabolieten kunnen in de gal worden afgescheiden, en kunnen op die manier de galafscheiding van indocyanine groen onderdrukken wat kan leiden tot een verzwakte indocyanine groen leverfunctie test.

Het gelijktijdige gebruik van bepaalde geneesmiddelen en injectievloeistoffen kan de absorptie veranderen. De absorptie wordt verminderd door injectievloeistoffen die natriumbisulfiet bevatten (in het bijzonder in combinatie met heparine). De volgende lijst geeft een overzicht van interactie met andere geneesmiddelen:

- Geneesmiddelen die de absorptie kunnen verminderen:
  anticonvulsiva
  bisulfiet verbindingen
  haloperidol
  heroïne
  pethidine
  metamizol
  methadon
  morfine
  nitrofurantoïne
  opium alkaloïden
  fenobarbital
  fenylbutazon.

- Geneesmiddelen die de absorptie kunnen verhogen:
  cyclopropaan
  probenicid
  rifamycine.

4.6 Zwangerschap en borstvoeding

Zwangerschap
Gegevens afkomstig uit een onderzoek bij een gelimiteerd aantal (242) zwangerschappen laten geen nadelige effecten zien van indocyanine groen op de zwangerschap of op de gezondheid van de foetus/pasgeboren kind. Tot op heden zijn er geen andere relevante epidemiologische gegevens beschikbaar. Er zijn geen studies betreffende reproductie, teratogeniteit of carcinogene eigenschappen uitgevoerd bij dieren. Het potentiële risico voor de mens is niet gekend.

Voorzichtigheid is geboden bij gebruik in zwangere vrouwen. Herhaalde toepassingen op één dag moeten worden vermeden.

Borstvoeding

Het is niet bekend of dit geneesmiddel in de moedermelk wordt uitgescheiden. Omdat vele geneesmiddelen in moedermelk worden uitgescheiden, moet men voorzichtig zijn wanneer indocyanine groen wordt toegediend aan een moeder die borstvoeding geeft.

4.7 Beïnvloeding van de rijvaardigheid en het vermogen om machines te besturen

Er werden geen studies uitgevoerd naar de effecten op het vermogen om te rijden of om machines te bedienen.

4.8 Bijwerkingen

Anafylactische of urticariële reacties werden gerapporteerd bij patiënten met of zonder voorgeschiedenis van allergie ten opzichte van jodiden.
Ook werden in zeer zeldzame gevallen spasmen van de kransslagader beschreven.

Het is bekend dat injectie van indocyanine groen preparaten in zeer zeldzame gevallen nausea en anafylactoïde of anafylactische reacties (<1/10000) kan veroorzaken. Bij patiënten met terminale renale insufficiëntie lijkt de mogelijkheid dat een anafylactische reactie optreedt, verhoogd. Symptomen die moeten worden vermeld zijn: onrust, gevoel van warmte, pruritus, urticaria, versnelling van de hartfrequentie, daling van de bloeddruk en kortademigheid, bronchospasmen, blozen, hartstilstand, laryngospasmen, gezichtsoedeem, nausea. Samen met de anafylactoïde reactie kan hypereosinofilie voorkomen.

Als, in tegenstelling tot de verwachtingen, de symptomen van anafylaxie voorkomen, moeten de volgende maatregelen onmiddellijk worden getroffen:
- stop de verdere toediening van VERDYE
- laat de injectiekatheter of -canule in de ader
- houd de luchtwegen vrij
- injecteer 100–300 mg hydrocortisone of een gelijkwaardig preparaat door middel van vlugge intraveneuze injectie
- volumesubstitutie met een isotone elektrolytoplossing
- geef zuurstof, controleer de circulatie
- trage intraveneuze toediening van antihistaminica

De volgende bijkomende maatregelen zijn aangewezen in geval van anafylactische shock:
- plaats de patiënt in een achterover liggende houding met de benen omhoog - vlugge volumesubstitutie met b.v. isotone elektrolytoplossing (drukinfuus), plasma-expanders.
- onmiddellijke intraveneuze toediening van 0.1–0.5 mg adrenaline (epinephrine) verdund tot 10 ml met 0.9 % fysiologische zoutoplossing (na 10 minuten herhalen indien noodzakelijk).

Huidreacties met urticaria kwamen zeer zelden voor (<1/10000).

Twee anafylactische sterfgevallen werden gerapporteerd na indocyanine groen toediening tijdens hartkatheterisatie. Een van de sterfgevallen was een patiënt met een voorgeschiedenis van penicilline en sulfa allergie. Doden als gevolg van anafylaxie kwamen voor in minder dan 1/330000 (schatting) met inbegrip van afzonderlijke meldingen.

Melding van vermoedelijke bijwerkingen
Het is belangrijk om na toelating van het geneesmiddel vermoedelijke bijwerkingen te melden. Op deze wijze kan de verhouding tussen voordelen en risico's van het geneesmiddel voortdurend worden gevolgd. Beroepsbeoefenaren in de gezondheidszorg wordt verzocht alle vermoedelijke bijwerkingen te melden via *Federaal agentschap voor geneesmiddelen en gezondheidsproducten, Afdeling Vigilantie, EUROSTATION II, Victor Hortaplein, 40/ 40, B-1060 Brussel, Website: www.fagg.be, e-mail: adversedrugreactions@fagg-afmps.be.*

4.9 Overdosering

Tot op heden werden er geen gevallen van overdosering of laboratoriumbevindingen betreffende overdosering van VERDYE gemeld.

5. FARMACOLOGISCHE EIGENSCHAPPEN

5.1 Farmacodynamische eigenschappen

Farmacotherapeutische categorie: Andere diagnostische agentia
ATC code: V04CX

Het actief bestanddeel in VERDYE is 2-{7-[1,1-dimethyl-3-(4-sulfobutyl)-benz[e]indolin-2-ylidene]-1,3,5-heptatrienyl}-1,1-dimethyl-3-(sulfobutyl)-1*H*-benz[e]-indolium hydroxide, kernzout, natrium zout).

De moleculaire formule is $C_{43}H_{47}N_2NaO_6S_2$. Het moleculair gewicht bedraagt 774.96 dalton.

Indocyanine groen heeft een scherp gedefinieerde spectrale piekabsorptie van nabij-infrarood licht bij 800 nm in bloedplasma of bloed. Dit is de zelfde golflengte waarbij de optische dichtheid van geoxideerde hemoglobine in bloed ongeveer gelijk is aan die van gereduceerde hemoglobine. Daardoor maakt deze samenvallende lichtabsorptie het mogelijk om indocyanine groen concentraties te meten in bloed, plasma en serum in termen van zijn optische dichtheid bij 800 nm, onafhankelijk van de schommelingen op het niveau van de zuurstofverzadiging.

Indocyanine groen maakt het vastleggen van de indicator verdunningscurven mogelijk voor zowel diagnostische als voor onderzoeksdoeleinden.
Indocyanine groen vertoont geen farmacologische effecten bij intraveneuze toediening.

5.2 Farmacokinetische gegevens

Distributie
Na intraveneuze injectie ondergaat indocyanine groen geen significante extrahepatische of enterohepatische circulatie; simultane arteriële en veneuze bloedbepalingen hebben aangetoond dat nier, perifere en long opname van de kleurstof verwaarloosbaar is. Bij gezonde vrijwilligers kan indocyanine groen niet worden aangetoond in urine noch in cerebrospinale vloeistof. Indocyanine groen passeert de placenta barrière niet. Het distributievolume komt overeen met het

bloedvolume. Na orale of rectale toediening wordt indocyanine groen niet geabsorbeerd door het darmkanaal.

Eiwitbinding
Na intraveneuze injectie, wordt indocyanine groen vlug gebonden aan het plasma-eiwit, waarvan het bèta apolipoproteïne B de belangrijkste drager is (95 %).

Metabolisme
Indocyanine groen wordt niet gemetaboliseerd.

Eliminatie
De eliminatie uit het plasma is tweefasig, met een initiële eliminatie halfwaardetijd t1/2 van 3-4 min en een secundaire fase met een doseringsafhankelijke t1/2 van ongeveer 60-80 min.

Indocyanine groen wordt bijna uitsluitend door de parenchymatische cellen van de lever uit het plasma opgenomen met een maximum opnamesnelheid (transport maximum: T_m van ongeveer 0,1 mg/minuut/kg) en wordt niet-gemetaboliseerd en niet-geconjugeerd volledig in de gal uitgescheiden. De maximale concentratie in de gal wordt bereikt na ongeveer ½ tot 2 uur afhankelijk van de ingespoten hoeveelheid.

Na obstructie in de gal, verschijnt de kleurstof in de leverlymfe, onafhankelijk van de gal, wat doet veronderstellen dat de galmucosa voldoende intact is om diffusie van de kleurstof te verhinderen, maar wel diffusie van de bilirubine toelaat.

Daar indocyanine groen niet opnieuw wordt geabsorbeerd in de darm is er geen enterohepatische circulatie.

5.3 Gegevens uit het preklinisch veiligheidsonderzoek

Acute toxiciteit: de LD_{50} na éénmalige i.v. dosering was 87 mg/kg bij ratten, 60 mg/kg bij muizen, en tussen 50 mg/kg en 80 mg/kg bij konijnen. Na oplossing in water voor injectie en toediening door intraperitoneale injectie bij muizen was de LD_{50} 650 mg/kg lichaamsgewicht. Geen macroscopische of histopathologische veranderingen werden geobserveerd.

Genetische toxiciteit: indocyanine groen was niet mutageen in de uitgevoerde testen (Ames test, gen mutatie test - thymidine kinase locus/$TK^{+/-}$ - in muis lymfoom L5178Y cellen, chromosoom aberratie test bij Chinese hamster V79 cellen).

Studies over reproductie, teratogeniteit, of kankerverwekkende eigenschappen in dieren zijn niet beschikbaar. Maar decennia van ervaring bij mensen hebben geen incidentie van deze eigenschappen geopenbaard.

6. FARMACEUTISCHE GEGEVENS

6.1 Lijst van hulpstoffen

Geen.

6.2 Gevallen van onverenigbaarheid

Dit geneesmiddel mag niet worden verdund met oplossingen die zouten bevatten (fysiologische zoutoplossing , Ringer-oplossing, enz) daar dit kan leiden tot neerslag

van de kleurstof. Dit geneesmiddel mag niet worden gemengd met andere geneesmiddelen dan die vermeld zijn in 6.6.

6.3 Houdbaarheid

5 jaar.
Na reconstitutie, moet de oplossing onmiddellijk worden gebruikt, beschermd tegen invloed van licht.

6.4 Speciale voorzorgsmaatregelen bij bewaren

Bewaren beneden 30 C. De injectieflacons in de buitenverpakking bewaren ter bescherming tegen invloed van licht. Voor de bewaarcondities van het geneesmiddel na reconstitutie, zie rubriek 6.3.

6.5 Aard en inhoud van de verpakking

Container: amberkleurige glazen injectieflacon (type I)
Sluiting: rubberstop (broombutyl, grijs) vastgemaakt door een aluminium kapje bedekt door een blauw polypropyleen beschermkapje

5 injectieflacons, elk met een inhoud van 25 mg poeder voor oplossing voor injectie.
5 injectieflacons, elk met een inhoud van 50 mg poeder voor oplossing voor injectie.

6.6 Speciale voorzorgsmaatregelen voor het verwijderen en andere instructies

Dit geneesmiddel mag enkel onmiddellijk voor gebruik worden gereconstitueerd.
Dit geneesmiddel wordt gereconstitueerd door toevoeging van respectievelijk 5 ml water voor injectie bij de injectieflacon die 25 mg van het actief bestanddeel bevat of 10 ml water voor injectie bij de injectieflacon die 50 mg van het actieve bestanddeel bevat. In beide gevallen wordt een donkergroene oplossing voor injectie bekomen met een concentratie van 5 mg/ml (0.5 % w/v).

Indien er een onverenigbaarheid wordt geconstateerd in de vorm van een troebele oplossing moet de gereconstitueerde oplossing onmiddellijk worden verwijderd. Inspecteer visueel de gereconstitueerde oplossing. Gebruik enkel heldere oplossingen zonder zichtbare deeltjes.

Dit geneesmiddel is alleen geschikt voor éénmalig gebruik.

7. HOUDER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

Diagnostic Green GmbH
Otto-Hahn-Str. 20
85609 Aschheim-Dornach
Duitsland

8. NUMMER VAN DE VERGUNNING VOOR HET IN DE HANDEL BRENGEN

BE274671 (25 mg)
BE273892 (50 mg)

9. DATUM VAN EERSTE VERGUNNING/HERNIEUWING VAN DE VERGUNNING

A. Datum van eerste vergunning: 04/07/2005.
B. Datum van hernieuwing van de vergunning: 15/10/2007.

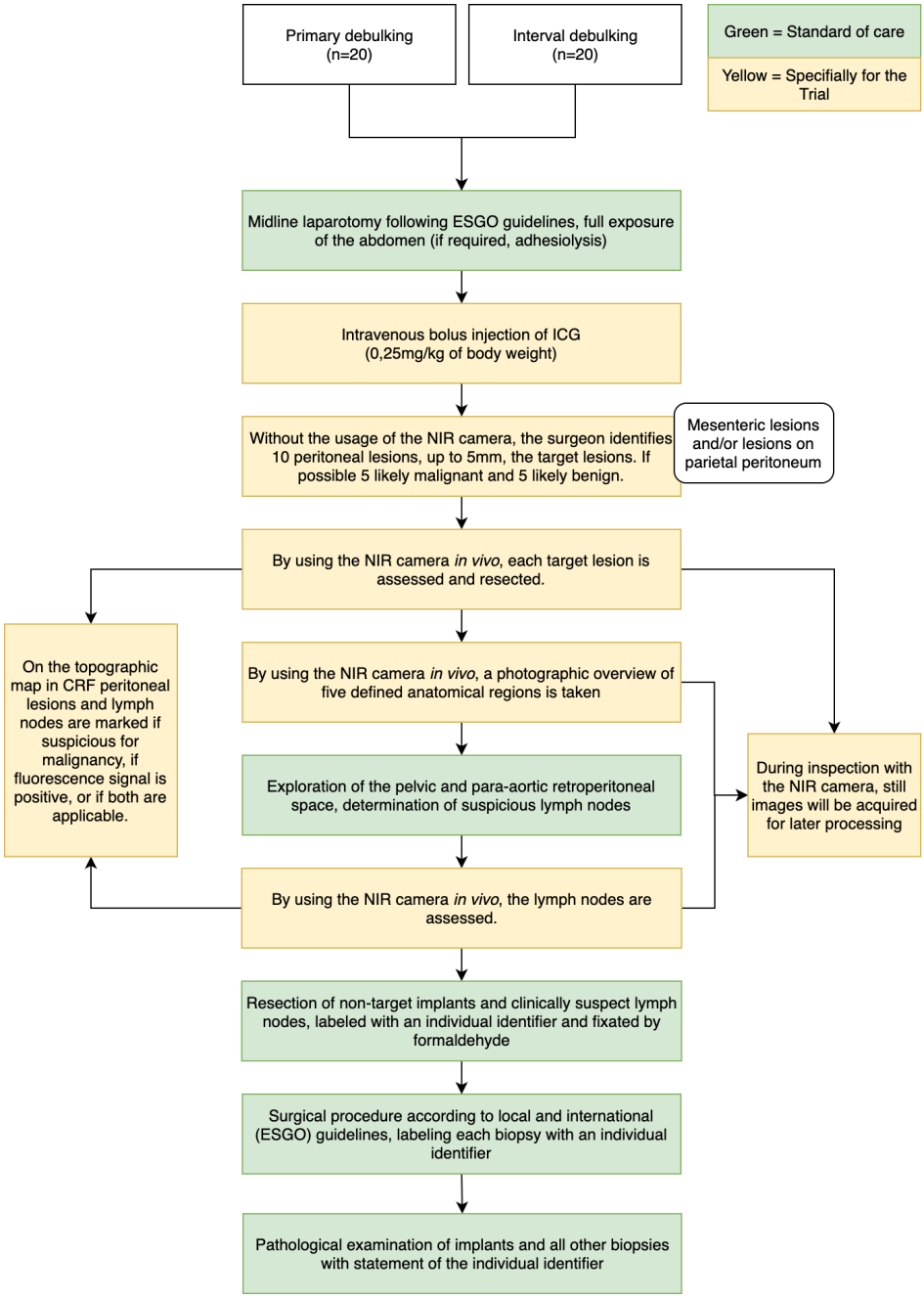
10. DATUM VAN HERZIENING VAN DE TEKST

01/2016
Goedkeuringsdatum: 02/2016

VIPIDO Case Report File

Trial: Visualisation of Indocyanine Green in Primary and Interval Debulking for Ovarian Cancer (VIPIDO) **S-number**: S65525 **Principal Investigator:** Toon Van Gorp **Trial Site**: UZ Leuven	Trial-specific participant identifier

Trial Flowchart



Please fill in all steps. All data will be stored in the electronic Case Report File.

Stap 1: Systematische foto's van het abdomen

Belangrijk! Deze foto's moeten in zwart wit zijn! Te vinden in camera settings: monochromatic

Neem foto's van de 5 onderstaande regio's, zowel zonder fluorescentie als met fluorescentie.
Gelieve hieronder aan te duiden welke foto's effectief werden genomen.

Regio	**Zonder fluorescentie**	**Met fluorescentie**
1. Pelvis	☐	☐
2. Omentum	☐	☐
3. Mesenterium	☐	☐
4. Rechter paracolische goot	☐	☐
5. Rechter middenrif	☐	☐

Stap 2: Benoem 10 peritoneale target lesions, vul deze vakjes in en noteer de anatomische locatie op het APO blad.

Lesion number 1	
Locatie	
Voor fluorescentie	<u>Meest waarschijnlijk</u> *Maligne* *Benigne* <u>Graad van zekerheid:</u> *Zeker* *Waarschijnlijk* *Onzeker*
Na fluorescentie	<u>Meest waarschijnlijk</u> *Maligne* *Benigne* <u>Graad van zekerheid:</u> *Zeker* *Waarschijnlijk* *Onzeker*
Werd er een foto genomen (zwart-wit!)?	*Ja* *Neen*

Gelieve de juiste *schuingedrukte* term te omcirkelen

Lesion number 2	
Locatie	
Voor fluorescentie	<u>Meest waarschijnlijk</u> *Maligne* *Benigne* <u>Graad van zekerheid:</u> *Zeker* *Waarschijnlijk* *Onzeker*
Na fluorescentie	<u>Meest waarschijnlijk</u> *Maligne* *Benigne* <u>Graad van zekerheid:</u> *Zeker* *Waarschijnlijk* *Onzeker*
Werd er een foto genomen (zwart-wit!)?	*Ja* *Neen*

Gelieve de juiste *schuingedrukte* term te omcirkelen

Lesion number 3	
Locatie	
Voor fluorescentie	<u>Meest waarschijnlijk</u> *Maligne* *Benigne* <u>Graad van zekerheid:</u> *Zeker* *Waarschijnlijk* *Onzeker*
Na fluorescentie	<u>Meest waarschijnlijk</u> *Maligne* *Benigne* <u>Graad van zekerheid:</u> *Zeker* *Waarschijnlijk* *Onzeker*
Werd er een foto genomen (zwart-wit!)?	*Ja* *Neen*

Gelieve de juiste *schuingedrukte* term te omcirkelen

Lesion number 4	
Locatie	
Voor fluorescentie	<u>Meest waarschijnlijk</u> *Maligne* *Benigne* <u>Graad van zekerheid:</u> *Zeker* *Waarschijnlijk* *Onzeker*
Na fluorescentie	<u>Meest waarschijnlijk</u> *Maligne* *Benigne* <u>Graad van zekerheid:</u> *Zeker* *Waarschijnlijk* *Onzeker*
Werd er een foto genomen (zwart-wit!)?	*Ja* *Neen*

Gelieve de juiste *schuingedrukte* term te omcirkelen

Lesion number 5	
Locatie	
Voor fluorescentie	<u>Meest waarschijnlijk</u> *Maligne* *Benigne* <u>Graad van zekerheid:</u> *Zeker* *Waarschijnlijk* *Onzeker*
Na fluorescentie	<u>Meest waarschijnlijk</u> *Maligne* *Benigne* <u>Graad van zekerheid:</u> *Zeker* *Waarschijnlijk* *Onzeker*
Werd er een foto genomen (zwart-wit!)?	*Ja* *Neen*

Gelieve de juiste *schuingedrukte* term te omcirkelen

Lesion number 6	
Locatie	
Voor fluorescentie	Meest waarschijnlijk *Maligne* *Benigne* Graad van zekerheid: *Zeker* *Waarschijnlijk* *Onzeker*
Na fluorescentie	Meest waarschijnlijk *Maligne* *Benigne* Graad van zekerheid: *Zeker* *Waarschijnlijk* *Onzeker*
Werd er een foto genomen (zwart-wit!)?	*Ja* *Neen*

Gelieve de juiste *schuingedrukte* term te omcirkelen

Lesion number 7	
Locatie	
Voor fluorescentie	Meest waarschijnlijk *Maligne* *Benigne* Graad van zekerheid: *Zeker* *Waarschijnlijk* *Onzeker*
Na fluorescentie	Meest waarschijnlijk *Maligne* *Benigne* Graad van zekerheid: *Zeker* *Waarschijnlijk* *Onzeker*
Werd er een foto genomen (zwart-wit!)?	*Ja* *Neen*

Gelieve de juiste *schuingedrukte* term te omcirkelen

Lesion number 8	
Locatie	
Voor fluorescentie	Meest waarschijnlijk *Maligne* *Benigne* Graad van zekerheid: *Zeker* *Waarschijnlijk* *Onzeker*
Na fluorescentie	Meest waarschijnlijk *Maligne* *Benigne* Graad van zekerheid: *Zeker* *Waarschijnlijk* *Onzeker*
Werd er een foto genomen (zwart-wit!)?	*Ja* *Neen*

Gelieve de juiste *schuingedrukte* term te omcirkelen

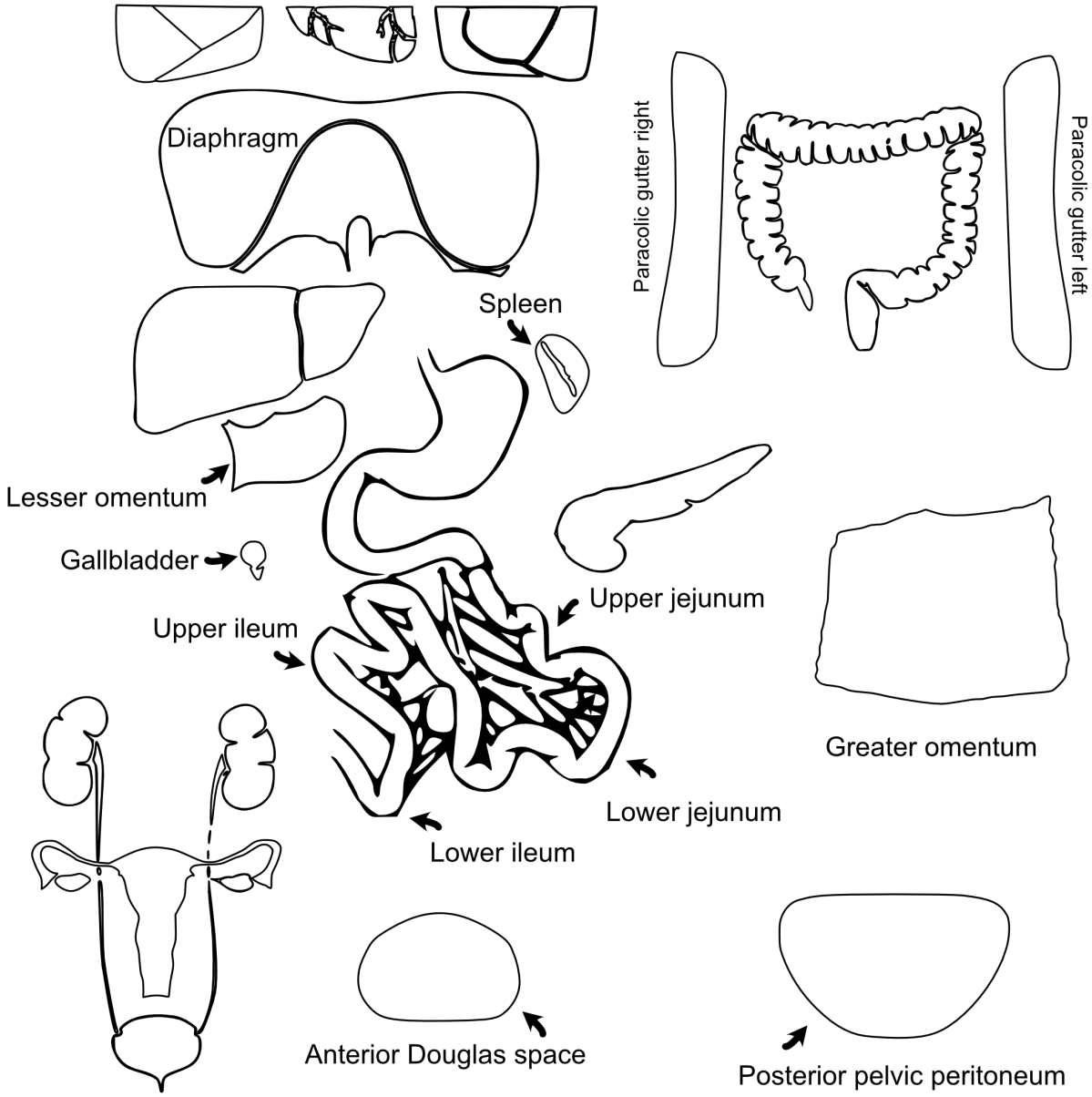
Lesion number 9	
Locatie	
Voor fluorescentie	Meest waarschijnlijk *Maligne* *Benigne* Graad van zekerheid: *Zeker* *Waarschijnlijk* *Onzeker*
Na fluorescentie	Meest waarschijnlijk *Maligne* *Benigne* Graad van zekerheid: *Zeker* *Waarschijnlijk* *Onzeker*
Werd er een foto genomen (zwart-wit!)?	*Ja* *Neen*

Gelieve de juiste *schuingedrukte* term te omcirkelen

Lesion number 10	
Locatie	
Voor fluorescentie	<u>Meest waarschijnlijk</u> *Maligne* *Benigne* <u>Graad van zekerheid:</u> *Zeker* *Waarschijnlijk* *Onzeker*
Na fluorescentie	<u>Meest waarschijnlijk</u> *Maligne* *Benigne* <u>Graad van zekerheid:</u> *Zeker* *Waarschijnlijk* *Onzeker*
Werd er een foto genomen (zwart-wit!)?	*Ja* *Neen*

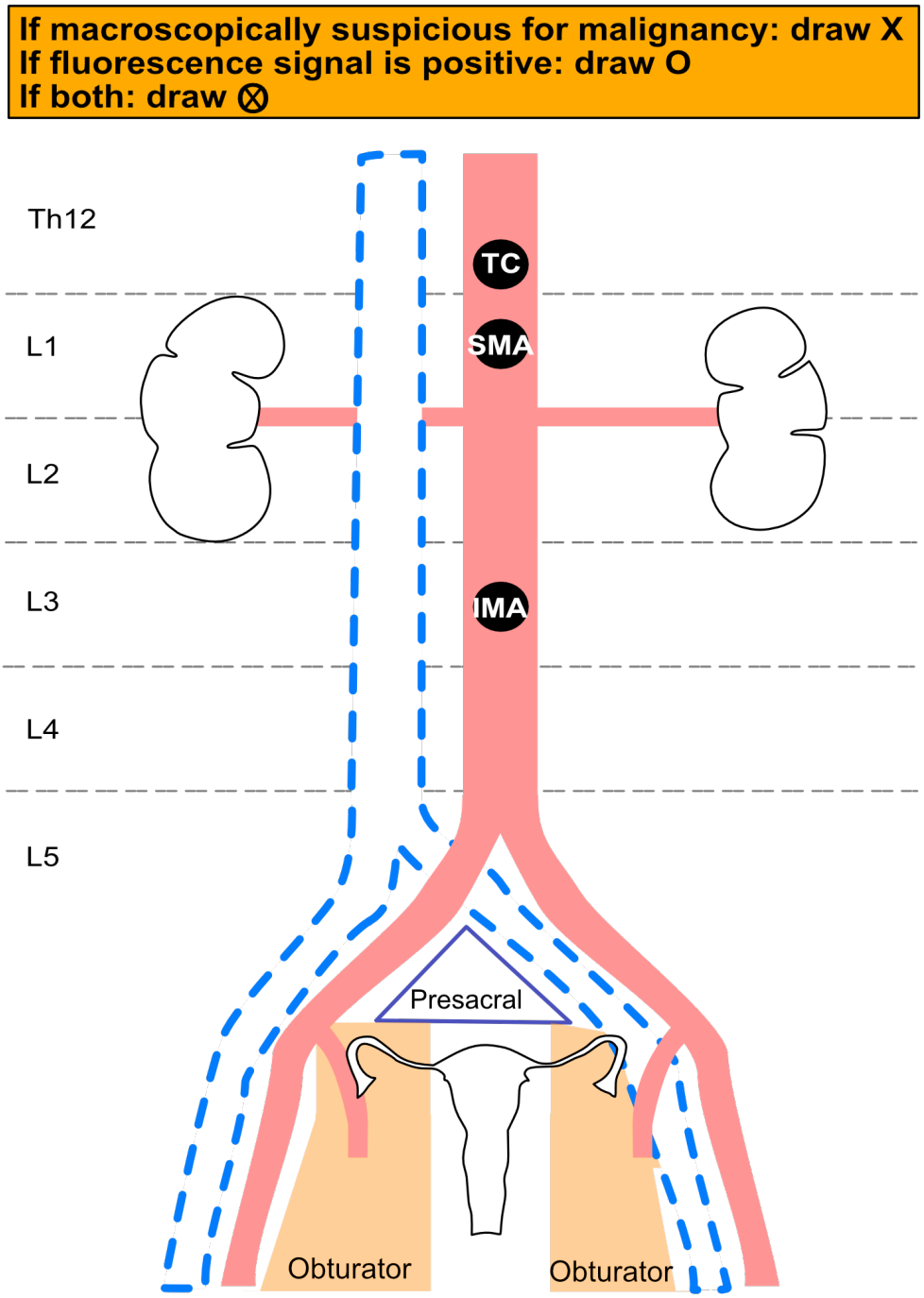
Gelieve de juiste *schuingedrukte* term te omcirkelen

Stap 3: Identificieer de target lesions door de corresponderende nummers te noteren op de topografische kaart.



Step 4: Bekijk de pelvische en para-aortische retropteritoneale ruimten

1. Markeer alle macroscopisch verdachte klieren op de tekening hieronder met een X
2. Markeer alle fluorescentie positieve klieren op de tekening hieronder met een 0
3. Als een klier zowel verdacht is als fluorescentie positief, zet een X met een cirkel errond.



Stap 5: Hoeveel percent van de peritoneale letsels was fluorescentie positief?

%

Stap 6: Gelieve zoveel mogelijk informatie op te nemen in het operatieverslag

Stap 7: Dit document terug bezorgen

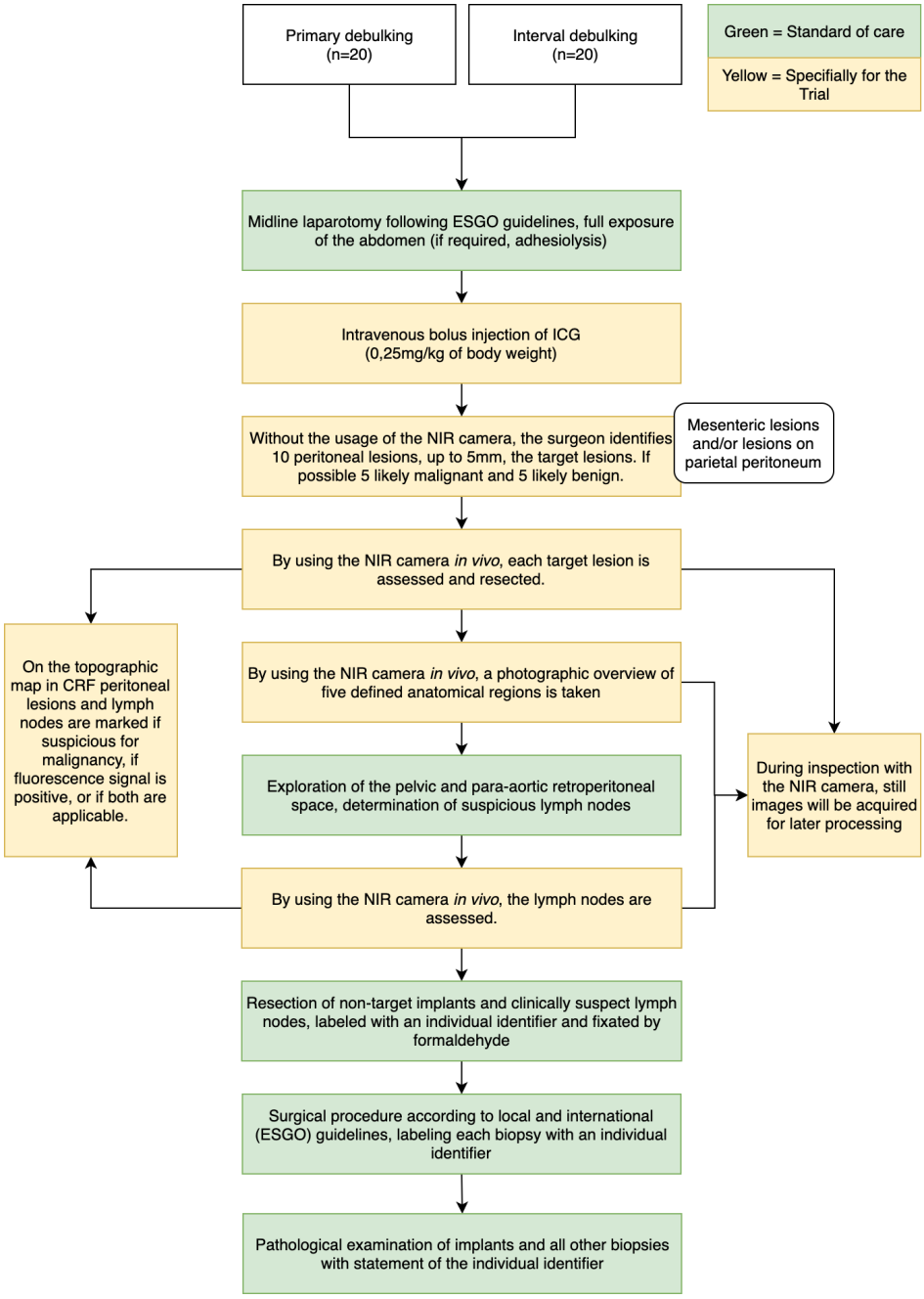
Gelieve dit document te bezorgen aan prof. Van Gorp of Sander Dumont (sander.dumont@uzleuven.be, DECT 42293, GSM: 0496 317 301).

Heel erg bedankt!!

VIPIDO Case Report File

Trial: Visualisation of Indocyanine Green in Primary and Interval Debulking for Ovarian Cancer (VIPIDO) **S-number**: S65525 **Principal Investigator:** Toon Van Gorp **Trial Site**: UZ Leuven	Trial-specific participant identifier

Trial Flowchart



Please fill in all steps. All data will be stored in the electronic Case Report File.

Step 1: Indicate 10 peritoneal target lesions and add this number to the pathology report

Lesion number 1	
Location	
Before fluorescence	Most likely: *Malignant* *Benign* Grade of certainty: *Certain* *Probably* *Uncertain*
After fluorescence	Most likely: *Malignant* *Benign* Grade of certainty: *Certain* *Probably* *Uncertain*
A photograph was taken?	*Yes* *No*

Please circle the appropriate *italic* term

Lesion number 2	
Location	
Before fluorescence	Most likely: *Malignant* *Benign* Grade of certainty: *Certain* *Probably* *Uncertain*
After fluorescence	Most likely: *Malignant* *Benign* Grade of certainty: *Certain* *Probably* *Uncertain*
A photograph was taken?	*Yes* *No*

Please circle the appropriate *italic* term

Lesion number 3	
Location	
Before fluorescence	Most likely: *Malignant* *Benign* Grade of certainty: *Certain* *Probably* *Uncertain*
After fluorescence	Most likely: *Malignant* *Benign* Grade of certainty: *Certain* *Probably* *Uncertain*
A photograph was taken?	*Yes* *No*

Please circle the appropriate *italic* term

Lesion number 4	
Location	
Before fluorescence	Most likely: *Malignant* *Benign* Grade of certainty: *Certain* *Probably* *Uncertain*
After fluorescence	Most likely: *Malignant* *Benign* Grade of certainty: *Certain* *Probably* *Uncertain*
A photograph was taken?	*Yes* *No*

Please circle the appropriate *italic* term

Lesion number 5	
Location	
Before fluorescence	Most likely: *Malignant* *Benign* Grade of certainty: *Certain* *Probably* *Uncertain*
After fluorescence	Most likely: *Malignant* *Benign* Grade of certainty: *Certain* *Probably* *Uncertain*
A photograph was taken?	*Yes* *No*

Lesion number 6	
Location	
Before fluorescence	Most likely: *Malignant* *Benign* Grade of certainty: *Certain* *Probably* *Uncertain*
After fluorescence	Most likely: *Malignant* *Benign* Grade of certainty: *Certain* *Probably* *Uncertain*
A photograph was taken?	*Yes* *No*

Please circle the appropriate *italic* term

Lesion number 7	
Location	
Before fluorescence	Most likely: *Malignant* *Benign* Grade of certainty: *Certain* *Probably* *Uncertain*
After fluorescence	Most likely: *Malignant* *Benign* Grade of certainty: *Certain* *Probably* *Uncertain*
A photograph was taken?	*Yes* *No*

Please circle the appropriate *italic* term

Lesion number 8	
Location	
Before fluorescence	Most likely: *Malignant* *Benign* Grade of certainty: *Certain* *Probably* *Uncertain*
After fluorescence	Most likely: *Malignant* *Benign* Grade of certainty: *Certain* *Probably* *Uncertain*
A photograph was taken?	*Yes* *No*

Please circle the appropriate *italic* term

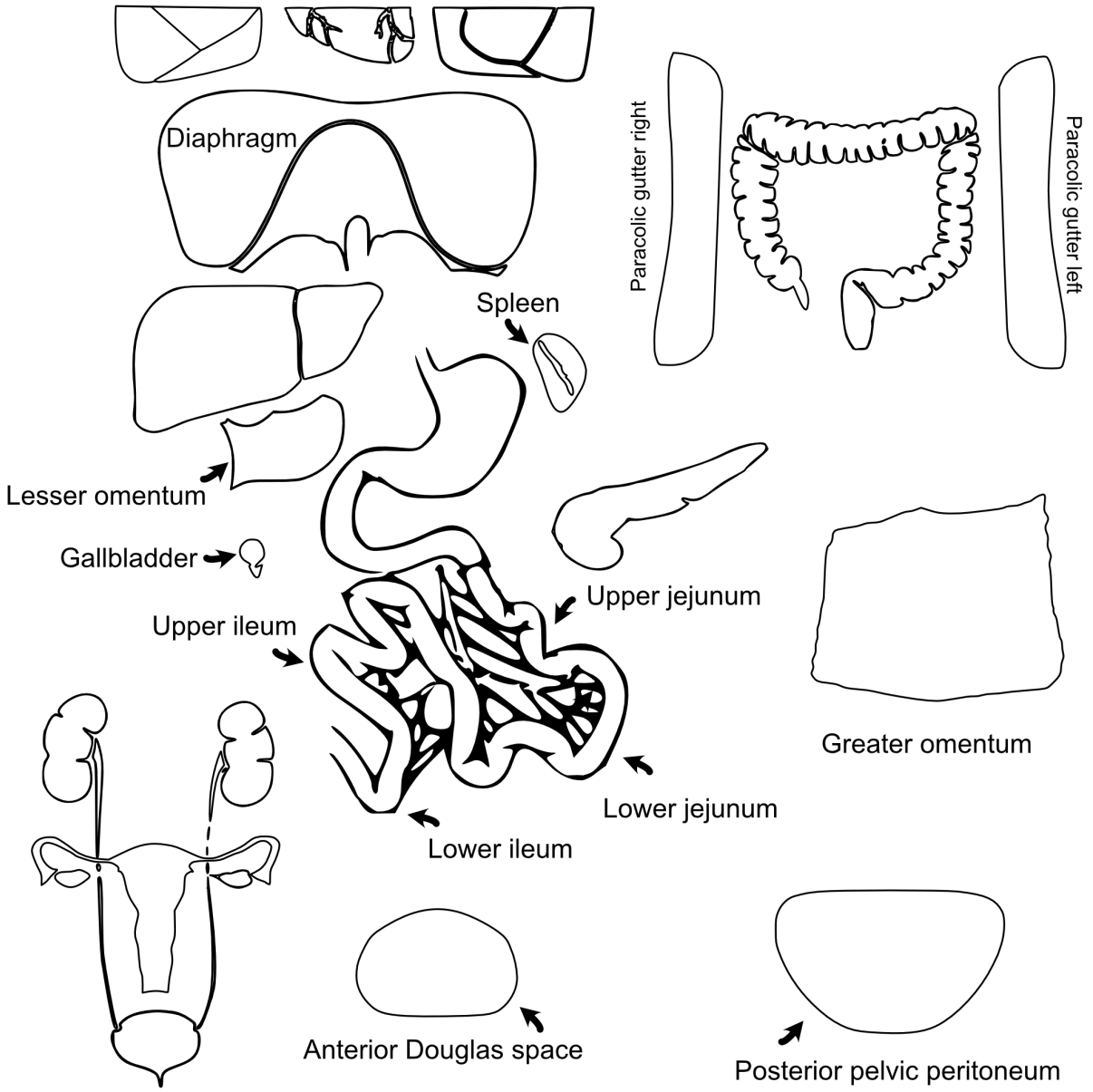
Lesion number 9	
Location	
Before fluorescence	Most likely: *Malignant* *Benign* Grade of certainty: *Certain* *Probably* *Uncertain*
After fluorescence	Most likely: *Malignant* *Benign* Grade of certainty: *Certain* *Probably* *Uncertain*
A photograph was taken?	*Yes* *No*

Lesion number 10	
Location	
Before fluorescence	Most likely: *Malignant* *Benign* Grade of certainty: *Certain* *Probably* *Uncertain*
After fluorescence	Most likely: *Malignant* *Benign* Grade of certainty: *Certain* *Probably* *Uncertain*
A photograph was taken?	*Yes* *No*

Please circle the appropriate *italic* term

Step 2: Indicate each target lesion on the topographic map

Please identify each target lesion by writing down the appropriate number on its topographic location.



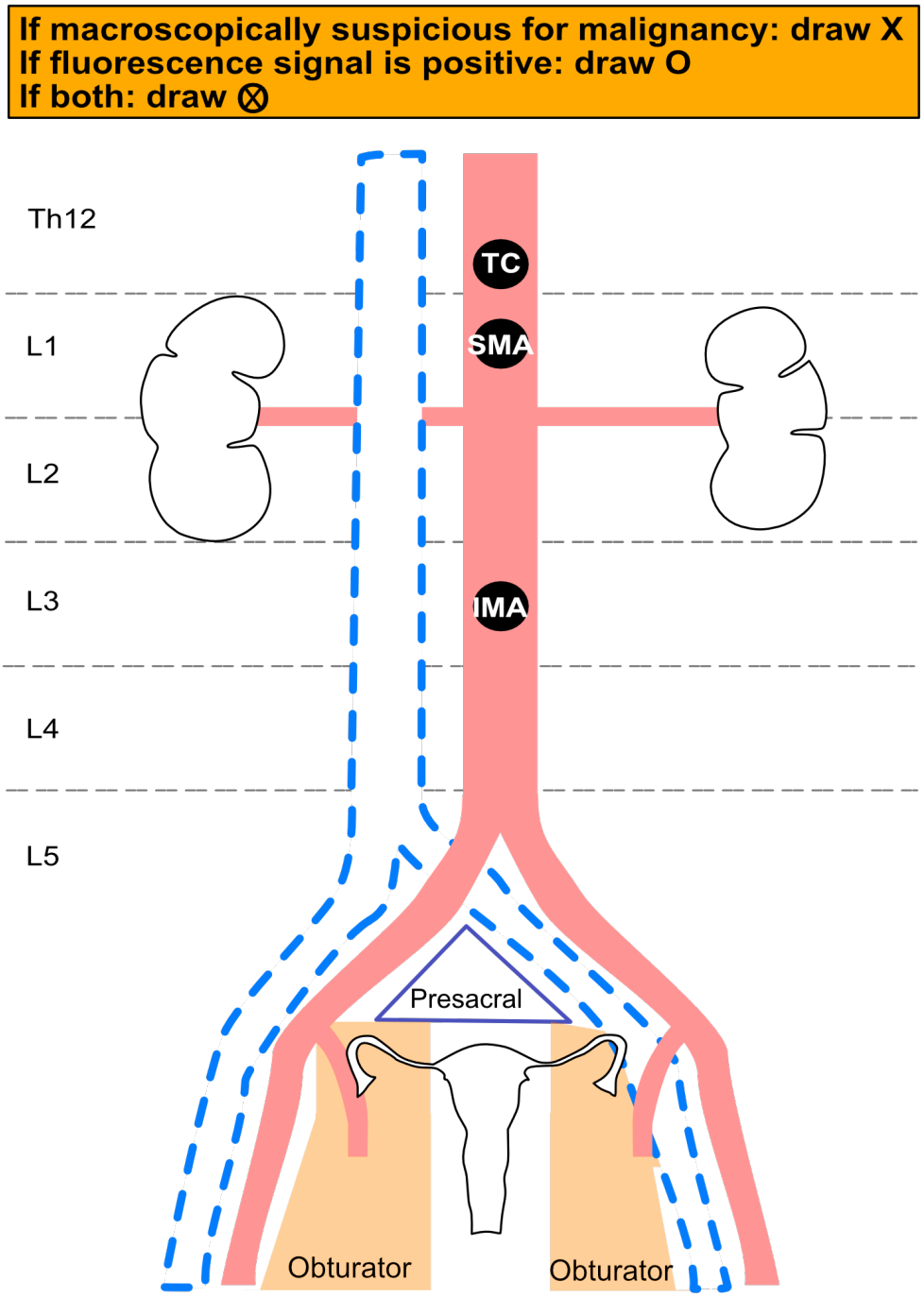
Step 3: Explore the abdomen

The abdomen is assessed macroscopically.
The surgeon obtains 2 photographs of 5 anatomically regions: 1 photograph without fluorescence and 1 photograph with fluorescence.
Please check the appropriate boxes of the procured images:

Region	**Without fluorescence**	**With fluorescence**
1. Pelvis	☐	☐
2. Omentum	☐	☐
3. Mesentery	☐	☐
4. Right paracolic gutter	☐	☐
5. Right-sided diaphragm	☐	☐

Step 4: Explore pelvic and para-aortic retroperitoneal space

1. Please identify all macroscopically suspicious lymph nodes and mark them with an X on the topographic map.
2. Should an area be fluorescence positive without a peritoneal lesion, please mark this location with a circle.
3. If the lymph node is macroscopically suspicious and fluorescence positive, please add a circle around the X.



Step 5: Indicate fluorescence positive ratio

Of all peritoneal lesions, what percentage is deemed fluorescence positive?

%

Step 6: When resecting peritoneal lesions or lymph nodes, please add as much information about its aspect, fluorescence positivity, and location in the surgical report

Step 7: Please submit this file

This form can be submitted to prof. Van Gorp or Sander Dumont (sander.dumont@uzleuven.be, DECT 42293, GSM: 0496 317 301).

Thank you for your cooperation!

FORMULIER GEÏNFORMEERDE TOESTEMMING

Visualisation of Indocyanine Green in Primary and Interval Debulking for Ovarian Cancer

Officiële titel van de studie:

Visualisatie van indocyanine groen bij primaire en interval debulking bij eierstokkanker

Afkorting: ***VIPIDO***

EU-nummer: 2021-002449-13

Studie nummer: S65525

ClinicalTrials.gov code: NCT04891185

Opdrachtgever van de studie: Universitaire Ziekenhuizen Leuven (UZ Leuven)

Naam studiecentrum: Universitaire Ziekenhuizen Leuven (UZ Leuven)

Hoofd adres studiecentrum: Herestraat 49, 3000 Leuven

Versie nummer: 1-3 / 28-07-2021

Met wie kan ik contact opnemen als ik vragen heb?

Naam	Functie	Voor	Contact-gegevens
prof. dr. Toon Van Gorp	Hoofdonderzoeker van het studiecentrum	Informatie, problemen, bezorgdheden	016 34 47 50 toon.vangorp @uzleuven.be
	Studiepersoneel	Informatie, problemen, bezorgdheden	016 34 47 50
	Contact voor dringende gevallen	Noodgeval (buiten de kantooruren)	016 34 08 03
	Ombudspersoon patiëntenrechten	Bezorgdheden over je rechten als deelnemer aan een studie	016 34 48 18
Amlin Insurance SE, Van Breda Risk & Benefits NV, Plantin en Moretuslei 297, 2140 Antwerpen	Verzekeraar	Betwisting of klacht over een schadeclaim	Polisnr. 299.053.700
	Functionaris voor gegevensbescherming van het studiecentrum	Vragen over de vertrouwelijkheid van je gegevens	dpo@uzleuven.be
	Belgische gegevensbeschermingsautoriteit	Klachten over de vertrouwelijkheid van je gegevens	contact@apd-gba.be

Inhoudsopgave

DE STUDIE IN EEN OOGOPSLAG

Beste mevrouw,

Recent werd er bij je **eierstokkanker** vastgesteld. Al dan niet werd je hiervoor al behandeld met chemotherapie. De volgende stap in je behandeling is een ingreep, de zogenaamde "**debulking**". Tijdens deze ingreep zal de chirurg al het zichtbare tumorweefsel verwijderen zodat uw overleving wordt gemaximaliseerd.

We nodigen je uit om deel te nemen aan een klinische studie (verder "studie" genoemd) die bedoeld is om deze ingreep te verbeteren en vooral om al het tumorweefsel te kunnen zien om te verwijderen.

Voor je ermee instemt deel te nemen aan deze studie, willen we je volledig informeren over wat de studie met zich meebrengt op het vlak van organisatie, de mogelijke risico's en voordelen. Zo kan je voor jezelf beslissen over je deelname. Dit noemt men "**geïnformeerde toestemming**" geven.

Dit hoofdstuk zal je reeds een idee geven wat deze studie inhoudt. Toch willen we je vragen om alle bladzijden te lezen, ook al zal het je veel tijd vragen. Het is belangrijk dat je alles leest én begrijpt. Als je dit niet doet, zal je deelnemen aan de studie zonder dat je weet waaraan je begint. Stel daarom al je vragen aan mij.

In deze studie zal het **studiegeneesmiddel Verdye®** worden getest. Dit studiegeneesmiddel is **door de Belgische overheid goedgekeurd, maar nog niet voor het gebruik in eierstokkanker**. **Daarom is het momenteel onzeker of je er voordeel bij zal hebben**. Dat willen we nu juist te weten komen: werkt het studiegeneesmiddel goed bij eierstokkanker.

Concreet betekent dit dat het studiegeneesmiddel zal worden toegediend tijdens je ingreep ("debulking") terwijl je in slaap bent. Dit studiegeneesmiddel zorgt ervoor dat de chirurg tijdens de ingreep **klein tumorweefsel beter kan zien** omdat deze zichtbaar worden door een fluorescente camera. Hierdoor hopen we dat ook het kleinste tumorweefsel volledig kunnen worden verwijderd, ook diegene die niet verdacht lijken of moeilijk te zien zijn met het blote oog.

Als je toestemt om deel te nemen aan de studie, zal ik de **al beschikbare onderzoeken bekijken** om na te gaan of je aan alle voorwaarden voldoet om aanvaard te worden voor deze studie.

Deze studie zal voor je slechts **één dag** duren, de dag van je ingreep ("debulking"). Dan zal het studiegeneesmiddel éénmalig worden toegediend. Voor deze studie moet je geen bijkomende onderzoeken ondergaan of bijkomend op consultatie komen.

Het is ook bijzonder belangrijk dat je weet dat alle geneesmiddelen **bijwerkingen** kunnen hebben. Die bijwerkingen kunnen zelfs heel erg zijn. Daarom moet je goed begrijpen dat je deze **bijwerkingen of elk nieuw gezondheidsprobleem aan mij moet melden**.

De opdrachtgever, **Universitaire Ziekenhuizen Leuven (UZ Leuven)**, heeft voor deze studie een **verzekering** afgesloten.

Deelnemen aan deze studie is volledig **gratis voor jou**. Alle **andere** onderzoeken of behandelingen die je anders ook zou krijgen indien je niet zou deelnemen, moeten **wel door de ziekteverzekering en jezelf betaald worden.**

De gegevens die tijdens deze studie verzameld worden, zullen **vertrouwelijk worden behandeld.**

In kader van deze studie zullen er geen bijkomende biologische stalen (zoals bloed) of onderzoeken (zoals scanner) worden genomen/uitgevoerd. Enkel de stalen en onderzoeken die de chirurg nodig heeft om de diagnose te kunnen stellen of om veilig te kunnen werken zullen worden genomen/uitgevoerd.

Eén ding wil ik heel sterk benadrukken: je bent absoluut niet verplicht om aan deze studie deel te nemen. Zelfs al ben je gestart met de studie dan nog kan je er altijd uitstappen. Daar zal ik steeds alle begrip voor opbrengen en je verder blijven verzorgen zoals voordien.

De studie werd geëvalueerd door de overheid en een ethisch comité. Het is niet omdat zij deze studie hebben goedgekeurd dat je je verplicht moet voelen om deel te nemen.

Om te kunnen deelnemen aan deze studie moet je, voor je eigen veiligheid, **ermee akkoord gaan dat ik als onderzoeker, je behandelende artsen, op de hoogte breng** van je deelname aan deze studie. Je mag **niet gelijktijdig aan een andere klinische studie deelnemen zonder de onderzoeker of het studiepersoneel daarvan op de hoogte te hebben gebracht**. Wij kunnen die deelname om gemotiveerde redenen weigeren.

Als je ermee akkoord gaat om deel te nemen, onderteken je het formulier voor geïnformeerde toestemming. Ik zal het formulier eveneens ondertekenen en daardoor bevestigen dat je de noodzakelijke informatie over de studie hebt gekregen. Je ontvangt een ondertekend en gedateerde exemplaar van het formulier.

Nu je al enig idee hebt wat deze studie inhoudt, kan je rustig de andere bladzijden van dit document lezen. Je hoeft dat niet in één keer te doen. Belangrijk is vooral dat je begrijpt wat je leest. Indien je dat wenst, mag deze studie zeker ook met andere vertrouwenspersonen (zoals je huisarts, familie of vrienden) bespreken. Mijn medewerkers en ikzelf staan ook klaar je te helpen mochten er zaken zijn die niet duidelijk zijn. Het is onze taak om er voor te zorgen dat jij alles goed begrijpt.

Met vriendelijke groeten,

Je behandelend arts en onderzoeker

Prof. dr. Toon Van Gorp

HOOFDSTUK I - BESCHRIJVING VAN DE STUDIE EN JE RECHTEN BIJ DEELNAME

1. Waarom doen we deze studie?

Deze klinische studie (verder "studie" genoemd) wordt uitgevoerd om het onderzochte geneesmiddel of "studiegeneesmiddel", Verdye®, te evalueren voor de diagnostiek van eierstokkanker.

Het doel van deze studie is om kleine tumorspots goed te kunnen visualiseren tijdens een "debulking" ingreep. Door deze fluorescente stof te injecteren zullen moeilijk zichtbare tumorspots makkelijker herkenbaar zijn voor de chirurg. Dit studiegeneesmiddel is reeds lange tijd op de markt in België voor andere toepassing zoals oogingrepen of meten van de leverfunctie. Bij eierstokkanker werd dit studiegeneesmiddel al gebruikt bij zo'n 26 patiënten in verschillende studies.

2. Waarom wordt mij gevraagd deel te nemen?

Er werd bij jou eierstokkanker vastgesteld. Je wordt gevraagd om deel te nemen aan deze studie omdat je binnenkort een "debulking" ingreep zal ondergaan omdat je bent vastgesteld met (of een vermoeden hebt voor) een stadium 3 of 4 eierstokkanker. Je kan niet deelnemen aan deze studie als je een voorgeschiedenis hebt van bepaalde schildklieraandoeningen of uitgebreide buikoperaties, ernstige nierinsufficiëntie hebt, of allergisch bent voor jood. Ook als je bepaalde medicamenten neemt kan je niet deelnemen, deze medicatie zullen we overlopen voordat je kan deelnemen aan de studie.

Op dit moment bestaat er geen alternatieve – door de Belgische overheid goedgekeurde – methode om de kleine tumorspots te kunnen zichtbaar maken tijdens de operatie voor de chirurg. De chirurg zal zonder dit studiegeneesmiddel enkel zijn/haar blote oog gebruiken om alle tumorspots te verwijderen.

De onderzoeker of het studiepersoneel zal met jou de voorwaarden bespreken om tot de studie te kunnen worden toegelaten.

3. Moet ik deelnemen aan een studie?

Je deelname aan een studie gebeurt vrijwillig en mag nooit onder druk gebeuren. Dit betekent dat je het recht hebt om niet deel te nemen aan de studie. Je mag je ook op elk moment terugtrekken zonder dat je hiervoor een reden hoeft te geven, zelfs al heb je eerder toegestemd om deel te nemen. Je beslissing zal geen invloed hebben op je relatie met de onderzoeker of je behandelende arts, noch op de kwaliteit van je toekomstige medische zorgen.

Indien andere behandelingen beschikbaar zijn voor je eierstokkanker, zal de onderzoeker of zijn/haar afgevaardigde die behandelingen met jou bespreken.

4. Wat gaat er tijdens de studie gebeuren?

Bij deze studie zullen ongeveer 40 deelnemers over de hele wereld betrokken zijn, waaronder ongeveer 40 in België.

Deze studie is een éénmalige toediening van een fluorescente stof in uw ader. Deze stof is niet radioactief en wordt reeds decennialang gebruikt bij andere toepassingen binnen de chirurgie met een gunstig veiligheidsprofiel. Deze stof heeft Verdye®.

Tijdens uw "debulking" ingreep zal de chirurg al de zichtbare kanker spots verwijderen. Wij hopen dat deze stof het voor de chirurg makkelijker maakt om zeer kleine spots op te sporen en zo te verwijderen. Dit is erg belangrijk omdat hoe beter de kanker verwijderd wordt, hoe beter de overleving is van eierstokkanker.

De stof zal slechts éénmaal bij u worden toegediend tijdens de ingreep terwijl u al in slaap bent. U zal dus niet merken dat deze stof zal worden toegediend. De toegediende dosis is 0,25mg/kg lichaamsgewicht. Deze dosis is ruim onder de toxische marges en werd al gebruikt in voorafgaande studies. Deze stof wordt vanzelf door uw lichaam afgebroken op relatief korte tijd (minder dan 24 uur).

Er zullen tijdens deze studie geen bijkomende onderzoeken gebeuren. Alle onderzoeken – zoals bloedafname, scanners, andere beeldvorming, hartfilmpje, … - zullen enkel plaatsvinden als uw behandeld arts dit nodig vindt om de operatie te kunnen uitvoeren of om de diagnose correcter te stellen. Je zal dus niet worden gevraagd bijkomende onderzoeken te ondergaan, je behandeld arts zal ook geen bijkomende onderzoeken voorstellen omdat je deelneemt aan deze studie.

Na deze studie moet je niet op een controle afspraak komen voor deze studie. Alle vervolgafspraken zullen enkel worden gemaakt omdat de behandelend arts dit nodig vindt, niet omdat je deelnam in deze studie.

Je deelname aan de studie zal voor je in totaal ongeveer 1 dag duren (tijdens de ingreep) en geen bijkomende bezoeken inhouden.

Indien je voldoet aan alle voorwaarden voor deelname en besluit deel te nemen aan de studie, zal je de bovenvermelde testen en onderzoeken, ondergaan. In het geval van belangrijke bijwerkingen kan het zijn dat de onderzoeker het nodig acht bijkomende testen te doen, die dan zullen worden beschouwd als studie specifiek.

5. Zal ik voordeel halen uit de studie?

De informatie die tijdens de studie verkregen wordt, kan bijdragen tot een beter inzicht in het gebruik van het studiegeneesmiddel of tot de ontwikkeling van een nieuw geneesmiddel voor de behandeling van jezelf of toekomstige patiënten.

Het studiegeneesmiddel kan al dan niet gunstig blijken te zijn voor de behandeling van je ziekte of het verlichten van je symptomen. Zelfs als het effect gunstig blijkt, is een terugkeer of verergering van de symptomen, de ziekte of de aandoening nog altijd mogelijk.

6. Welke zijn de mogelijke risico's en ongemakken bij deelname aan de studie?

6.1. Welke zijn de mogelijke bijwerkingen van Verdye®?

Deelnemen aan een studie houdt enig risico in.

Elk geneesmiddel kan bijwerkingen hebben. Sommige daarvan zijn al gekend, andere niet. Ook al hebben voorgaande studies uitgewezen dat Verdye® normaal goed werd verdragen, kan je toch nog de volgende bijwerkingen ondervinden:

- Allergische huidreactie
    - Zeer zelden: Bij 1 op 10 000 à 100 000 patiënten
- Ernstige veralgemeende allergische reactie
    - Zeer zelden: Bij 1 op 10 000 à 100 000 patiënten

6.2. Welke zijn de mogelijke risico's of ongemakken van de onderzoeken tijdens de studie?

Aan de onderzoeken tijdens de studie zijn geen gekende risico's verbonden.

6.3. Mag ik tijdens de studie andere geneesmiddelen nemen?

Je mag andere geneesmiddelen gebruiken. Voor de deelname in de studie zal je huidige medicatie worden overlopen als dit veilig is om in te nemen tijdens de studie. Wanner je geneesmiddel niet veilig zou zijn kan je niet deelnemen aan de studie.

Aarzel niet om je onderzoeker meer uitleg te vragen over het gebruik van andere geneesmiddelen.

6.4. Zal mijn deelname aan de studie een invloed hebben op mijn dagelijkse activiteiten?

Neen

6.5. Mag ik zwanger worden of mag ik borstvoeding geven tijdens de studie?

Omdat tijdens deze ingreep de eierstokken worden verwijderd, kan je niet meer zwanger worden of borstvoeding geven.

7. Wat als er tijdens de studie iets fout gaat?

Zelfs als er geen sprake is van fout, is de opdrachtgever aansprakelijk voor de schade die je lijdt en die rechtstreeks of onrechtstreeks verband houdt met je deelname aan de studie. De opdrachtgever heeft voor die aansprakelijkheid een verzekering afgesloten (met "FOUTLOZE" AANSPRAKELIJKHEID) (Ref. 1). Een kopie van het verzekeringsattest kan verkregen worden via de onderzoeker of het studiepersoneel.

Indien je (of bij overlijden je erfgenamen) een vergoeding wenst voor de schade die je oploopt als rechtstreeks of onrechtstreeks gevolg van je deelname aan de studie, moet je de onderzoeker of het studiepersoneel daarvan zo snel mogelijk op de hoogte brengen.

Als de onderzoeker gelooft dat een verband tussen nieuwe of verergerde gezondheidsklacht(en) en de studie mogelijk is, zal hij/zij dat melden bij de opdrachtgever van de studie. De opdrachtgever zal dan meteen een aangifte doen bij zijn verzekeringsmaatschappij. Indien de maatschappij het nodig vindt, zal zij een expert aanstellen om na te gaan of er een verband is tussen je gemelde gezondheidsklacht(en) en de studie. De verzekering dekt niet de natuurlijke evolutie van je ziekte/aandoening of de gekende bijwerkingen van de behandeling die je zou hebben gekregen zonder deel te nemen aan de studie (dit is je standaardbehandeling).

Wanneer je het nodig vindt of in geval van onenigheid met de onderzoeker of met de expert van de verzekeringsmaatschappij, kunnen jij of je erfgenamen de verzekeraar contacteren of indien nodig dagvaarden. De contactgegevens vind je op het voorblad van dit formulier.

8. Wat als er tijdens de studie andere behandelingen of nieuwe informatie over het studiegeneesmiddel beschikbaar worden?

In de loop van de studie zou nieuwe belangrijke informatie beschikbaar kunnen worden, die een invloed zou kunnen hebben op je beslissing om (verder) deel te nemen. Zo kunnen bijvoorbeeld andere behandelingen voor je ziekte of belangrijke nieuwe informatie over het studiegeneesmiddel beschikbaar worden. Het is de plicht van de onderzoeker deze nieuwe informatie met jou te bespreken en je de kans te geven je deelname aan de studie te herbekijken.

Indien je besluit je deelname aan de studie te beëindigen of indien je niet langer kan deelnemen, zal je onderzoeker erop toezien dat je de best mogelijke behandeling blijft krijgen.

9. Kan mijn deelname aan de studie vroegtijdig eindigen?

Zoals verder in dit deel gedetailleerd besproken wordt, kan je deelname aan de studie vroegtijdig eindigen wanneer

- je besluit je toestemming in te trekken,
- de onderzoeker besluit je deelname aan de studie te stoppen, of
- andere instanties de studie onderbreken of beëindigen.

In elk geval, als je deelname aan de studie vroegtijdig stopt, zal de onderzoeker je verdere medische zorg met jou bespreken. De opdrachtgever kan gegevens die reeds werden verzameld vóór de beëindiging van je deelname, blijven bewaren en gebruiken. Dit is bedoeld om een foutieve interpretatie van de studieresultaten te vermijden (zoals beschreven in paragraaf I.§ 12.4, pagina 14).

Als je een bijwerking ondervindt op het moment waarop je met het studiegeneesmiddel stopt, kan de onderzoeker nadien contact met je opnemen om na te gaan of de bijwerking verdwenen is of niet na afloop van je deelname aan de studie.

Als je na het beëindigen van je deelname aan de studie een nieuwe bijwerking ondervindt, mag je de onderzoeker contacteren en vragen om opvolging daarvan.

9.1. Je besluit je toestemming in te trekken

Je hebt het recht je toestemming in te trekken zonder een reden op te geven. Wel moet je, voor je eigen veiligheid, de onderzoeker op de hoogte brengen van je beslissing. Ook al is het niet verplicht, kan het voor de onderzoeker en voor de opdrachtgever nuttig zijn de reden voor je beslissing te kennen (bv. bijwerkingen, te veel verplaatsingen, ...).

Als je je toestemming intrekt, betekent dit dat je besluit te stoppen met

- de behandeling met het studiegeneesmiddel, en
- alle aan de studie verbonden raadplegingen en onderzoeken.

Gelieve met de onderzoeker de praktische kant van de stopzetting van je deelname te bespreken (afhankelijk van je situatie), met inbegrip van je verdere opvolging.

Er zullen alleszins geen nieuwe gegevens bezorgd worden aan de opdrachtgever.

Als je biologische stalen (bv. bloedstalen, urinestalen) reeds werden gebruikt of getest vóór de intrekking van je toestemming, heeft de opdrachtgever nog steeds het recht de resultaten van die tests te gebruiken.

Ook je biologische stalen die verzameld werden (maar nog niet getest) vóór het intrekken van je toestemming, en de gegevens die daaruit worden verkregen, kunnen nog steeds worden gebruikt door de opdrachtgever. Je kan vragen om deze stalen te vernietigen. Om een foutieve interpretatie van de studieresultaten te vermijden, kan dit uitgesteld worden tot het einde van de studie.

Indien je een bijkomend toestemmingsformulier hebt ondertekend voor het gebruik van je stalen bij toekomstig onderzoek en je deze bijkomende toestemming niet intrekt, kunnen je stalen voor dat onderzoek nog steeds gebruikt worden.

9.2. De onderzoeker besluit je deelname aan de studie te stoppen

De onderzoeker kan je deelname aan de studie beëindigen omdat

- het beter is voor je gezondheid,
- hij/zij ervaart dat je de instructies die de deelnemers krijgen niet volgt, of
- er een andere reden is die je zal worden uitgelegd.

9.3. Andere instanties kunnen de studie onderbreken of beëindigen

De opdrachtgever, en de bevoegde Belgische gezondheidsautoriteiten kunnen de studie onderbreken of beëindigen,

- omdat uit de verzamelde informatie blijkt dat het studiegeneesmiddel niet goed genoeg werkt (onvoldoende verbetering in de gezondheid van de deelnemers aan de studie oplevert),
- omdat het studiegeneesmiddel meer (ernstige) bijwerkingen veroorzaakt dan verwacht, of
- om een andere reden die door de betrokken instantie zal worden uitgelegd.

10. Welke behandeling zal ik krijgen na mijn deelname aan de studie?

Nadat je gestopt bent met de behandeling met het studiegeneesmiddel, zal de onderzoeker je gezondheidstoestand evalueren. Indien nodig zal hij/zij je de beste beschikbare standaardbehandeling voorschrijven of je doorverwijzen naar een andere behandelende arts van je keuze.

De opdrachtgever zal je na deze studie toegang verlenen tot het studiegeneesmiddel als

- de voordelen voor de deelnemers groter zijn dan de nadelen en er geen gepaste behandeling beschikbaar is op de markt in België,

- de bevoegde Belgische gezondheidsautoriteiten deze toegang goedkeuren, en
- de ontwikkeling en productie van het studiegeneesmiddel wordt voortgezet.

11. Zal mijn deelname aan de studie bijkomende kosten met zich meebrengen voor mij?

11.1. Onderzoeken en behandelingen betaald door de opdrachtgever

De opdrachtgever vergoedt het ziekenhuis voor

- de bezoeken/raadplegingen en alle geplande onderzoeken die specifiek zijn voor de studie,
- de bestudeerde behandeling (studiegeneesmiddel, en elke andere medicatie en ander materiaal specifiek gebruikt voor de studie).

In deze studie zullen er geen specifieke onderzoeken moeten gebeuren voor of na de ingreep. Hierdoor zal deze studie er niet voor zorgen dat u meer zal moeten betalen dan een patiënt die niet deelneemt aan de studie. De gebruikelijke onderzoeken en/of behandelingen die plaatsvinden om de diagnose te stellen en om de ingreep mogelijk te maken, behoren tot de standaardbehandeling en worden voorgeschreven door de behandelende arts. Deze onderzoeken kunnen wel worden aangerekend aan jou of je mutualiteit (Belgische sociale zekerheid).

De raadplegingen en behandelingen die een gevolg zijn van een bijwerking worden ook beschouwd als studiespecifiek.

Als het studiegeneesmiddel zou worden gebruikt bij een bijkomende operatie buiten deze studie, zal het studiegeneesmiddel vermoedelijk niet worden betaald door de opdrachtgever en zal dit ten laste komen van de patiënt en/of de sociale zekerheid.

11.2. Andere uitgaven die betaald worden door de opdrachtgever

Omdat je niet bijkomend je moet verplaatsen of andere uitgaven doen voor deze studie, is er geen vergoeding voorzien.

12. Welke gegevens worden over mij verzameld tijdens de studie en wat gaat ermee gebeuren?

12.1. Welke gegevens worden tijdens de studie verzameld en verwerkt?

De verzamelde en verwerkte persoonsgegevens gaan over je gezondheid en medische toestand, met inbegrip van je medische geschiedenis, een deel van je achtergrondinformatie (bv. je leeftijd, geslacht en etnische afkomst) en de resultaten van de studieonderzoeken.

12.2. Hoe zal de onderzoeker mijn persoonsgegevens behandelen?

De onderzoeker is gebonden door het beroepsgeheim bij het verzamelen en verwerken van je gegevens.

Dit betekent dat hij/zij je identiteit nooit zal bekendmaken, ook niet in een wetenschappelijke publicatie of een voordracht, en dat hij/zij je gegevens zal coderen (d.w.z. je identiteit in de studie vervangt door een identificatiecode) alvorens ze naar de opdrachtgever te sturen.

Daardoor zullen de onderzoeker, en het studiepersoneel onder de verantwoordelijkheid van de onderzoeker, de enigen zijn die je identiteit zullen kunnen koppelen aan de gegevens die tijdens de studie zijn doorgegeven, met de uitzonderingen vermeld onder § 12.6.

De gegevens die de opdrachtgever krijgt, zullen hem dus niet in staat stellen je te identificeren.

12.3. Wat zal er gebeuren met de informatie over mij die tijdens de studie verzameld wordt?

Je deelname aan de studie betekent dat je persoonsgegevens

- door de onderzoeker worden verzameld, en
- in gecodeerde vorm gebruikt worden door de opdrachtgever van het onderzoek.

De onderzoeker en de opdrachtgever mogen de gecodeerde persoonsgegevens alleen gebruiken voor onderzoeksdoeleinden in verband met wetenschappelijke publicaties in het kader van de studie waaraan je deelneemt.

Indien ruimer gebruik van de gecodeerde gegevens gepland is, zal dat hieronder vermeld staan.

Bovendien kan de opdrachtgever externe onderzoekers (die niet betrokken zijn bij deze studie) toegang verlenen tot de gecodeerde gegevens. Indien een externe onderzoeker de gegevens wil gebruiken in onderzoek dat nog niet beschreven staat in dit document, moet dit onderzoek door een Ethisch Comité goedgekeurd worden. Als je gecodeerde gegevens worden doorgegeven, al dan niet tegen betaling, verkocht, zal je daarvoor niet vergoed worden. Wel zal de sponsor ervoor zorgen dat je gegevens nooit doorgegeven zullen worden voor marketingdoeleinden. Je gegevens zouden doorgegeven kunnen worden in het kader van onderzoeksdoeleinden.

12.4. Hoe zullen mijn gegevens verwerkt worden?

Je studiegegevens zullen verwerkt worden in overeenstemming met de Algemene Verordening Gegevensbescherming (AVG) (Ref. 2) en de Belgische wet over gegevensbescherming van 30 juli 2018 (Ref. 3). De opdrachtgever is hiervoor verantwoordelijk. De reden waarom wij je persoonsgegevens mogen verwerken, is dat we wetenschappelijk onderzoek verrichten en we een taak moeten uitvoeren die gebeurt in het algemeen belang.

De verwerking van uw persoonsgegevens is noodzakelijk om de wetenschappelijke onderzoeksdoeleinden zoals hierin beschreven te kunnen realiseren. Het uitvoeren van academische onderzoek behoort tot wettelijke opdrachten van UZ Leuven als opdrachtgever. Als universitair ziekenhuis verbonden aan de KU Leuven dient UZ Leuven immers wetenschap en onderwijs in het algemeen belang te ondersteunen. UZ Leuven verduidelijkt u graag dat de noodzakelijkheid van de verwerking voor het uitvoeren van wetenschappelijk onderzoek en dit als taak van algemeen belang, de wettelijke toelatingsgrond vormt op basis waarvan UZ Leuven in het kader van dit onderzoek uw gegevens verwerkt. Daarnaast is UZ Leuven onderhevig aan specifieke wettelijke verplichtingen die de verwerking van uw gegevens mogelijks noodzakelijk maken in het kader van veiligheidsrapportering (zoals bijvoorbeeld het melden van bijwerkingen aan toezichthoudende overheidsinstanties).

12.5. Heb ik toegang tot mijn gegevens die tijdens de studie verzameld en verwerkt zijn en kan ik ze rechtzetten?

Je hebt het recht om aan de onderzoeker te vragen welke gegevens over jou worden verzameld en waarvoor ze gebruikt worden in deze studie.

Je hebt het recht om:

- toegang te krijgen tot deze gegevens en ze na te kijken
- al je gegevens te laten schrappen
- correctie te vragen als ze niet juist zijn
- de verwerking van je gegevens te beperken

12.6. Wie anders dan de onderzoeker en zijn personeel heeft toegang tot mijn persoonsgegevens?

Om de kwaliteit van de studie te controleren kan het gebeuren dat je niet-gecodeerde persoonsgegevens of voor deze studie relevante informatie uit je medisch dossier geïnspecteerd worden door andere mensen dan het studiepersoneel. Deze inzage gebeurt onder het toezicht van de onderzoeker en deze personen zijn gebonden aan het beroepsgeheim of via een vertrouwelijkheidsovereenkomst. Het kan gaan om:

- door de opdrachtgever aangeduid personeel (MONITORS en AUDITORS) en mensen of organisaties die diensten leveren aan of samenwerken met de opdrachtgever. Zij zullen echter nooit je naam en contactgegevens doorgeven aan de opdrachtgever.
- inspecteurs van de bevoegde gezondheidsautoriteiten van over de hele wereld
- een onafhankelijke auditgroep
- personen aangeduid door het Ethisch Comité.

Indien nodig voor de studie mogen de gecodeerde studiegegevens naar andere landen binnen en buiten de Europese Unie (EU) worden gestuurd en worden nagekeken door:

- personeel (andere dan de inspecteurs) van de bevoegde gezondheidsautoriteiten van België (Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten, FAGG) of andere landen binnen en buiten de EU,
- het/de Belgisch(e) evaluerend(e) Ethisch(e) Comité(s),
- externe onderzoekers,
- de opdrachtgever van de studie, door de opdrachtgever aangeduid personeel en mensen of organisaties die diensten leveren aan of samenwerken met de opdrachtgever, en/of
- bedrijven uit de groep van de opdrachtgever in België en in andere landen binnen en buiten de EU.

De Europese regelgeving en de Belgische wetgeving over gegevensbescherming leggen beperkingen op voor de overdracht van gegevens naar niet-EU landen. De opdrachtgever moet altijd verzekeren dat je gecodeerde studiegegevens gelijkwaardig beschermd worden bij

overdracht naar een niet-EU land. Indien de opdrachtgever hiervoor een overeenkomst over databescherming afsluit, kan een kopie van deze overeenkomst worden verkregen via de onderzoeker.

Je kan altijd met je onderzoeker contact opnemen voor meer informatie over zulke overdracht.

12.7. Wat zal er gebeuren met de resultaten van de studie?

Na afsluiting van de studie zal een beschrijving en de resultaten van de studie gepubliceerd worden in gespecialiseerde medische tijdschriften. Een kopie van de wetenschappelijke publicatie is verkrijgbaar via de onderzoeker of het studiepersoneel.

Een beschrijving van de studie zal ook beschikbaar zijn op https://www.clinicaltrialsregister.eu/ en https://www.Clinicaltrials.gov. Met behulp van het studienummer dat je vindt op het voorblad van dit document, kan je deze studie raadplegen. Binnen 1 jaar na afsluiting van de studie zullen de websites een samenvatting van de resultaten bevatten (Ref. 4).

Deze websites of publicaties zullen geen informatie bevatten waarmee je te identificeren bent.

12.8. Zullen mijn gegevens gebruikt worden voor andere doeleinden dan de studie waaraan ik deelneem?

De resultaten van de studie zullen alleen worden gebruikt om een antwoord te geven op de wetenschappelijke vragen in deze studie.

Elk bijkomend of toekomstig onderzoek buiten de studie, moet steeds goedgekeurd worden door een erkend Belgisch Ethisch Comité.

12.9. Hoe lang worden mijn gegevens bijgehouden?

Na afloop van de studie zullen je gecodeerde gegevens minstens 25 jaar worden bijgehouden (Ref. 5) om de geldigheid van het onderzoek te verzekeren. Dat zal ook het geval zijn indien je voortijdig met je deelname aan de studie stopt.

13. Welke biologische stalen worden van mij verzameld tijdens de studie en wat gebeurt ermee?

13.1. Welke biologische stalen worden van mij verzameld tijdens de studie?

Biologische stalen zijn stalen van menselijk lichaamsmateriaal (zoals bv. bloed, weefsel, urine, stoelgang, …).

In deze studie zullen de volgende biologische stalen genomen worden:

- Bloed in kader van de standaard bloedafnames welke bij elke diagnose van eikerstokkanker gebeuren en om veilig de ingreep te kunnen uitvoeren.
- Weefselstalen die worden weggenomen tijdens de ingreep, er worden geen bijkomende weefselstalen weggenomen die anders niet zouden worden weggenomen bij je.

13.2. Wat zal er gebeuren met de verzamelde biologische stalen?

De verzamelde biologische stalen zullen worden beheerd en bewaard in UZ Leuven, departement Pathologische ontleedkunde, gedurende 10 jaren. De bloedstalen zullen worden beheerd en bewaard in UZ Leuven, departement Laboratoriumgeneeskunde, gedurende de wettelijke periode.

Deze biologische stalen zullen worden geanalyseerd met het oog op de doelstellingen van de studie.

Het kan gebeuren dat uit de resultaten van de analyse van je biologische stalen toevallig (en bovenop de doelstellingen van de studie), informatie aan het licht komt die van belang kan zijn voor je gezondheid of die van je bloedverwanten. Deze gegevens worden "toevallige vondsten" genoemd en zullen behandeld worden zoals beschreven in Hoofdstuk I, § 15 op pagina 18.

13.3. Hoe zullen mijn biologische stalen behandeld worden?

De procedure om je biologische stalen te coderen is dezelfde als de procedure voor je persoonsgegevens (zie I § 12.3, pagina 14, Ref. 6). Stalen die naar de opdrachtgever worden gezonden, of naar organisaties die samenwerken met de opdrachtgever, zullen daarom alleen gekenmerkt worden met je studie identificatiecode.

Als onderdeel van de onderzoeken binnen de studie zou de opdrachtgever (een deel van) je stalen kunnen overmaken aan een meewerkend laboratorium. Dat laboratorium mag je stalen alleen gebruiken zoals vermeld in dit document. De traceerbaarheid wordt door de opdrachtgever verzekerd, tenzij je hebt toegestemd met de anonimisatie van je stalen.

Je biologische stalen zijn een gift. Je zal geen enkel financieel voordeel ontvangen in verband met de ontwikkeling van nieuwe therapieën die voortvloeien uit het gebruik van je biologische stalen en die een commerciële waarde zouden kunnen hebben.

13.4. Wat gebeurt er met de overschotten van biologische stalen zodra de in dit document beschreven analyses verricht zijn?

De opdrachtgever zal ze gebruiken binnen de context van de studie waaraan je deelneemt, zoals hiervoor beschreven.

13.5. Zullen bijkomende (of extra) biologische stalen voor aanvullend onderzoek verzameld en gebruikt worden?

Neen, niet van toepassing

14. Wie heeft de documenten inzake de studie nagekeken en goedgekeurd?

De studiedocumenten werden nagekeken door:

- de Belgische bevoegde gezondheidsautoriteiten (FAGG) of indien van toepassing, door de nationale bevoegde gezondheidsautoriteiten van andere EU lidstaten, en
- een onafhankelijk Belgisch Ethisch Comité

De bevoegde gezondheidsautoriteiten en de ethische comités hebben als taak de personen die aan een studie deelnemen te beschermen. De bevoegde gezondheidsautoriteiten zullen erop toezien dat de studie gebeurt in overeenstemming met de toepasselijke wetgeving.

Je mag hun goedkeuring niet opvatten als een stimulans om deel te nemen aan de studie.

15. Wat gebeurt er in het geval van toevallige vondsten?

Een resultaat dat toevallig tijdens de studie en bovenop de doelstellingen wordt gevonden, wordt een toevallige vondst genoemd. Indien dit resultaat van belang kan zijn voor je gezondheid of die van je bloedverwanten, zal de opdrachtgever de onderzoeker hierover inlichten. Met jouw toestemming zal de onderzoeker jou en je behandelende arts op de hoogte brengen van je resultaten en de mogelijke gevolgen. Indien nodig zal de onderzoeker en/of de behandelende arts je raad geven over wat je moet doen.

Je gaat al dan niet akkoord om geïnformeerd te worden, door het betreffende vakje in Hoofdstuk II op pagina 19 aan te vinken.

HOOFDSTUK II - GEÏNFORMEERDE TOESTEMMING

DEELNEMER

VEREISTEN VOOR JE DEELNAME AAN DE STUDIE

- Ik verklaar dat ik geïnformeerd ben over het doel van de studie, de duur en de gevolgen ervan, mogelijke risico's en ongemakken, de voorzorgen die ik moet nemen en wat van mij verwacht wordt, en dat ik dit alles begrepen heb. Mijn rechten als deelnemer aan een studie zijn mij uitgelegd en ik heb ze begrepen.
- Ik heb voldoende tijd gehad om erover na te denken en erover te praten met een vertrouwenspersoon (bv. vrienden, familie, behandelende arts, ...).
- Ik heb de kans gekregen om alle vragen te stellen die bij me opkwamen en ik heb een bevredigend antwoord gekregen.
- Ik begrijp dat ik vrijwillig en zonder daartoe gedwongen te zijn, zal deelnemen aan deze studie en dat ik op ieder moment mijn deelname aan de studie stop kan zetten
- Ik begrijp dat er gegevens over mij zullen worden verzameld en dat deze vertrouwelijk zullen behandeld worden.
- Ik begrijp dat het uitvoeren van deze studie door UZ Leuven het algemeen belang dient en de verwerking van mijn persoonsgegevens noodzakelijk is voor het uitvoeren van deze studie.
- Ik begrijp dat de opdrachtgever een verzekering heeft afgesloten voor het geval ik schade zou lijden in verband met mijn deelname aan deze studie.
- Ik begrijp dat ik bij deelname aan deze studie geen kosten heb, tenzij deze voor de standaardbehandeling van mijn ziekte.
- Ik stem ermee in dat mijn behandelende arts(en) op de hoogte worden gebracht van mijn deelname aan deze studie.
- Wanneer ik deelneem aan een andere interventionele studie, dien ik dit aan de onderzoeker of het studiepersoneel te laten weten. Ik stem ermee in dat ik niet gelijktijdig aan een andere interventionele studie (bijvoorbeeld met een studiegeneesmiddel, medisch hulpmiddel, experimentele chirurgische technieken) deelneem zonder de onderzoeker of het studiepersoneel daarvan op de hoogte te hebben gebracht, en dat deelname om gemotiveerde redenen kan geweigerd worden. Ik begrijp dat ik moet meewerken en de instructies van de onderzoeker en van het studiepersoneel rond de studie moet volgen.
- Ik begrijp dat mijn deelname aan de studie zonder mijn toestemming kan beëindigd worden als ik een andere behandeling nodig heb, het studieschema niet volg, een letsel heb dat met de studie te maken heeft of om gelijk welke andere gerechtvaardigde reden.
- Ik bevestig dat alle informatie die ik heb gegeven over mijn medische geschiedenis, correct is. Ik begrijp dat het me schade kan berokkenen, als ik nalaat de onderzoeker op de hoogte te brengen van of te wijzen op mogelijke uitsluitingscriteria.

OPTIONELE TOESTEMMINGEN DIE GEEN ABSOLUTE VOORWAARDEN ZIJN VOOR JE DEELNAME AAN DEZE STUDIE

1. Zoals beschreven in Hoofdstuk I, § 13 pagina 16 en § 15 pagina 18 kan het gebeuren dat toevallige vondsten aan het licht komen die van belang kunnen zijn voor je gezondheid of voor de gezondheid van je bloedverwanten.

   Als dat gebeurt, wil je dan dat de onderzoeker je (direct of via je behandelend arts) op de hoogte brengt van dit resultaat?

   (Vink het gepaste vakje aan; als je deze vraag open laat, gaan we ervan uit dat het antwoord is "Ja, ik wil op de hoogte gebracht worden".)

☐ **Neen, ik wil niet op de hoogte gebracht worden**	☐ **Ja, ik wil op de hoogte gebracht worden**

Ik stem in met deelname aan de studie, met bovenstaande beperking, en ik heb een ondertekende en gedateerde kopie ontvangen van alle bladzijden van dit document.

Naam en voornaam van de deelnemer:

Datum (DD/MMM/JJJJ):

Handtekening van de deelnemer:

ONDERZOEKER

Ik, de ondergetekende onderzoeker, bevestig

- dat de deelnemer mondeling de noodzakelijke informatie over de studie heeft gekregen, dat de inhoud hem/haar is uitgelegd en dat hij/zij een origineel ondertekende versie van dit document heeft gekregen.
- dat ik heb nagegaan of de deelnemer de studie heeft begrepen.
- dat ik de deelnemer voldoende tijd heb gegeven om na te denken over zijn/haar deelname en om vragen te stellen.
- dat geen enkele druk op de deelnemer werd uitgeoefend om hem/haar te doen toestemmen in deelname aan de studie.
- dat ik werk in overeenstemming met de ethische beginselen zoals vermeld in de meest recente versie van de "Verklaring van Helsinki", de "Goede klinische praktijken" en de Belgische wet (Ref. 7).

Naam en voornaam van de afgevaardigde van de onderzoeker:

Hoedanigheid van de afgevaardigde van de onderzoeker:

Datum (DD/MM/JJJJ):

Handtekening van de afgevaardigde van de onderzoeker:

Naam en voornaam van de onderzoeker: prof. dr. Toon Van Gorp

Datum (DD/MMM/JJJJ):

Handtekening onderzoeker:

VERKLARENDE WOORDENLIJST

FAGG

- Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten

GBA

- De Belgische Gegevensbeschermingsautoriteit zorgt ervoor dat persoonsgegevens zorgvuldig worden gebruikt en beveiligd, en dat je privacy ook in de toekomst gewaarborgd blijft.

MONITOR en AUDITOR:

- Zowel de monitor als de auditor werkt voor de opdrachtgever. De monitor zorgt voor een continue kwaliteitscontrole tijdens het verloop van de studie. De auditor voert een onderzoek na afloop van de studie. Ze controleren of de studie wordt/werd uitgevoerd volgens het protocol, of de gerapporteerde gegevens betrouwbaar zijn en of de studie in overeenstemming is met de geldende wetten.

VERZEKERING MET "FOUTLOZE" AANSPRAKELIJKHEID:

- De opdrachtgever is aansprakelijk voor elk letsel of elke schade aan de deelnemer die rechtstreeks of onrechtstreeks verband houdt met de studie. Hiervoor dient door jou geen fout te worden aangetoond.

REFERENTIES

1 Dit strookt met artikel 29 van de Belgische wet van 7 mei 2004 inzake experimenten op de mensen en de toepasselijke koninklijke besluiten.
2 Algemene Verordening Gegevensbescherming nr. 2016/679 van het Europees Parlement en van de Raad van 27 april 2016 betreffende de bescherming van natuurlijke personen in verband met de verwerking van persoonsgegevens en betreffende het vrije verkeer van die gegevens en tot intrekking van Richtlijn 95/46/EG.
3 Belgische wet van 30 juli 2018 betreffende de bescherming van natuurlijke personen met betrekking tot de verwerking van persoonsgegevens.
4 Overeenkomstig hoofdstuk 4.3. van de richtlijn van de Commissie : Richtsnoeren voor het plaatsen en publiceren van resultaatgerelateerde informatie over klinische proeven in verband met de tenuitvoerlegging van artikel 57, lid 2, van Verordening (EG) nr. 726/2004 en artikel 41, lid 2, van Verordening (EG) nr. 1901/2006 - 2012/302/03.
5 Overeenkomstig artikel 58 van de verordening (EU) nr. 536/2014 van het Europees Parlement en de Raad van 16 april 2014 betreffende klinische proeven met geneesmiddelen voor menselijk gebruik en tot intrekking van Richtlijn 2001/20/EG.
6 Belgische wet van 19 december 2008 inzake het verkrijgen en het gebruik van menselijk lichaamsmateriaal met het oog op de geneeskundige toepassing op de mens of het wetenschappelijk onderzoek, en de koninklijke besluiten van toepassing daarop.
7 Belgische wet van 7 mei 2004 inzake experimenten op mensen en de toepasselijke koninklijke besluiten.

FOR CLINICAL TRIAL USE ONLY
ENKEL VOOR STUDIE GEBRUIK

IMP: Indocyanine groen (Verdye®), 0,25mg/kg
Poeder voor oplossing voor injectie

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Eudra-CT nummer: 2021-002449-13

Sponsor: Universitair Ziekenhuis Leuven
CI: Toon Van Gorp
Herestraat 49, B-3000 Leuven, België
Tel: +32 (0)16 34 47 50

Common Terminology Criteria for Adverse Events (CTCAE)

Version 5.0

Published: November 27, 2017

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute

Common Terminology Criteria for Adverse Events (CTCAE) v5.0
Publish Date: November 27, 2017

Introduction
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.

SOC
System Organ Class (SOC), the highest level of the MedDRA[1] hierarchy, is identified by anatomical or physiological system, etiology, or purpose (e.g., SOC Investigations for laboratory test results). CTCAE terms are grouped by MedDRA Primary SOCs. Within each SOC, AEs are listed and accompanied by descriptions of severity (Grade).

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

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.

Definitions
A brief Definition is provided to clarify the meaning of each AE term. A single dash (-) indicates a Definition is not available.

Navigational Notes
A Navigational Note is used to assist the reporter in choosing a correct AE. It may list other AEs that should be considered in addition to or in place of the AE in question. A single dash (-) indicates a Navigational Note has not been defined for the AE term.

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.

[1] CTCAE v5.0 incorporates certain elements of the MedDRA terminology. For further details on MedDRA refer to the MedDRA MSSO Web site (https://www.meddra.org/).

Table of Contents

Blood and lymphatic system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Anemia	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a reduction in the amount of hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy, and fatigability. **Navigational Note:** -					
Bone marrow hypocellular	Mildly hypocellular or <=25% reduction from normal cellularity for age	Moderately hypocellular or >25 - <50% reduction from normal cellularity for age	Severely hypocellular or >50 - <=75% reduction cellularity from normal for age	Aplastic persistent for longer than 2 weeks	Death
Definition: A disorder characterized by the inability of the bone marrow to produce hematopoietic elements. **Navigational Note:** -					
Disseminated intravascular coagulation	-	Laboratory findings with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by systemic pathological activation of blood clotting mechanisms which results in clot formation throughout the body. There is an increase in the risk of hemorrhage as the body is depleted of platelets and coagulation factors. **Navigational Note:** -					
Eosinophilia	>ULN and >Baseline	-	Steroids initiated	-	-
Definition: A disorder characterized by laboratory test results that indicate an increased number of eosinophils in the blood. **Navigational Note:** -					
Febrile neutropenia	-	-	ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an ANC <1000/mm3 and a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of >=38 degrees C (100.4 degrees F) for more than one hour. **Navigational Note:** -					
Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test; DAT; Coombs'; schistocytes; decreased haptoglobin)	Evidence of hemolysis and >=2 g decrease in hemoglobin	Transfusion or medical intervention indicated (e.g., steroids)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate widespread erythrocyte cell membrane destruction. **Navigational Note:** -					

Blood and lymphatic system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hemolytic uremic syndrome	-	-	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death
Definition: A disorder characterized by a form of thrombotic microangiopathy with renal failure, hemolytic anemia, and severe thrombocytopenia. **Navigational Note:** -					
Leukocytosis	-	-	>100,000/mm3	Clinical manifestations of leucostasis; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate an increased number of white blood cells in the blood. **Navigational Note:** -					
Lymph node pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in a lymph node. **Navigational Note:** -					
Methemoglobinemia	-	>ULN	Requiring urgent intervention	Life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate increased methemoglobin in the blood. **Navigational Note:** -					
Thrombotic thrombocytopenic purpura	-	-	Laboratory findings with clinical consequences (e.g., renal insufficiency, petechiae)	Life-threatening consequences, (e.g., CNS hemorrhage or thrombosis/embolism or renal failure)	Death
Definition: A disorder characterized by the presence of microangiopathic hemolytic anemia, thrombocytopenic purpura, fever, renal abnormalities and neurological abnormalities such as seizures, hemiplegia, and visual disturbances. It is an acute or subacute condition. **Navigational Note:** -					
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; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Cardiac disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Aortic valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characterized by a defect in aortic valve function or structure. **Navigational Note:** -					
Asystole	Periods of asystole; non-urgent medical management indicated	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia without cardiac electrical activity. Typically, this is accompanied by cessation of the pumping function of the heart. **Navigational Note:** -					
Atrial fibrillation	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic, urgent intervention indicated; device (e.g., pacemaker); ablation; new onset	Life-threatening consequences; embolus requiring urgent intervention	Death
Definition: A disorder characterized by a dysrhythmia without discernible P waves and an irregular ventricular response due to multiple reentry circuits. The rhythm disturbance originates above the ventricles. **Navigational Note:** -					
Atrial flutter	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic, urgent intervention indicated; device (e.g., pacemaker); ablation	Life-threatening consequences; embolus requiring urgent intervention	Death
Definition: A disorder characterized by a dysrhythmia with organized rhythmic atrial contractions with a rate of 200-300 beats per minute. The rhythm disturbance originates in the atria. **Navigational Note:** -					
Atrioventricular block complete	-	Non-urgent intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker); new onset	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with complete failure of atrial electrical impulse conduction through the AV node to the ventricles. **Navigational Note:** -					
Atrioventricular block first degree	Asymptomatic, intervention not indicated	Non-urgent intervention indicated	-	-	-
Definition: A disorder characterized by a dysrhythmia with a delay in the time required for the conduction of an electrical impulse through the atrioventricular (AV) node beyond 0.2 seconds; prolongation of the PR interval greater than 200 milliseconds. **Navigational Note:** -					

Cardiac disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Cardiac arrest	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by cessation of the pumping function of the heart. **Navigational Note:** -					
Chest pain - cardiac	Mild pain	Moderate pain; pain on exertion; limiting instrumental ADL; hemodynamically stable	Pain at rest; limiting self care ADL; cardiac catheterization; new onset cardiac chest pain; unstable angina	-	-
Definition: A disorder characterized by substernal discomfort due to insufficient myocardial oxygenation e.g., angina pectoris. **Navigational Note:** Also consider Cardiac disorders: Myocardial infarction.					
Conduction disorder	Mild symptoms; intervention not indicated	Non-urgent medical intervention indicated	Symptomatic, urgent intervention indicated	Life-threatening consequences	Death
Definition: A disorder characterized by pathological irregularities in the cardiac conduction system. **Navigational Note:** -					
Cyanosis	-	Present	-	-	-
Definition: A disorder characterized by a bluish discoloration of the skin and/or mucous membranes. **Navigational Note:** -					
Heart failure	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with moderate activity or exertion	Symptoms at rest or with minimal activity or exertion; hospitalization; new onset of symptoms	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death
Definition: A disorder characterized by the inability of the heart to pump blood at an adequate volume to meet tissue metabolic requirements, or, the ability to do so only at an elevation in the filling pressure. **Navigational Note:** If left sided use Cardiac disorders: Left ventricular systolic dysfunction; also consider Cardiac disorders: Restrictive cardiomyopathy, Investigations: Ejection fraction decreased.					
Left ventricular systolic dysfunction	-	-	Symptomatic due to drop in ejection fraction responsive to intervention	Refractory or poorly controlled heart failure due to drop in ejection fraction; intervention such as ventricular assist device, intravenous vasopressor support, or heart transplant indicated	Death
Definition: A disorder characterized by failure of the left ventricle to produce adequate output. **Navigational Note:** Also consider Investigations: Ejection fraction decreased.					

Cardiac disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Mitral valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characterized by a defect in mitral valve function or structure. **Navigational Note:** -					
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); new onset	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with relatively constant PR interval prior to the block of an atrial impulse. This is the result of intermittent failure of atrial electrical impulse conduction through the atrioventricular (AV) node to the ventricles. **Navigational Note:** -					
Mobitz type I	Asymptomatic, intervention not indicated	Symptomatic; medical intervention indicated	Symptomatic and incompletely controlled medically, or controlled with device (e.g., pacemaker)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a progressively lengthening PR interval prior to the blocking of an atrial impulse. This is the result of intermittent failure of atrial electrical impulse conduction through the atrioventricular (AV) node to the ventricles. **Navigational Note:** -					
Myocardial infarction	-	Asymptomatic and cardiac enzymes minimally abnormal and no evidence of ischemic ECG changes	Severe symptoms; cardiac enzymes abnormal; hemodynamically stable; ECG changes consistent with infarction	Life-threatening consequences; hemodynamically unstable	Death
Definition: A disorder characterized by gross necrosis of the myocardium; this is due to an interruption of blood supply to the area. **Navigational Note:** -					
Myocarditis	-	Symptoms with moderate activity or exertion	Severe with symptoms at rest or with minimal activity or exertion; intervention indicated; new onset of symptoms	Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)	Death
Definition: A disorder characterized by inflammation of the muscle tissue of the heart. **Navigational Note:** -					

Cardiac disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Palpitations	Mild symptoms; intervention not indicated	Intervention indicated	-	-	-
Definition: A disorder characterized by an unpleasant sensation of irregular and/or forceful beating of the heart. **Navigational Note:** -					
Paroxysmal atrial tachycardia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic, urgent intervention indicated; ablation	Life-threatening consequences; incompletely controlled medically; cardioversion indicated	Death
Definition: A disorder characterized by a dysrhythmia with abrupt onset and sudden termination of atrial contractions with a rate of 150-250 beats per minute. The rhythm disturbance originates in the atria. **Navigational Note:** -					
Pericardial effusion	-	Asymptomatic effusion size small to moderate	Effusion with physiologic consequences	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by fluid collection within the pericardial sac, usually due to inflammation. **Navigational Note:** -					
Pericardial tamponade	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in intrapericardial pressure due to the collection of blood or fluid in the pericardium. **Navigational Note:** -					
Pericarditis	Asymptomatic, ECG or physical findings (e.g., rub) consistent with pericarditis	Symptomatic pericarditis (e.g., chest pain)	Pericarditis with physiologic consequences (e.g., pericardial constriction)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by irritation to the layers of the pericardium (the protective sac around the heart). **Navigational Note:** -					
Pulmonary valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis by imaging	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis by imaging; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characterized by a defect in pulmonary valve function or structure. **Navigational Note:** -					
Restrictive cardiomyopathy	Imaging findings only	Symptomatic without signs of heart failure	Symptomatic heart failure or other cardiac symptoms, responsive to intervention; new onset of symptoms	Refractory heart failure or other poorly controlled cardiac symptoms	Death
Definition: A disorder characterized by an inability of the ventricles to fill with blood because the myocardium (heart muscle) stiffens and loses its flexibility. **Navigational Note:** -					

Cardiac disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Right ventricular dysfunction	Asymptomatic with laboratory (e.g., BNP [B-Natriuretic Peptide]) or cardiac imaging abnormalities	Symptoms with moderate activity or exertion	Severe symptoms, associated with hypoxia, right heart failure; oxygen indicated	Life-threatening consequences; urgent intervention indicated (e.g., ventricular assist device); heart transplant indicated	Death
Definition: A disorder characterized by impairment of right ventricular function associated with low ejection fraction and a decrease in motility of the right ventricular wall. **Navigational Note:** -					
Sick sinus syndrome	Asymptomatic, intervention not indicated	Symptomatic, intervention not indicated; change in medication initiated	Symptomatic, intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with alternating periods of bradycardia and atrial tachycardia accompanied by syncope, fatigue and dizziness. **Navigational Note:** -					
Sinus bradycardia	Asymptomatic, intervention not indicated	Symptomatic, intervention not indicated; change in medication initiated	Symptomatic, intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate less than 60 beats per minute that originates in the sinus node. **Navigational Note:** -					
Sinus tachycardia	Asymptomatic, intervention not indicated	Symptomatic; non-urgent medical intervention indicated	Urgent medical intervention indicated	-	-
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates in the sinus node. **Navigational Note:** -					
Supraventricular tachycardia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic, urgent intervention indicated	Life-threatening consequences	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates above the ventricles. **Navigational Note:** -					
Tricuspid valve disease	Asymptomatic valvular thickening with or without mild valvular regurgitation or stenosis	Asymptomatic; moderate regurgitation or stenosis by imaging	Symptomatic; severe regurgitation or stenosis; symptoms controlled with medical intervention	Life-threatening consequences; urgent intervention indicated (e.g., valve replacement, valvuloplasty)	Death
Definition: A disorder characterized by a defect in tricuspid valve function or structure. **Navigational Note:** -					
Ventricular arrhythmia	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Urgent intervention indicated	Life-threatening consequences; hemodynamic compromise	Death
Definition: A disorder characterized by a dysrhythmia that originates in the ventricles. **Navigational Note:** -					

Cardiac disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Ventricular fibrillation	-	-	-	Life-threatening consequences; hemodynamic compromise	Death
Definition: A disorder characterized by a dysrhythmia without discernible QRS complexes due to rapid repetitive excitation of myocardial fibers without coordinated contraction of the ventricles. **Navigational Note:** -					
Ventricular tachycardia	-	Non-urgent medical intervention indicated	Symptomatic, urgent intervention indicated	Life-threatening consequences; hemodynamic compromise	Death
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates distal to the bundle of His. **Navigational Note:** -					
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; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

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

Ear and labyrinth disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Ear pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the ear. **Navigational Note:** -					
External ear pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the external ear region. **Navigational Note:** -					
Hearing impaired	**Adults** enrolled on a Monitoring Program (on a 1, 2, 4, 3, 6, and 8 kHz audiogram): Threshold shift of 15 - 25 dB averaged at 2 contiguous test frequencies in at least one ear; **Adults** not enrolled on a Monitoring Program: Subjective change in hearing in the absence of documented hearing loss; **Pediatric** (on a 1, 2, 3, 4, 6, and 8 kHz audiogram): Threshold shift >20 dB hearing loss (HL) (i.e., 25 dB HL or greater); sensorineural hearing loss (SNHL) above 4 kHz (i.e., 6 or 8 kHz) in at least one ear	**Adults** enrolled on a 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 on a Monitoring Program: Hearing loss with 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 in at least one ear	**Adults** enrolled on a 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 on a 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 2 to < 4 kHz in at least one ear	**Adults:** Decrease in hearing to profound bilateral loss (absolute threshold >80 dB HL at 2 kHz and above); nonservicable hearing **Pediatric:** Audiologic indication for cochlear implant; > 40 dB HL (i.e., 45 dB HL or more); SNHL at 2 kHz and above	-
Definition: A disorder characterized by partial or complete loss of the ability to detect or understand sounds resulting from damage to ear structures. **Navigational Note:** -					
Middle ear inflammation	Serous otitis	Serous otitis, medical intervention indicated	Mastoiditis; necrosis of canal soft tissue or bone	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation (physiologic response to irritation), swelling and redness to the middle ear. **Navigational Note:** -					

Ear and labyrinth disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Tinnitus	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by noise in the ears, such as ringing, buzzing, roaring or clicking. **Navigational Note:** -					
Vertigo	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation as if the external world were revolving around the patient (objective vertigo) or as if he himself were revolving in space (subjective vertigo). **Navigational Note:** -					
Vestibular disorder	-	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dizziness, imbalance, nausea, and vision problems. **Navigational Note:** -					
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; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Endocrine disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Adrenal insufficiency	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the adrenal cortex not producing enough of the hormone cortisol and in some cases, the hormone aldosterone. It may be due to a disorder of the adrenal cortex as in Addison's disease or primary adrenal insufficiency. **Navigational Note:** -					
Cushingoid	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms, medical intervention or hospitalization indicated	-	-
Definition: A disorder characterized by signs and symptoms that resemble Cushing's disease or syndrome: buffalo hump obesity, striations, adiposity, hypertension, diabetes, and osteoporosis, usually due to exogenous corticosteroids. **Navigational Note:** -					
Delayed puberty	-	No breast development by age 13 yrs for females; testes volume of <3 cc or no Tanner Stage 2 development by age 14.5 yrs for males	No breast development by age 14 yrs for females; no increase in testes volume or no Tanner Stage 2 by age 16 yrs for males; hormone replacement indicated	-	-
Definition: A disorder characterized by unusually late sexual maturity. **Navigational Note:** -					
Growth accelerated	-	>= +2 SD (standard deviation) above mid parental height or target height	-	-	-
Definition: A disorder characterized by greater growth than expected for age. **Navigational Note:** -					
Hyperparathyroidism	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by an increase in production of parathyroid hormone by the parathyroid glands. This results in hypercalcemia (abnormally high levels of calcium in the blood). **Navigational Note:** -					
Hyperthyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by excessive levels of thyroid hormone in the body. Common causes include an overactive thyroid gland or thyroid hormone overdose. **Navigational Note:** -					

Endocrine disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hypoparathyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; medical intervention or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a decrease in production of parathyroid hormone by the parathyroid glands. **Navigational Note:** -					
Hypophysitis	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; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation and cellular infiltration of the pituitary gland. **Navigational Note:** -					
Hypopituitarism	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; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a decrease in production of hormones from the pituitary gland. **Navigational Note:** -					
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a decrease in production of thyroid hormone by the thyroid gland. **Navigational Note:** -					
Precocious puberty	Physical signs of puberty with no biochemical markers for females <8 years and males <9 years	Physical signs and biochemical markers of puberty for females <8 years and males <9 years	-	-	-
Definition: A disorder characterized by unusually early development of secondary sexual features; the onset of sexual maturation begins usually before age 8 for girls and before age 9 for boys. **Navigational Note:** -					
Testosterone deficiency	Asymptomatic; mild symptoms with no intervention indicated	Replacement therapy initiated	-	-	-
Definition: A disorder characterized by low testosterone. **Navigational Note:** -					

Endocrine disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Virilization	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by inappropriate masculinization occurring in a female or prepubertal male. **Navigational Note:** -					
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; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Eye disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Blurred vision	Intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by visual perception of unclear or fuzzy images. **Navigational Note:** -					
Cataract	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); glare symptoms affecting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by partial or complete opacity of the crystalline lens of one or both eyes. This results in a decrease in visual acuity and eventual blindness if untreated. **Navigational Note:** -					
Corneal ulcer	-	-	Corneal ulcer without perforation in the affected eye	Perforation in the affected eye	-
Definition: A disorder characterized by an area of epithelial tissue loss on the surface of the cornea. It is associated with inflammatory cells in the cornea and anterior chamber. **Navigational Note:** -					
Dry eye	Asymptomatic; clinical or diagnostic observations only; symptoms relieved by lubricants	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	-	-
Definition: A disorder characterized by dryness of the cornea and conjunctiva. **Navigational Note:** If corneal ulcer is present, grade under Eye disorders: Corneal ulcer.					
Extraocular muscle paresis	Asymptomatic; clinical or diagnostic observations only	Unilateral paresis without double vision	Bilateral paresis or unilateral paresis causing double vision in peripheral gaze, but not in central gaze	Bilateral paresis requiring head turning to see beyond central 60 degrees or double vision in central gaze	-
Definition: A disorder characterized by incomplete paralysis of an extraocular muscle. **Navigational Note:** -					

Eye disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Eye pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the eye. **Navigational Note:** -					
Eyelid function disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; nonoperative intervention indicated; limiting instrumental ADL	Limiting self care ADL; operative intervention indicated	-	-
Definition: A disorder characterized by impaired eyelid function. **Navigational Note:** -					
Flashing lights	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by a sudden or brief burst of light. **Navigational Note:** Also consider Eye disorders: Retinal tear or Retinal detachment					
Floaters	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by an individual seeing spots before their eyes. The spots are shadows of opaque cell fragments in the vitreous humor or lens. **Navigational Note:** Also consider Eye disorders: Retinal tear or Retinal detachment					
Glaucoma	Less than 8 mmHg of elevated intraocular pressure (EIOP); no visual field deficit	EIOP which can be reduced to 21 mmHg or under with topical medications and no visual field deficit	EIOP causing visual field deficits	Visual field deficit within the central 10 degrees of the visual field in the affected eye	-
Definition: A disorder characterized by an increase in pressure in the eyeball due to obstruction of the aqueous humor outflow. **Navigational Note:** -					
Keratitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); corneal ulcer; limiting self care ADL	Perforation; best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by inflammation to the cornea of the eye. **Navigational Note:** Also consider Eye disorders: Corneal ulcer					

Eye disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Night blindness	Symptomatic but not limiting ADL	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by an inability to see clearly in dim light. **Navigational Note:** -					
Optic nerve disorder	Asymptomatic; clinical or diagnostic observations only	Moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200)	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by involvement of the optic nerve (second cranial nerve). **Navigational Note:** -					
Papilledema	Asymptomatic; no visual field deficit	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200)	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by swelling around the optic disc. **Navigational Note:** -					
Periorbital edema	Soft or non-pitting	Indurated or pitting edema; topical intervention indicated	Edema associated with visual disturbance; increased intraocular pressure, glaucoma or retinal hemorrhage; optic neuritis; diuretics indicated; operative intervention indicated	-	-
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid around the orbits of the face. **Navigational Note:** -					
Photophobia	Symptomatic but not limiting ADL	Limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by fear and avoidance of light. **Navigational Note:** -					

Eye disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Retinal detachment	-	-	Macular sparing rhegmatogenous detachment	Macula-off rhegmatogenous retinal detachment	-
Definition: A disorder characterized by the separation of the inner retina layers from the underlying pigment epithelium. **Navigational Note:** -					
Retinal tear	No retinal detachment and treatment not indicated	No retinal detachment and treatment indicated	-	-	-
Definition: A disorder characterized by a small laceration of the retina, this occurs when the vitreous separates from the retina. Symptoms include flashes and floaters. **Navigational Note:** If retinal detachment is present, grade under Eye disorders: Retinal detachment					
Retinal vascular disorder	-	Retinal vascular disorder without neovascularization	Retinal vascular disorder with neovascularization	-	-
Definition: A disorder characterized by pathological retinal blood vessels that adversely affects vision. **Navigational Note:** If vitreous hemorrhage is present, report under Eye disorders: Vitreous hemorrhage.					
Retinopathy	Asymptomatic; clinical or diagnostic observations only	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder involving the retina. **Navigational Note:** If vitreous hemorrhage is present, report under Eye disorders: Vitreous hemorrhage.					
Scleral disorder	No change in vision from baseline	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by involvement of the sclera of the eye. **Navigational Note:** -					
Uveitis	Anterior uveitis with trace cells	Anterior uveitis with 1+ or 2+ cells	Anterior uveitis with 3+ or greater cells; intermediate posterior or pan-uveitis	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by inflammation to the uvea of the eye. **Navigational Note:** -					

Eye disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Vision decreased	-	Moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200)	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by a decrease in visual acuity. **Navigational Note:** If etiology is known, use a more specific CTCAE term.					
Vitreous hemorrhage	Intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline); limiting instrumental ADL	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL; vitrectomy indicated	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by bleeding into the vitreous humor. **Navigational Note:** -					
Watering eyes	Intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200)	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by excessive tearing in the eyes; it can be caused by overproduction of tears or impaired drainage of the tear duct. **Navigational Note:** -					
Eye disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; no change in vision	Moderate; minimal, local or noninvasive intervention indicated; limiting instrumental ADL; best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline	Severe or medically significant but not immediately sight-threatening; limiting self care ADL; decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200)	Sight-threatening consequences; urgent intervention indicated; best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: - **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Abdominal distension	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe discomfort; limiting self care ADL	-	-
Definition: A disorder characterized by swelling of the abdomen. **Navigational Note:** -					
Abdominal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the abdominal region. **Navigational Note:** -					
Anal fissure	Asymptomatic	Symptomatic	Invasive intervention indicated	-	-
Definition: A disorder characterized by a tear in the lining of the anus. **Navigational Note:** -					
Anal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the opening in the anal canal to the perianal skin. **Navigational Note:** -					
Anal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the anal region. **Navigational Note:** -					
Anal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by ulceration or inflammation of the mucous membrane of the anus. **Navigational Note:** Report Grade 4 and 5 as Gastrointestinal disorders: Anal ulcer					
Anal necrosis	-	-	TPN or hospitalization indicated; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the anal region. **Navigational Note:** -					
Anal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the anal region. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Anal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Symptomatic and severely altered GI function; non-emergent operative intervention indicated; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the anal canal. **Navigational Note:** -					
Anal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the anal canal. **Navigational Note:** -					
Ascites	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by accumulation of serous or hemorrhagic fluid in the peritoneal cavity. **Navigational Note:** -					
Belching	Increase from baseline	Intervention initiated (including over the counter medications)	-	-	-
Definition: To expel gas noisily from the mouth. **Navigational Note:** Synonym: Burping					
Bloating	No change in bowel function or oral intake	Symptomatic, decreased oral intake; change in bowel function	-	-	-
Definition: A disorder characterized by subject-reported feeling of uncomfortable fullness of the abdomen. **Navigational Note:** -					
Cecal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the cecum. **Navigational Note:** -					
Cheilitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; intervention indicated	-	-
Definition: A disorder characterized by inflammation of the lip. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Chylous ascites	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., fat-restricted diet); paracentesis or tube drainage indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by accumulation of milky fluid in the peritoneal cavity. **Navigational Note:** -					
Colitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe abdominal pain; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the colon. **Navigational Note:** -					
Colonic fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the large intestine and another organ or anatomic site. **Navigational Note:** -					
Colonic hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the colon. **Navigational Note:** -					
Colonic obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Hospitalization indicated; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the colon. **Navigational Note:** -					
Colonic perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the colonic wall. **Navigational Note:** -					
Colonic stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the colon. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Colonic ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the colon. **Navigational Note:** -					
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas; limiting instrumental ADL	Obstipation with manual evacuation indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by irregular and infrequent or difficult evacuation of the bowels. **Navigational Note:** -					
Dental caries	One or more dental caries, not involving the root	Dental caries involving the root	Dental caries resulting in pulpitis or periapical abscess or resulting in tooth loss	-	-
Definition: A disorder characterized by the decay of a tooth, in which it becomes softened, discolored and/or porous. **Navigational Note:** -					
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; limiting instrumental ADL	Increase of >=7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in frequency and/or loose or watery bowel movements. **Navigational Note:** -					
Dry mouth	Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1 ml/min	-	-
Definition: A disorder characterized by reduced salivary flow in the oral cavity. **Navigational Note:** -					
Duodenal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the duodenum and another organ or anatomic site. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Duodenal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the duodenum. **Navigational Note:** -					
Duodenal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Hospitalization indicated; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of stomach contents through the duodenum. **Navigational Note:** -					
Duodenal perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the duodenal wall. **Navigational Note:** -					
Duodenal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the duodenum. **Navigational Note:** -					
Duodenal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severely altered GI function; TPN indicated; elective invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the duodenal wall. **Navigational Note:** -					
Dyspepsia	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; operative intervention indicated	-	-
Definition: A disorder characterized by an uncomfortable, often painful feeling in the stomach, resulting from impaired digestion. Symptoms include burning stomach, bloating, heartburn, nausea and vomiting. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Dysphagia	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating/swallowing; tube feeding, TPN, or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by difficulty in swallowing. **Navigational Note:** -					
Enterocolitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Abdominal pain; mucus or blood in stool	Severe or persistent abdominal pain; fever; ileus; peritoneal signs	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the small and large intestines. **Navigational Note:** If reporting a known abnormality of the colon, use Gastrointestinal disorders: Colitis. If reporting a documented infection, use Infections and infestations: Enterocolitis infectious.					
Enterovesical fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the urinary bladder and the intestine. **Navigational Note:** -					
Esophageal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the esophagus and another organ or anatomic site. **Navigational Note:** -					
Esophageal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the esophagus. **Navigational Note:** -					
Esophageal necrosis	-	-	Inability to aliment adequately by GI tract; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the esophageal wall. **Navigational Note:** -					
Esophageal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the contents in the esophagus. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Esophageal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the esophageal region. **Navigational Note:** -					
Esophageal perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the wall of the esophagus. **Navigational Note:** -					
Esophageal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the esophagus. **Navigational Note:** -					
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 invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the esophageal wall. **Navigational Note:** -					
Esophageal varices hemorrhage	-	Self-limited; intervention not indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from esophageal varices. **Navigational Note:** -					
Esophagitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered eating/swallowing; oral supplements indicated	Severely altered eating/swallowing; tube feeding, TPN, or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the esophageal wall. **Navigational Note:** -					
Fecal incontinence	Occasional use of pads required	Daily use of pads required	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by inability to control the escape of stool from the rectum. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Flatulence	Mild symptoms; intervention not indicated	Moderate; persistent; psychosocial sequelae	-	-	-
Definition: A disorder characterized by a discharge of excessive gas from the lower GI tract. **Navigational Note:** -					
Gastric fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the stomach and another organ or anatomic site. **Navigational Note:** -					
Gastric hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the gastric wall. **Navigational Note:** -					
Gastric necrosis	-	-	Inability to aliment adequately by GI tract; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the gastric wall. **Navigational Note:** -					
Gastric perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the stomach wall. **Navigational Note:** -					
Gastric stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the stomach. **Navigational Note:** -					
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 invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the stomach. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Gastritis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; medical intervention indicated	Severely altered eating or gastric function; TPN or hospitalization indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation of the stomach. **Navigational Note:** -					
Gastroesophageal reflux disease	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; operative intervention indicated	-	-
Definition: A disorder characterized by reflux of the gastric and/or duodenal contents into the distal esophagus. It is chronic in nature and usually caused by incompetence of the lower esophageal sphincter, and may result in injury to the esophageal mucosal. Symptoms include heartburn and acid indigestion. **Navigational Note:** -					
Gastrointestinal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between any part of the gastrointestinal system and another organ or anatomic site. **Navigational Note:** -					
Gastrointestinal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the gastrointestinal region. **Navigational Note:** -					
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 >=20% from baseline; tube feeding or TPN indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by an incomplete paralysis of the muscles of the stomach wall resulting in delayed emptying of the gastric contents into the small intestine. **Navigational Note:** -					
Gingival pain	Mild pain	Moderate pain interfering with oral intake	Severe pain; inability to aliment orally	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the gingival region. **Navigational Note:** -					
Hemorrhoidal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the hemorrhoids. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hemorrhoids	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; banding or medical intervention indicated	Severe symptoms; invasive intervention indicated	-	-
Definition: A disorder characterized by the presence of dilated veins in the rectum and surrounding area. **Navigational Note:** -					
Ileal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the ileum and another organ or anatomic site. **Navigational Note:** -					
Ileal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the ileal wall. **Navigational Note:** -					
Ileal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL; naso-gastric tube indicated	Hospitalization indicated; invasive intervention indicated; limiting self care ADL; long intestinal tube indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the ileum. **Navigational Note:** -					
Ileal perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the ileal wall. **Navigational Note:** -					
Ileal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the ileum. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Ileal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the ileum. **Navigational Note:** -					
Ileus	Asymptomatic and radiologic observations only	Symptomatic; altered GI function; bowel rest indicated	Severely altered GI function; TPN indicated; tube placement indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by failure of the ileum to transport intestinal contents. **Navigational Note:** -					
Intra-abdominal hemorrhage	-	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding in the abdominal cavity. **Navigational Note:** -					
Jejunal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the jejunum and another organ or anatomic site. **Navigational Note:** -					
Jejunal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the jejunal wall. **Navigational Note:** -					
Jejunal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the jejunum. **Navigational Note:** -					
Jejunal perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the jejunal wall. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Jejunal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the jejunum. **Navigational Note:** -					
Jejunal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; TPN indicated; elective invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the jejunum. **Navigational Note:** -					
Lip pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort of the lip. **Navigational Note:** -					
Lower gastrointestinal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the lower gastrointestinal tract (small intestine, large intestine, and anus). **Navigational Note:** -					
Malabsorption	-	Altered diet; oral intervention indicated	Inability to aliment adequately; TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inadequate absorption of nutrients in the small intestine. Symptoms include abdominal marked discomfort, bloating and diarrhea. **Navigational Note:** -					
Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain or ulcer that does not interfere with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by ulceration or inflammation of the oral mucosal. **Navigational Note:** -					
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Definition: A disorder characterized by a queasy sensation and/or the urge to vomit. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Obstruction gastric	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the contents in the stomach. **Navigational Note:** -					
Oral cavity fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the oral cavity and another organ or anatomic site. **Navigational Note:** -					
Oral dysesthesia	Mild discomfort; not interfering with oral intake	Moderate pain; interfering with oral intake	Disabling pain; tube feeding or TPN indicated	-	-
Definition: A disorder characterized by a burning or tingling sensation on the lips, tongue or entire mouth. **Navigational Note:** -					
Oral hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the mouth. **Navigational Note:** -					
Oral pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the mouth, tongue or lips. **Navigational Note:** -					
Pancreatic duct stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the pancreatic duct. **Navigational Note:** -					
Pancreatic fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the pancreas and another organ or anatomic site. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Pancreatic hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the pancreas. **Navigational Note:** -					
Pancreatic necrosis	-	-	Tube feeding or TPN indicated; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the pancreas. **Navigational Note:** -					
Pancreatitis	-	Enzyme elevation; radiologic findings only	Severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the pancreas with no documented pancreas infection. **Navigational Note:** -					
Periodontal disease	Gingival recession or gingivitis; limited bleeding on probing; mild local bone loss	Moderate gingival recession or gingivitis; multiple sites of bleeding on probing; moderate bone loss	Spontaneous bleeding; severe bone loss with or without tooth loss; osteonecrosis of maxilla or mandible	-	-
Definition: A disorder in the gingival tissue around the teeth. **Navigational Note:** -					
Peritoneal necrosis	-	-	Tube feeding or TPN indicated; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the peritoneum. **Navigational Note:** -					
Proctitis	Rectal discomfort, intervention not indicated	Symptomatic (e.g., rectal discomfort, passing blood or mucus); medical intervention indicated; limiting instrumental ADL	Severe symptoms; fecal urgency or stool incontinence; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the rectum. **Navigational Note:** -					
Rectal fissure	Asymptomatic	Symptomatic	Invasive intervention indicated	-	-
Definition: A disorder characterized by a tear in the lining of the rectum. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Rectal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the rectum and another organ or anatomic site. **Navigational Note:** -					
Rectal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the rectal wall and discharged from the anus. **Navigational Note:** -					
Rectal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by ulceration or inflammation of the mucous membrane of the rectum. **Navigational Note:** -					
Rectal necrosis	-	-	Tube feeding or TPN indicated; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the rectal wall. **Navigational Note:** -					
Rectal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents in the rectum. **Navigational Note:** -					
Rectal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the rectal region. **Navigational Note:** -					
Rectal perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the rectal wall. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Rectal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Severely altered GI function; tube feeding or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the rectum. **Navigational Note:** -					
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 invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the rectum. **Navigational Note:** -					
Retroperitoneal hemorrhage	-	Self-limited; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the retroperitoneal area. **Navigational Note:** -					
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	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the salivary duct. **Navigational Note:** -					
Salivary gland fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between a salivary gland and another organ or anatomic site. **Navigational Note:** -					
Small intestinal mucositis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe pain; interfering with oral intake; tube feeding, TPN or hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by ulceration or inflammation of the mucous membrane of the small intestine. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Small intestinal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; limiting instrumental ADL	Hospitalization indicated; invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the intestinal contents of the small intestine. **Navigational Note:** -					
Small intestinal perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the small intestine wall. **Navigational Note:** -					
Small intestinal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function	Symptomatic and severely altered GI function; tube feeding, TPN or hospitalization indicated; non-emergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the small intestine. **Navigational Note:** -					
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 invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the mucosal surface of the small intestine. **Navigational Note:** -					
Stomach pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the stomach. **Navigational Note:** -					
Tooth development disorder	Asymptomatic; hypoplasia of tooth or enamel	Impairment correctable with oral surgery	Maldevelopment with impairment not surgically correctable; limiting self care ADL	-	-
Definition: A disorder characterized by a pathological process of the teeth occurring during tooth development. **Navigational Note:** -					
Tooth discoloration	Surface stains	-	-	-	-
Definition: A disorder characterized by a change in tooth hue or tint. **Navigational Note:** -					

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Toothache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the tooth. **Navigational Note:** -					
Typhlitis	-	-	Symptomatic (e.g., abdominal pain, fever, change in bowel habits with ileus); peritoneal signs	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by necrotizing enterocolitis in neutropenic patients. **Navigational Note:** Also report Investigations: Neutrophil count decreased					
Upper gastrointestinal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the upper gastrointestinal tract (oral cavity, pharynx, esophagus, and stomach). **Navigational Note:** -					
Visceral arterial ischemia	-	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (>=24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A disorder characterized by a decrease in blood supply due to narrowing or blockage of a visceral (mesenteric) artery. **Navigational Note:** -					
Vomiting	Intervention not indicated	Outpatient IV hydration; medical intervention indicated	Tube feeding, TPN, or hospitalization indicated	Life-threatening consequences	Death
Definition: A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth. **Navigational Note:** -					
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; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

General disorders and administration site conditions					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Chills	Mild sensation of cold; shivering; chattering of teeth	Moderate tremor of the entire body; narcotics indicated	Severe or prolonged, not responsive to narcotics	-	-
Definition: A disorder characterized by a sensation of cold that often marks a physiologic response to sweating after a fever. **Navigational Note:** -					
Death neonatal	-	-	-	Neonatal loss of life	-
Definition: Newborn death occurring during the first 28 days after birth. **Navigational Note:** -					
Death NOS	-	-	-	-	Death
Definition: Death that cannot be attributed to a CTCAE term associated with Grade 5. **Navigational Note:** If death is due to an AE (ex., Cardiac disorders: Cardiac arrest), report as a Grade 5 event under that AE.					
Disease progression	-	-	-	-	Death
Definition: Death due to disease progression that cannot be attributed to a CTCAE term associated with Grade 5. **Navigational Note:** If death is due to an AE (ex., Cardiac disorders: Cardiac arrest), report as a Grade 5 event under that AE.					
Edema face	Localized facial edema	Moderate localized facial edema; limiting instrumental ADL	Severe swelling; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation in facial tissues. **Navigational Note:** -					
Edema limbs	5 - 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection	>10 - 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	>30% inter-limb discrepancy in volume; gross deviation from normal anatomic contour; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation in the upper or lower extremities. **Navigational Note:** -					

General disorders and administration site conditions					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Edema trunk	Swelling or obscuration of anatomic architecture on close inspection	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	Gross deviation from normal anatomic contour; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation in the trunk area. **Navigational Note:** -					
Facial pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the face. **Navigational Note:** -					
Fatigue	Fatigue relieved by rest	Fatigue not relieved by rest; limiting instrumental ADL	Fatigue not relieved by rest, limiting self care ADL	-	-
Definition: A disorder characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities. **Navigational Note:** -					
Fever	38.0 - 39.0 degrees C (100.4 - 102.2 degrees F)	>39.0 - 40.0 degrees C (102.3 - 104.0 degrees F)	>40.0 degrees C (>104.0 degrees F) for <=24 hrs	>40.0 degrees C (>104.0 degrees F) for >24 hrs	Death
Definition: A disorder characterized by elevation of the body's temperature above the upper limit of normal. **Navigational Note:** -					
Flu like symptoms	Mild flu-like symptoms present	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a group of symptoms similar to those observed in patients with the flu. It includes fever, chills, body aches, malaise, loss of appetite and dry cough. **Navigational Note:** Synonym: Flu, Influenza					
Gait disturbance	Mild change in gait (e.g., wide-based, limping or hobbling)	Moderate change in gait (e.g., wide-based, limping or hobbling); assistive device indicated; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by walking difficulties. **Navigational Note:** -					
Generalized edema	Noted on exam; 1+ pitting edema	Interfering with instrumental ADLs; oral therapy initiated	Interferes with self care ADL; intravenous therapy indicated; skin breakdown	Life-threatening consequences	-
Definition: A disorder characterized by fluid accumulation in the tissues of the body including the skin. **Navigational Note:** -					

General disorders and administration site conditions					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hypothermia	-	35 - >32 degrees C; 95 - >89.6 degrees F	32 - >28 degrees C; 89.6 - >82.4 degrees F	<=28 degrees C; 82.4 degrees F; life-threatening consequences (e.g., coma, hypotension, pulmonary edema, acidemia, ventricular fibrillation)	Death
Definition: A disorder characterized by an abnormally low body temperature. Treatment is required when the body temperature is 35C (95F) or below. **Navigational Note:** -					
Infusion site extravasation	Painless edema	Erythema with associated symptoms (e.g., edema, pain, induration, phlebitis)	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by leakage of the infusion into the surrounding tissue. Signs and symptoms may include induration, erythema, swelling, burning sensation and marked discomfort at the infusion site. **Navigational Note:** -					
Injection site reaction	Tenderness with or without associated symptoms (e.g., warmth, erythema, itching)	Pain; lipodystrophy; edema; phlebitis	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an intense adverse reaction (usually immunologic) developing at the site of an injection. **Navigational Note:** -					
Localized edema	Localized to dependent areas, no disability or functional impairment	Moderate localized edema and intervention indicated; limiting instrumental ADL	Severe localized edema and intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation at a specific anatomic site. **Navigational Note:** Prior to using this term consider specific edema areas: General disorders and administration site conditions: Edema face, Edema limbs, Edema trunk, or Edema neck; Nervous system disorders: Edema cerebral; Reproductive system and breast disorders: Genital edema; Respiratory, thoracic and mediastinal disorders: Laryngeal edema or Pulmonary edema; Skin and subcutaneous tissue disorders: Periorbital edema; Vascular disorders: Lymphedema					
Malaise	Uneasiness or lack of well being	Uneasiness or lack of well being limiting instrumental ADL	Uneasiness or lack of well being limiting self-care ADL	-	-
Definition: A disorder characterized by a feeling of general discomfort or uneasiness, an out-of-sorts feeling. **Navigational Note:** -					
Multi-organ failure	-	-	Shock with azotemia and acid-base disturbances; significant coagulation abnormalities	Life-threatening consequences (e.g., vasopressor dependent and oliguric or anuric or ischemic colitis or lactic acidosis)	Death
Definition: A disorder characterized by progressive deterioration of the lungs, liver, kidney and clotting mechanisms. **Navigational Note:** -					

General disorders and administration site conditions					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
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	Vascular or respiratory impairment requiring urgent intervention	-
Definition: A disorder characterized by swelling due to an accumulation of excessive fluid in the neck. **Navigational Note:** -					
Non-cardiac chest pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the chest unrelated to a heart disorder. **Navigational Note:** -					
Pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by the sensation of marked discomfort, distress or agony. **Navigational Note:** Prior to using this term consider using a specific body part pain term found throughout the CTCAE (over 40 different pain terms).					
Sudden death NOS	-	-	-	-	Death
Definition: An unexpected death that cannot be attributed to a CTCAE term associated with Grade 5. **Navigational Note:** If death is due to an AE (ex., Cardiac disorders: Cardiac arrest), report as a Grade 5 event under that AE.					
Vaccination site lymphadenopathy	Local lymph node enlargement	Localized ulceration; generalized lymph node enlargement	-	-	-
Definition: A disorder characterized by lymph node enlargement after vaccination. **Navigational Note:** -					
General disorders and administration site conditions - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Hepatobiliary disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 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; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a narrowing of the lumen of the bile duct. **Navigational Note:** -					
Biliary fistula	-	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the bile ducts and another organ or anatomic site. **Navigational Note:** -					
Budd-Chiari syndrome	-	Medical management indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; asterixis; mild encephalopathy	Life-threatening consequences; moderate to severe encephalopathy; coma	Death
Definition: A disorder characterized by occlusion of the hepatic veins and typically presents with abdominal pain, ascites and hepatomegaly. **Navigational Note:** -					
Cholecystitis	-	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by inflammation involving the gallbladder. It may be associated with the presence of gallstones. **Navigational Note:** -					
Gallbladder fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the gallbladder and another organ or anatomic site. **Navigational Note:** -					
Gallbladder necrosis	-	-	-	Life-threatening consequences; urgent invasive intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the gallbladder. **Navigational Note:** -					

Hepatobiliary disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Gallbladder obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; altered GI function; IV fluids indicated <24 hrs	Symptomatic and severely altered GI function; tube feeding, TPN or hospitalization indicated; non-emergent operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the contents of the gallbladder. **Navigational Note:** -					
Gallbladder pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the gallbladder region. **Navigational Note:** -					
Gallbladder perforation	-	-	-	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the gallbladder wall. **Navigational Note:** -					
Hepatic failure	-	-	Asterixis; mild encephalopathy; drug-induced liver injury (DILI); limiting self care ADL	Life-threatening consequences; moderate to severe encephalopathy; coma	Death
Definition: A disorder characterized by the inability of the liver to metabolize chemicals in the body. Laboratory test results reveal abnormal plasma levels of ammonia, bilirubin, lactic dehydrogenase, alkaline phosphatase, aminotransferase, and/or prolongation of prothrombin time (INR.) Drug-induced liever injury (DILI) as defined by Hy's Law. **Navigational Note:** -					
Hepatic hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the liver. **Navigational Note:** -					
Hepatic necrosis	-	-	-	Life-threatening consequences; urgent invasive intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the hepatic parenchyma. **Navigational Note:** -					
Hepatic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the liver region. **Navigational Note:** -					

Hepatobiliary disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Perforation bile duct	-	-	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the wall of the extrahepatic or intrahepatic bile duct. **Navigational Note:** -					
Portal hypertension	-	Decreased portal vein flow	Reversal/retrograde portal vein flow; associated with varices and/or ascites	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in blood pressure in the portal venous system. **Navigational Note:** -					
Portal vein thrombosis	-	Intervention not indicated	Medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the formation of a thrombus (blood clot) in the portal vein. **Navigational Note:** -					
Sinusoidal obstruction syndrome	-	Blood bilirubin 2-5 mg/dL; minor interventions required (i.e., blood product, diuretic, oxygen)	Blood bilirubin >5 mg/dL; coagulation modifier indicated (e.g., defibrotide); reversal of flow on ultrasound	Life-threatening consequences (e.g., ventilatory support, dialysis, plasmapheresis, peritoneal drainage)	Death
Definition: A disorder characterized by severe hepatic injury as a result of the blood vessels of the liver becoming inflamed and/or blocked. **Navigational Note:** -					
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; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Immune system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Allergic reaction	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen. **Navigational Note:** If related to infusion, use Injury, poisoning and procedural complications: Infusion related reaction. Do not report both.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death. **Navigational Note:** -					
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 characterized by loss of function or tissue destruction of an organ or multiple organs, arising from humoral or cellular immune responses of the individual to his own tissue constituents. **Navigational Note:** Prior to using this term consider specific autoimmune AEs					
Cytokine release syndrome	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to <40% O2	Hypotension managed with one pressor; hypoxia requiring ≥ 40% O2	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines. **Navigational Note:** Also consider reporting other organ dysfunctions including neurological toxicities such as: Psychiatric disorders: Hallucinations or Confusion; Nervous system disorders: Seizure, Dysphasia, Tremor, or Headache					
Serum sickness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate arthralgia; fever, rash, urticaria, antihistamines indicated	Severe arthralgia or arthritis; extensive rash; steroids or IV fluids indicated	Life-threatening consequences; pressor or ventilatory support indicated	Death
Definition: A disorder characterized by a delayed-type hypersensitivity reaction to foreign proteins derived from an animal serum. It occurs approximately six to twenty-one days following the administration of the foreign antigen. Symptoms include fever, arthralgias, myalgias, skin eruptions, lymphadenopathy, chest marked discomfort and dyspnea. **Navigational Note:** -					

Immune system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
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; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Abdominal infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the abdominal cavity. **Navigational Note:** -					
Anorectal infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the anal area and the rectum. **Navigational Note:** -					
Appendicitis	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation to the vermiform appendix caused by a pathogenic agent. **Navigational Note:** -					
Appendicitis perforated	-	-	Medical intervention indicated; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation to the vermiform appendix caused by a pathogenic agent with gangrenous changes resulting in the rupture of the appendiceal wall. The appendiceal wall rupture causes the release of inflammatory and bacterial contents from the appendiceal lumen into the abdominal cavity. **Navigational Note:** -					
Arteritis infective	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving an artery. **Navigational Note:** -					
Bacteremia	-	Blood culture positive with no signs or symptoms	-	-	-
Definition: A disorder characterized by the presence of bacteria in the blood stream. **Navigational Note:** Consider Infections and infestations: Sepsis (Grades 3, 4 & 5)					
Biliary tract infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the biliary tract. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Bladder infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the bladder. **Navigational Note:** -					
Bone infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the bones. **Navigational Note:** -					
Breast infection	-	Local infection with moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; severe infection; axillary adenitis	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the breast. **Navigational Note:** -					
Bronchial infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the bronchi. **Navigational Note:** -					
Catheter related infection	-	Localized; local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process that arises secondary to catheter use. **Navigational Note:** -					
Cecal infection	-	Localized; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the cecum. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Cervicitis infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the uterine cervix. **Navigational Note:** -					
Conjunctivitis	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limiting self care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by inflammation, swelling and redness to the conjunctiva of the eye. **Navigational Note:** Consider Infections and infestations: Conjunctivitis infective if caused by infection					
Conjunctivitis infective	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by an infectious process involving the conjunctiva. Clinical manifestations include pink or red color in the eyes. **Navigational Note:** -					
Corneal infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the cornea. **Navigational Note:** -					
Cranial nerve infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a cranial nerve. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Cytomegalovirus infection reactivation	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; IV intervention indicated	Life-threatening consequences; urgent intervention indicated; blindness	Death
Definition: A disorder characterized by the reactivation of cytomegalovirus (CMV). **Navigational Note:** Synonym: CMV					
Device related infection	-	Oral intervention indicated (e.g., antibiotic, antifungal)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the use of a medical device. **Navigational Note:** -					
Duodenal infection	-	Moderate symptoms; medical intervention indicated (e.g., oral antibiotics)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the duodenum. **Navigational Note:** -					
Encephalitis infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; severe changes in mental status; self-limited seizure activity; focal neurologic abnormalities	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the brain tissue. **Navigational Note:** -					
Encephalomyelitis infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the brain and spinal cord tissues. **Navigational Note:** -					
Endocarditis infective	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the endocardial layer of the heart. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Endophthalmitis	-	Local intervention indicated	Systemic intervention; hospitalization indicated	Best corrected visual acuity of 20/200 or worse in the affected eye	-
Definition: A disorder characterized by an infectious process involving the internal structures of the eye. **Navigational Note:** -					
Enterocolitis infectious	-	Passage of >3 unformed stools per 24 hrs or duration of illness >48 hrs; moderate abdominal pain; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated; profuse watery diarrhea with signs of hypovolemia; bloody diarrhea; fever; severe abdominal pain; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the small and large intestines. **Navigational Note:** Includes Clostridium difficile (c. diff, c. difficile).					
Epstein-Barr virus infection reactivation	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; IV intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the reactivation of Epstein-Barr virus (EBV). **Navigational Note:** Synonym: EBV					
Esophageal infection	-	Local intervention indicated (e.g., oral antibiotic, antifungal, antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the esophagus. **Navigational Note:** -					
Eye infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated; enucleation	Death
Definition: A disorder characterized by an infectious process involving the eye. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Folliculitis	Covering <10% of the body surface area; no intervention indicated	Covering 10-30% of the body surface area; topical intervention initiated	>30% BSA; systemic intervention indicated	-	-
Definition: A disorder characterized by inflammation or infection of the hair follicles. **Navigational Note:** -					
Fungemia	-	Moderate symptoms; medical intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	-	-
Definition: A disorder characterized by the presence of fungus in the blood stream. **Navigational Note:** -					
Gallbladder infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the gallbladder. **Navigational Note:** -					
Gum infection	Local therapy indicated (swish and swallow)	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the gums. **Navigational Note:** -					
Hepatic infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the liver. **Navigational Note:** -					
Hepatitis B reactivation	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; IV intervention indicated	Life-threatening consequences; urgent intervention indicated; severe decompensated liver function (e.g., coagulopathy, encephalopathy, coma)	Death
Definition: A disorder characterized by the reactivation of hepatitis B virus. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hepatitis viral	Asymptomatic, intervention not indicated	Moderate symptoms; medical intervention indicated	Symptomatic liver dysfunction; fibrosis by biopsy; compensated cirrhosis; hospitalization or prolongation of existing hospitalization indicated	Life-threatening consequences; severe decompensated liver function (e.g., coagulopathy, encephalopathy, coma)	Death
Definition: A disorder characterized by a viral pathologic process involving the liver parenchyma. **Navigational Note:** -					
Herpes simplex reactivation	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; IV intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the reactivation of Herpes simplex virus. **Navigational Note:** -					
Infective myositis	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the skeletal muscles. **Navigational Note:** -					
Joint infection	-	Localized; local intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral); needle aspiration indicated (single or multiple)	Arthroscopic intervention indicated (e.g., drainage) or arthrotomy (e.g., open surgical drainage)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a joint. **Navigational Note:** -					
Kidney infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the kidney. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Laryngitis	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an inflammatory process involving the larynx. **Navigational Note:** For symptoms and no intervention, consider Respiratory, thoracic and mediastinal disorders: Sore throat or Hoarseness.					
Lip infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	-	-
Definition: A disorder characterized by an infectious process involving the lips. **Navigational Note:** -					
Lung infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the lungs, including pneumonia. **Navigational Note:** If infection is due to aspiration, consider reporting Respiratory, thoracic and mediastinal disorders: Apiration					
Lymph gland infection	-	Localized; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the lymph nodes. **Navigational Note:** -					
Mediastinal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the mediastinum. **Navigational Note:** -					
Meningitis	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated; focal neurologic deficit	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by acute inflammation of the meninges of the brain and/or spinal cord. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Mucosal infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a mucosal surface. **Navigational Note:** -					
Myelitis	Asymptomatic; mild signs (e.g., Babinski's reflex or Lhermitte's sign)	Moderate weakness or sensory loss; limiting instrumental ADL	Severe weakness or sensory loss; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation involving the spinal cord. Symptoms include weakness, paresthesia, sensory loss, marked discomfort and incontinence. **Navigational Note:** -					
Nail infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	-	-
Definition: A disorder characterized by an infectious process involving the nail. **Navigational Note:** -					
Otitis externa	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the outer ear and ear canal. Contributory factors include excessive water exposure (swimmer's ear infection) and cuts in the ear canal. Symptoms include fullness, itching, swelling and marked discomfort in the ear and ear drainage. **Navigational Note:** Changes associated with radiation to external ear (pinnae) are graded under Injury, poisoning and procedural complications: Dermatitis radiation					
Otitis media	-	Localized; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the middle ear. **Navigational Note:** -					
Ovarian infection	-	Localized; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the ovary. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Pancreas infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the pancreas. **Navigational Note:** -					
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 with or without mild symptoms	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; IV antibiotics indicated	Life-threatening consequences	Death
Definition: A disorder characterized by an eruption consisting of papules (a small, raised pimple) and pustules (a small pus filled blister), typically appearing in face, scalp, and upper chest and back. Unlike acne, this rash does not present with whiteheads or blackheads, and can be symptomatic, with itchy or tender lesions. **Navigational Note:** -					
Paronychia	Nail fold edema or erythema; disruption of the cuticle	Local 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	Operative intervention indicated; IV antibiotics indicated; limiting self care ADL	-	-
Definition: A disorder characterized by an infectious process involving the soft tissues around the nail. **Navigational Note:** -					
Pelvic infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the pelvic cavity. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Penile infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the penis. **Navigational Note:** -					
Periorbital infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the orbit of the eye. **Navigational Note:** -					
Peripheral nerve infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the peripheral nerves. **Navigational Note:** -					
Peritoneal infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the peritoneum. **Navigational Note:** -					
Pharyngitis	-	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the throat. **Navigational Note:** For Grade 1 Consider Respiratory, thoracic and mediastinal disorders: Sore throat					
Phlebitis infective	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the vein. Clinical manifestations include erythema, marked discomfort, swelling, and induration along the course of the infected vein. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Pleural infection	-	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the pleura. **Navigational Note:** -					
Prostate infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the prostate gland. **Navigational Note:** -					
Rash pustular	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	-	-
Definition: A disorder characterized by a circumscribed and elevated skin lesion filled with pus. **Navigational Note:** Synonym: Boil					
Rhinitis infective	-	Localized; local intervention indicated	-	-	-
Definition: A disorder characterized by an infectious process involving the nasal mucosal. **Navigational Note:** -					
Salivary gland infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the salivary gland. **Navigational Note:** -					
Scrotal infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the scrotum. **Navigational Note:** -					
Sepsis	-	-	Blood culture positive with signs or symptoms; treatment indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the presence of pathogenic microorganisms in the blood stream that cause a rapidly progressing systemic reaction that may lead to shock. **Navigational Note:** Includes SIRS. Also consider Infections and infestations: Bacteremia (Grade 2)					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Shingles	Localized, local intervention indicated	Local infection with moderate symptoms; oral intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; IV intervention indicated; limiting self-care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the reactivation of herpes zoster virus. **Navigational Note:** Synonym: Herpes zoster					
Sinusitis	-	Localized; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the mucous membranes of the paranasal sinuses. **Navigational Note:** -					
Skin infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the skin such as cellulitis. **Navigational Note:** -					
Small intestine infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the small intestine. **Navigational Note:** -					
Soft tissue infection	-	Localized; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving soft tissues. **Navigational Note:** -					
Splenic infection	-	-	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the spleen. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Stoma site infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a stoma (surgically created opening on the surface of the body). **Navigational Note:** -					
Thrush	Asymptomatic; local symptomatic management	Oral intervention indicated (e.g., antifungal)	IV antifungal intervention indicated	-	-
Definition: A disorder characterized by a suspected candidal infection involving an oral mucosal surface. **Navigational Note:** -					
Tooth infection	-	Localized; local intervention indicated (e.g., topical antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving a tooth. **Navigational Note:** -					
Tracheitis	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the trachea. **Navigational Note:** -					
Upper respiratory infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the upper respiratory tract (nose, paranasal sinuses, pharynx, larynx, or trachea). **Navigational Note:** -					
Urethral infection	-	Localized; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the urethra. **Navigational Note:** -					
Urinary tract infection	-	Localized; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the urinary tract, most commonly the bladder and the urethra. **Navigational Note:** -					

Infections and infestations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Uterine infection	-	Moderate symptoms; oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the endometrium. It may extend to the myometrium and parametrial tissues. **Navigational Note:** -					
Vaginal infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the vagina. **Navigational Note:** -					
Viremia	-	Moderate symptoms; medical intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	-	-
Definition: A disorder characterized by the presence of a virus in the blood stream. **Navigational Note:** -					
Vulval infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the vulva. **Navigational Note:** -					
Wound infection	Localized, local intervention indicated	Oral intervention indicated (e.g., antibiotic, antifungal, or antiviral)	IV antibiotic, antifungal, or antiviral intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an infectious process involving the wound. **Navigational Note:** -					
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; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Ankle fracture	Mild; non-operative intervention indicated	Limiting instrumental ADL; outpatient operative intervention indicated	Limiting self care ADL; elective operative intervention indicated requiring hospitalization	-	-
Definition: A finding of damage to the ankle joint characterized by a break in the continuity of the ankle bone. Symptoms include marked discomfort, swelling and difficulty moving the affected leg and foot. **Navigational Note:** -					
Aortic injury	-	Operative intervention not indicated	Severe symptoms; limiting self care ADL; 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. **Navigational Note:** -					
Arterial injury	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; repair or revision not indicated	Severe symptoms; limiting self care ADL; 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. **Navigational Note:** -					
Biliary anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of bile due to breakdown of a biliary anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Bladder anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of urine due to breakdown of a bladder anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Bruising	Localized or in a dependent area	Generalized	-	-	-
Definition: A finding of injury of the soft tissues or bone characterized by leakage of blood into surrounding tissues. **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Burn	Minimal symptoms; intervention not indicated	Medical intervention; minimal debridement indicated	Moderate to major debridement or reconstruction indicated	Life-threatening consequences	Death
Definition: A finding of impaired integrity to the anatomic site of an adverse thermal reaction. Burns can be caused by exposure to chemicals, direct heat, electricity, flames and radiation. The extent of damage depends on the length and intensity of exposure and time until provision of treatment. **Navigational Note:** -					
Dermatitis radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death
Definition: A finding of cutaneous inflammatory reaction occurring as a result of exposure to biologically effective levels of ionizing radiation. **Navigational Note:** Synonym: Radiation induced skin toxicities (CTCAE v3.0)					
Esophageal anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of an esophageal anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Fall	Minor with no resultant injuries; intervention not indicated	Symptomatic; noninvasive intervention indicated	Hospitalization indicated; invasive intervention indicated	-	-
Definition: A finding of sudden movement downward, usually resulting in injury. **Navigational Note:** -					
Fallopian tube anastomotic leak	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 finding of leakage due to breakdown of a fallopian tube anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Fallopian tube perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated (e.g., organ resection)	Death
Definition: A disorder characterized by a rupture of the fallopian tube wall. **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
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; limiting self care ADL; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of traumatic injury to the bone in which the continuity of the bone is broken. **Navigational Note:** Prior to using this term consider specific fracture areas: Injury, poisoning and procedural complications: Ankle fracture, Hip fracture, Spinal fracture, or Wrist fracture					
Gastric anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a gastric anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Gastrointestinal anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a gastrointestinal anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Gastrointestinal stoma necrosis	-	Superficial necrosis; intervention not indicated	Severe symptoms; hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the gastrointestinal tract stoma. **Navigational Note:** -					
Hip fracture	-	Hairline fracture; mild pain; limiting instrumental ADL; non-operative intervention indicated	Severe pain; hospitalization or intervention indicated for pain control (e.g., traction); operative intervention indicated	Life-threatening consequences; symptoms associated with neurovascular compromise	-
Definition: A finding of traumatic injury to the hip in which the continuity of either the femoral head, femoral neck, intertrochanteric or subtrochanteric regions is broken. **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Infusion related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances. **Navigational Note:** -					
Injury to carotid artery	-	Repair or revision not indicated	Severe symptoms; limiting self care ADL (e.g., transient cerebral ischemia); repair or revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the carotid artery. **Navigational Note:** -					
Injury to inferior vena cava	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; repair or revision not indicated	Severe symptoms; limiting self care ADL; repair or revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the inferior vena cava. **Navigational Note:** -					
Injury to jugular vein	-	Repair or revision not indicated	Symptomatic limiting self care ADL; repair or revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the jugular vein. **Navigational Note:** -					
Injury to superior vena cava	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; repair or revision not indicated	Severe symptoms; limiting self care ADL; repair or revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the superior vena cava. **Navigational Note:** -					
Intestinal stoma leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of contents from an intestinal stoma (surgically created opening on the surface of the body). **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Intestinal stoma obstruction	-	Self-limited; intervention not indicated	Severe symptoms; IV fluids, tube feeding, or TPN indicated >=24 hrs; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of the contents of the intestinal stoma. **Navigational Note:** -					
Intestinal stoma site bleeding	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Transfusion indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the intestinal stoma. **Navigational Note:** -					
Intraoperative arterial injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to an artery during a surgical procedure. **Navigational Note:** -					
Intraoperative breast injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the breast parenchyma during a surgical procedure. **Navigational Note:** -					
Intraoperative cardiac injury	-	-	Primary repair of injured organ/structure indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the heart during a surgical procedure. **Navigational Note:** -					
Intraoperative ear injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL (e.g., impaired hearing; impaired balance)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the ear during a surgical procedure. **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
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; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the endocrine gland during a surgical procedure. **Navigational Note:** -					
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; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the gastrointestinal system during a surgical procedure. **Navigational Note:** -					
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; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the head and neck during a surgical procedure. **Navigational Note:** -					
Intraoperative hemorrhage	-	-	Postoperative invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of uncontrolled bleeding during a surgical procedure. **Navigational Note:** -					
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; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the hepatic parenchyma and/or biliary tract during a surgical procedure. **Navigational Note:** -					
Intraoperative musculoskeletal injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the musculoskeletal system during a surgical procedure. **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
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; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the nervous system during a surgical procedure. **Navigational Note:** -					
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; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the eye during a surgical procedure. **Navigational Note:** -					
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; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the kidney during a surgical procedure. **Navigational Note:** -					
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; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the reproductive organs during a surgical procedure. **Navigational Note:** -					
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; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the respiratory system during a surgical procedure. **Navigational Note:** -					
Intraoperative splenic injury	-	Primary repair of injured organ/structure indicated	Resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the spleen during a surgical procedure. **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Intraoperative urinary injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to the urinary system during a surgical procedure. **Navigational Note:** -					
Intraoperative venous injury	Primary repair of injured organ/structure indicated	Partial resection of injured organ/structure indicated	Complete resection or reconstruction of injured organ/structure indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of damage to a vein during a surgical procedure. **Navigational Note:** -					
Kidney anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of urine due to breakdown of a kidney anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Large intestinal anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of an anastomosis (surgical connection of two separate anatomic structures) in the large intestine. **Navigational Note:** -					
Pancreatic anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a pancreatic anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Pharyngeal anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a pharyngeal anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Postoperative hemorrhage	Mild symptoms; intervention not indicated	Moderate bleeding requiring transfusion < 2 units (10 cc/kg for pediatrics) of pRBCs	Transfusion indicated of >=2 units (10 cc/kg for pediatrics) pRBCs; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding occurring after a surgical procedure. **Navigational Note:** -					
Postoperative thoracic procedure complication	-	Extubated within 24 - 72 hrs postoperatively	Extubated >72 hrs postoperatively, but before tracheostomy indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A finding of a previously undocumented problem that occurs after a thoracic procedure. **Navigational Note:** -					
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
Definition: A finding of protrusion of the intestinal stoma (surgically created opening on the surface of the body) above the abdominal surface. **Navigational Note:** -					
Prolapse of urostomy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Local care or maintenance; minor revision indicated	Dysfunctional stoma; elective operative intervention or major stomal revision indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A finding of displacement of the urostomy. **Navigational Note:** -					
Radiation recall reaction (dermatologic)	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated	Death
Definition: A finding of acute skin inflammatory reaction caused by drugs, especially chemotherapeutic agents, for weeks or months following radiotherapy. The inflammatory reaction is confined to the previously irradiated skin and the symptoms disappear after the removal of the pharmaceutical agent. **Navigational Note:** -					
Rectal anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a rectal anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Seroma	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; simple aspiration indicated	Symptomatic, elective invasive intervention indicated	-	-
Definition: A finding of tumor-like collection of serum in the tissues. **Navigational Note:** -					
Small intestinal anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of an anastomosis (surgical connection of two separate anatomic structures) in the small bowel. **Navigational Note:** -					
Spermatic cord anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a spermatic cord anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Spinal fracture	Mild back pain; nonprescription analgesics indicated	Moderate back pain; prescription analgesics indicated; limiting instrumental ADL	Severe back pain; hospitalization or intervention indicated for pain control (e.g., vertebroplasty); limiting self care ADL; disability	Life-threatening consequences; symptoms associated with neurovascular compromise	Death
Definition: A finding of traumatic injury to the spine in which the continuity of a vertebral bone is broken. **Navigational Note:** -					
Stenosis of gastrointestinal stoma	-	Symptomatic; IV fluids indicated <24 hrs; manual dilation at bedside	Severely altered GI function; tube feeding, TPN or hospitalization indicated; elective operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of narrowing of the gastrointestinal stoma (surgically created opening on the surface of the body). **Navigational Note:** -					
Stomal ulcer	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by a circumscribed, erosive lesion on the jejunal mucosal surface close to the anastomosis site following a gastroenterostomy procedure. **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Tracheal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the trachea. **Navigational Note:** -					
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 or respiratory distress limiting self care ADL; invasive intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by blockage of the lumen of the trachea. **Navigational Note:** -					
Tracheostomy site bleeding	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Transfusion indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the tracheostomy site. **Navigational Note:** -					
Ureteric anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a ureteral anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Urethral anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a urethral anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Urostomy leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage of contents from a urostomy. **Navigational Note:** -					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Urostomy obstruction	Asymptomatic; clinical or 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 disorder characterized by blockage of the urostomy. **Navigational Note:** -					
Urostomy site bleeding	Minimal bleeding identified on clinical exam; intervention not indicated	Moderate bleeding; medical intervention indicated	Transfusion indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the urostomy site. **Navigational Note:** -					
Urostomy stenosis	-	Symptomatic but no hydronephrosis, sepsis, or 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. **Navigational Note:** -					
Uterine anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a uterine anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Uterine perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the uterine wall. **Navigational Note:** -					
Vaccination complication	Mild pain; erythema 2.5-5cm; induration/swelling 2.5-5cm; does not interfere with activity	Moderate pain; Erythema 5.1-10 cm; Induration/swelling 5.1-10 cm; lipodystrophy; limiting instrumental ADL	Severe pain; Erythema > 10 cm; Induration/swelling > 10 cm; necrosis; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder that occurs after the injection of a substance with antigenic properties, administered to activate the immune system. **Navigational Note:** For systemic vaccination complications, consider Immune system disorders: Allergic reaction or Anaphylaxis.					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Vaginal anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a vaginal anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Vas deferens anastomotic leak	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A finding of leakage due to breakdown of a vas deferens anastomosis (surgical connection of two separate anatomic structures). **Navigational Note:** -					
Vascular access complication	TPA administration into line with no intent for systemic therapy indicated	Device dislodgement, blockage, leak, or malposition; device replacement indicated	Pulmonary embolism, deep vein or cardiac thrombosis; intervention indicated (e.g., anticoagulation, lysis, filter, invasive procedure)	Life-threatening consequences with hemodynamic or neurologic instability	Death
Definition: A finding of a previously undocumented problem related to the vascular access site. **Navigational Note:** -					
Venous injury	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic (e.g., claudication); repair or revision not indicated	Severe symptoms; limiting self care ADL; repair or revision indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A finding of damage to a vein. **Navigational Note:** -					
Wound complication	Observation only; topical intervention indicated	Bedside local care indicated	Operative intervention indicated	Life-threatening consequences	Death
Definition: A finding of development of a new problem at the site of an existing wound. **Navigational Note:** Prior to using this term consider Injury, poisoning and procedural complications: Wound dehiscence or Infections and infestations: Wound infection					
Wound dehiscence	Incisional separation, intervention not indicated	Incisional separation, local care (e.g., suturing) or medical intervention indicated (e.g., analgesic)	Fascial disruption or dehiscence without evisceration; 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. **Navigational Note:** Also consider Infections and infestations: Wound infection					

Injury, poisoning and procedural complications					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Wrist fracture	Mild; non-operative intervention indicated	Limiting instrumental ADL; outpatient operative intervention indicated	Limiting self care ADL; elective operative intervention indicated requiring hospitalization	-	-
Definition: A finding of traumatic injury to the wrist joint in which the continuity of a wrist bone is broken. **Navigational Note:** -					
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; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Investigations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Activated partial thromboplastin time prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; bleeding	-	-
Definition: A finding based on laboratory test results in which the partial thromboplastin time is found to be greater than the control value. As a possible indicator of coagulopathy, a prolonged partial thromboplastin time (PTT) may occur in a variety of diseases and disorders, both primary and related to treatment. **Navigational Note:** -					
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen. **Navigational Note:** Also consider Hepatobiliary disorders: Hepatic failure					
Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alkaline phosphatase in a blood specimen. **Navigational Note:** -					
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Definition: A finding based on laboratory test results that indicate an increase in the level of aspartate aminotransferase (AST or SGOT) in a blood specimen. **Navigational Note:** Also consider Hepatobiliary disorders: Hepatic failure					
Blood antidiuretic hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of antidiuretic hormone in the blood specimen. **Navigational Note:** -					
Blood bicarbonate decreased	<LLN and no intervention initiated	-	-	-	-
Definition: A finding based on laboratory test results that indicate a decrease in levels of bicarbonate in a venous blood specimen. **Navigational Note:** Also consider Metabolism and nutrition disorders: Acidosis or Alkalosis					
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal	-
Definition: A finding based on laboratory test results that indicate an abnormally high level of bilirubin in the blood. Excess bilirubin is associated with jaundice. **Navigational Note:** Also consider Hepatobiliary disorders: Hepatic failure					

Investigations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Blood corticotrophin decreased	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Hospitalization indicated	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of corticotrophin in a blood specimen. **Navigational Note:** -					
Blood gonadotrophin abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of gonadotrophin hormone in a blood specimen. **Navigational Note:** -					
Blood lactate dehydrogenase increased	>ULN	-	-	-	-
Definition: A finding based on laboratory test results that indicate increased levels of lactate dehydrogenase in the blood specimen. **Navigational Note:** -					
Blood prolactin abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	-	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of prolactin hormone in a blood specimen. **Navigational Note:** -					
Carbon monoxide diffusing capacity decreased	3 - 5 units below LLN; for follow-up, a decrease of 3 - 5 units (ml/min/mm Hg) below the baseline value; asymptomatic and intervention not indicated	6 - 8 units below LLN; for follow-up, an asymptomatic decrease of >5 - 8 units (ml/min/mm Hg) below the baseline value; symptomatic and intervention not indicated	Asymptomatic decrease of >8 units drop; >5 units drop along with the presence of pulmonary symptoms (e.g., >Grade 2 hypoxia or >Grade 2 dyspnea); intervention indicated	-	-
Definition: A finding based on lung function test results that indicate a decrease in the lung capacity to absorb carbon monoxide. **Navigational Note:** Also consider Respiratory, thoracic and mediastinal disorders: Respiratory failure or Dyspnea					
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer	-	-
Definition: A finding based on laboratory test results that indicate increased levels of cardiac troponin I in a biological specimen. **Navigational Note:** Also consider Cardiac disorders: Heart failure or Cardiac disorders: Myocardial infarction. Report Cardiac disorders: Heart failure or Cardiac disorders: Myocardial infarction if same grade event.					

Investigations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer	-	-
Definition: A finding based on laboratory test results that indicate increased levels of cardiac troponin T in a biological specimen. **Navigational Note:** Also consider Cardiac disorders: Heart failure or Cardiac disorders: Myocardial infarction. Report Cardiac disorders: Heart failure or Cardiac disorders: Myocardial infarction if same grade event.					
CD4 lymphocytes decreased	<LLN - 500/mm3; <LLN - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200 - 50/mm3; <0.2 x 0.05 - 10e9 /L	<50/mm3; <0.05 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of CD4 lymphocytes in a blood specimen. **Navigational Note:** -					
Cholesterol high	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L	-
Definition: A finding based on laboratory test results that indicate higher than normal levels of cholesterol in a blood specimen. **Navigational Note:** -					
CPK increased	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN	-
Definition: A finding based on laboratory test results that indicate an increase in levels of creatine phosphokinase in a blood specimen. **Navigational Note:** Also consider Cardiac disorders: Heart failure or Cardiac disorders: Myocardial infarction. Report Cardiac disorders: Heart failure or Cardiac disorders: Myocardial infarction if same grade event.					
Creatinine increased	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 x baseline; >3.0 - 6.0 x ULN	>6.0 x ULN	-
Definition: A finding based on laboratory test results that indicate increased levels of creatinine in a biological specimen. **Navigational Note:** Also consider Renal and urinary disorders: Acute kidney injury					
Ejection fraction decreased	-	Resting ejection fraction (EF) 50 - 40%; 10 - 19% drop from baseline	Resting ejection fraction (EF) 39 - 20%; >=20% drop from baseline	Resting ejection fraction (EF) <20%	-
Definition: The percentage computed when the amount of blood ejected during a ventricular contraction of the heart is compared to the amount that was present prior to the contraction. **Navigational Note:** Also consider Cardiac disorders: Left ventricular systolic dysfunction. Report Cardiac disorders: Left ventricular systolic dysfunction if same grade event.					
Electrocardiogram QT corrected interval prolonged	Average QTc 450 - 480 ms	Average QTc 481 - 500 ms	Average QTc >= 501 ms; >60 ms change from baseline	Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia	-
Definition: A finding of a cardiac dysrhythmia characterized by an abnormally long corrected QT interval. **Navigational Note:** -					

Investigations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Electrocardiogram T wave abnormal	T wave flattening	Nonspecific ST segment change	-	-	-
Definition: A disorder characterized by Electrocardiogram T wave amplitude changes. **Navigational Note:** -					
Fibrinogen decreased	<1.0 - 0.75 x LLN; if abnormal, <25% decrease from baseline	<0.75 - 0.5 x LLN; if abnormal, 25 - <50% decrease from baseline	<0.5 - 0.25 x LLN; if abnormal, 50 - <75% decrease from baseline	<0.25 x LLN; if abnormal, 75% decrease from baseline; absolute value <50 mg/dL	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of fibrinogen in a blood specimen. **Navigational Note:** -					
Forced expiratory volume decreased	FEV1% (percentages of observed FEV1 and FVC related to their respective predicted values) 99 - 70% predicted	FEV1 60 - 69%	50 - 59%	<= 49%	-
Definition: A finding based on test results that indicate a relative decrease in the fraction of the forced vital capacity that is exhaled in a specific number of seconds. **Navigational Note:** Also consider Respiratory, thoracic and mediastinal disorders: Respiratory failure or Dyspnea					
GGT increased	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Definition: A finding based on laboratory test results that indicate higher than normal levels of the enzyme gamma-glutamyltransferase in the blood specimen. GGT (gamma-glutamyltransferase) catalyzes the transfer of a gamma glutamyl group from a gamma glutamyl peptide to another peptide, amino acids or water. **Navigational Note:** -					
Growth hormone abnormal	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	-	-	-
Definition: A finding based on laboratory test results that indicate abnormal levels of growth hormone in a biological specimen. **Navigational Note:** -					
Haptoglobin decreased	<LLN	-	-	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of haptoglobin in a blood specimen. **Navigational Note:** -					
Hemoglobin increased	Increase in >0 - 2 g/dL	Increase in >2 - 4 g/dL	Increase in >4 g/dL	-	-
Definition: A finding based on laboratory test results that indicate increased levels of hemoglobin above normal. **Navigational Note:** -					
INR increased	>1.2 - 1.5; >1 - 1.5 x baseline if on anticoagulation; monitoring only indicated	>1.5 - 2.5; >1.5 - 2.5 x baseline if on anticoagulation; dose adjustment indicated	>2.5; >2.5 x baseline if on anticoagulation; bleeding	-	-
Definition: A finding based on laboratory test results that indicate an increase in the ratio of the patient's prothrombin time to a control sample in the blood. **Navigational Note:** -					

Investigations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic	>5.0 x ULN and with signs or symptoms	-
Definition: A finding based on laboratory test results that indicate an increase in the level of lipase in a biological specimen. **Navigational Note:** -					
Lymphocyte count decreased	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of lymphocytes in a blood specimen. **Navigational Note:** -					
Lymphocyte count increased	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-	-
Definition: A finding based on laboratory test results that indicate an abnormal increase in the number of lymphocytes in the blood, effusions or bone marrow. **Navigational Note:** -					
Neutrophil count decreased	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen. **Navigational Note:** -					
Pancreatic enzymes decreased	<LLN and asymptomatic	Increase in stool frequency, bulk, or odor; steatorrhea	Sequelae of absorption deficiency	-	-
Definition: A finding based on laboratory test results that indicate an decrease in levels of pancreatic enzymes in a biological specimen. **Navigational Note:** -					
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen. **Navigational Note:** -					
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 - 5.0 x ULN with signs or symptoms; >5.0 x ULN and asymptomatic	>5.0 x ULN and with signs or symptoms	-
Definition: A finding based on laboratory test results that indicate an increase in the levels of amylase in a serum specimen. **Navigational Note:** -					
Thyroid stimulating hormone increased	TSH increased and no intervention initiated	-	-	-	-
Definition: A disorder characterized by an increase in thyroid stimulating hormone. **Navigational Note:** If intervention initiated or symptomatic, report as Endocrine disorders: Hypothyroidism.					

Investigations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Urine output decreased	-	-	**Adult:** Oliguria (<80 ml in 8 hr); **Infants:** < 0.5 mL/kg per hour for 24 hours; **Children:** < 500 mL/1.73 m2 body surface area per day	**Adult:** Anuria (<240 ml in 24 hr); **Pediatric:** No urine output over 12 hours	-
Definition: A finding based on test results that indicate urine production is less relative to previous output. **Navigational Note:** -					
Vital capacity abnormal	90 - 75% of predicted value	<75 - 50% of predicted value; limiting instrumental ADL	<50% of predicted value; limiting self care ADL	-	-
Definition: A finding based on pulmonary function test results that indicate an abnormal vital capacity (amount of exhaled after a maximum inhalation) when compared to the predicted value. **Navigational Note:** Also consider Investigations: Forced Expiratory Volume; Respiratory, thoracic and mediastinal disorders: Respiratory failure or Dyspnea					
Weight gain	5 - <10% from baseline	10 - <20% from baseline	>=20% from baseline	-	-
Definition: A finding characterized by an unexpected or abnormal increase in overall body weight; for pediatrics, greater than the baseline growth curve. **Navigational Note:** Do not use Metabolism and nutrition disorders: Obesity, this term is being retired.					
Weight loss	5 to <10% from baseline; intervention not indicated	10 - <20% from baseline; nutritional support indicated	>=20% from baseline; tube feeding or TPN indicated	-	-
Definition: A finding characterized by a decrease in overall body weight; for pediatrics, less than the baseline growth curve. **Navigational Note:** -					
White blood cell decreased	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L	-
Definition: A finding based on laboratory test results that indicate an decrease in number of white blood cells in a blood specimen. **Navigational Note:** -					
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; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Metabolism and nutrition disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Acidosis	pH <normal, but >=7.3	-	pH <7.3	Life-threatening consequences	Death
Definition: A disorder characterized by abnormally high acidity (high hydrogen-ion concentration) of the blood and other body tissues. **Navigational Note:** -					
Alcohol intolerance	-	Present	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in sensitivity to the adverse effects of alcohol, which can include nasal congestion, skin flushes, heart dysrhythmias, nausea, vomiting, indigestion and headaches. **Navigational Note:** -					
Alkalosis	pH >normal, but <=7.5	-	pH >7.5	Life-threatening consequences	Death
Definition: A disorder characterized by abnormally high alkalinity (low hydrogen-ion concentration) of the blood and other body tissues. **Navigational Note:** -					
Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a loss of appetite. **Navigational Note:** -					
Dehydration	Increased oral fluids indicated; dry mucous membranes; diminished skin turgor	IV fluids indicated	Hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by excessive loss of water from the body. It is usually caused by severe diarrhea, vomiting or diaphoresis. **Navigational Note:** -					
Glucose intolerance	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; dietary modification or oral agent indicated	Severe symptoms; insulin indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an inability to properly metabolize glucose. **Navigational Note:** -					
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of calcium (corrected for albumin) in blood. **Navigational Note:** -					

Metabolism and nutrition disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hyperglycemia	Abnormal glucose above baseline with no medical intervention	Change in daily management from baseline for a diabetic; oral antiglycemic agent initiated; workup for diabetes	Insulin therapy initiated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of blood sugar. It is usually an indication of diabetes mellitus or glucose intolerance. **Navigational Note:** -					
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; intervention initiated	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of potassium in the blood; associated with kidney failure or sometimes with the use of diuretic drugs. **Navigational Note:** -					
Hyperlipidemia	Requiring diet changes	Requiring pharmaceutical intervention	Hospitalization; pancreatitis	Life-threatening consequences	-
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of lipids in blood. **Navigational Note:** -					
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of magnesium in the blood. **Navigational Note:** -					
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of sodium in the blood. **Navigational Note:** -					
Hyperphosphatemia	Laboratory finding only and intervention not indicated	Noninvasive intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	Life-threatening consequences; urgent intervention indicated (e.g., dialysis)	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of phosphate in a blood. **Navigational Note:** -					
Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of triglyceride concentration in the blood. **Navigational Note:** -					
Hyperuricemia	>ULN without physiologic consequences	-	>ULN with physiologic consequences	Life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate an elevation in the concentration of uric acid. **Navigational Note:** -					

Metabolism and nutrition disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of albumin in the blood. **Navigational Note:** -					
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9 - 0.8 mmol/L; hospitalization indicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L; Ionized calcium <0.8 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of calcium (corrected for albumin) in the blood. **Navigational Note:** -					
Hypoglycemia	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of glucose in the blood. **Navigational Note:** -					
Hypokalemia	<LLN - 3.0 mmol/L	Symptomatic with <LLN - 3.0 mmol/L; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of potassium in the blood. **Navigational Note:** -					
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of magnesium in the blood. **Navigational Note:** -					
Hyponatremia	<LLN - 130 mmol/L	125-129 mmol/L and asymptomatic	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms	<120 mmol/L; life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of sodium in the blood. **Navigational Note:** -					
Hypophosphatemia	Laboratory finding only and intervention not indicated	Oral replacement therapy indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated	Life-threatening consequences	Death
Definition: A disorder characterized by laboratory test results that indicate a low concentration of phosphates in the blood. **Navigational Note:** -					

Metabolism and nutrition disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Iron overload	-	Moderate symptoms; intervention not indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by accumulation of iron in the tissues. **Navigational Note:** -					
Obesity	-	BMI 25 - 29.9 kg/m2	BMI 30 - 39.9 kg/m2	BMI >=40 kg/m2	-
Definition: A disorder characterized by having a high amount of body fat. **Navigational Note:** Use term Investigations: Weight gain					
Tumor lysis syndrome	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by metabolic abnormalities that result from a spontaneous or therapy-related cytolysis of tumor cells. **Navigational Note:** -					
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; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Musculoskeletal and connective tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Abdominal soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the abdominal wall. **Navigational Note:** -					
Arthralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in a joint. **Navigational Note:** -					
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; limiting self care ADL	-	-
Definition: A disorder characterized by inflammation involving a joint. **Navigational Note:** -					
Avascular necrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by necrotic changes in the bone tissue due to interruption of blood supply. Most often affecting the epiphysis of the long bones, the necrotic changes result in the collapse and the destruction of the bone structure. **Navigational Note:** Use new term: Musculoskeletal and connective tissue disorders: Osteonecrosis					
Back pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the back region. **Navigational Note:** -					
Bone pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the bones. **Navigational Note:** -					
Buttock pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the buttocks. **Navigational Note:** -					

Musculoskeletal and connective tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Chest wall necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the chest wall including breast. **Navigational Note:** -					
Chest wall pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the chest wall. **Navigational Note:** -					
Exostosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	-	-
Definition: A disorder characterized by non-neoplastic overgrowth of bone. **Navigational Note:** -					
Fibrosis deep connective tissue	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death
Definition: A disorder characterized by fibrotic degeneration of the deep connective tissues. **Navigational Note:** -					
Flank pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort on the lateral side of the body in the region below the ribs and above the hip. **Navigational Note:** -					
Generalized muscle weakness	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by a reduction in the strength of muscles in multiple anatomic sites. **Navigational Note:** -					

Musculoskeletal and connective tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Growth suppression	Reduction in growth velocity by 10 - 29% ideally measured over the period of a year	Reduction in growth velocity by 30 - 49% ideally measured over the period of a year or 0 - 49% reduction in growth from the baseline growth curve	Reduction in growth velocity of >=50% ideally measured over the period of a year	-	-
Definition: A disorder characterized by stature that is smaller than normal as expected for age. **Navigational Note:** -					
Head soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the head. **Navigational Note:** -					
Joint effusion	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; limiting instrumental ADL	Severe symptoms; limiting self care ADL; invasive intervention indicated	-	-
Definition: A disorder characterized by excessive fluid in a joint, usually as a result of joint inflammation. **Navigational Note:** -					
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	-	-
Definition: A disorder characterized by a decrease in joint flexibility of any joint. **Navigational Note:** -					
Joint range of motion decreased cervical spine	Mild restriction of rotation or flexion between 60 - 70 degrees	Rotation <60 degrees to right or left; <60 degrees of flexion	Ankylosed/fused over multiple segments with no C-spine rotation	-	-
Definition: A disorder characterized by a decrease in flexibility of a cervical spine joint. **Navigational Note:** -					
Joint range of motion decreased lumbar spine	Stiffness; difficulty bending to the floor to pick up a very light object but able to do athletic activity	Pain with range of motion (ROM) in lumbar spine; requires a reaching aid to pick up a very light object from the floor	<50% lumbar spine flexion; associated with symptoms of ankylosis or fused over multiple segments with no L-spine flexion (e.g., unable to reach to floor to pick up a very light object)	-	-
Definition: A disorder characterized by a decrease in flexibility of a lumbar spine joint. **Navigational Note:** -					

Musculoskeletal and connective tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Kyphosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate accentuation; limiting instrumental ADL	Severe accentuation; operative intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by an abnormal increase in the curvature of the thoracic portion of the spine. **Navigational Note:** -					
Lordosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate accentuation; limiting instrumental ADL	Severe accentuation; operative intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by an abnormal increase in the curvature of the lumbar portion of the spine. **Navigational Note:** -					
Muscle cramp	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked cramping sensation originating from a muscle or group of muscles. **Navigational Note:** Synonym: Muscle spasm					
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	-	-
Definition: A disorder characterized by a reduction in the strength of the lower limb muscles. **Navigational Note:** -					
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	-	-
Definition: A disorder characterized by a reduction in the strength of the trunk muscles. **Navigational Note:** -					
Muscle weakness upper limb	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by a reduction in the strength of the upper limb muscles. **Navigational Note:** -					
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; limiting self care ADL	-	-
Definition: A disorder characterized by a malformation of the musculoskeletal system. **Navigational Note:** -					

Musculoskeletal and connective tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Myalgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by marked discomfort sensation originating from a muscle or group of muscles. **Navigational Note:** -					
Myositis	Mild pain	Moderate pain associated with weakness; pain limiting instrumental ADL	Pain associated with severe weakness; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by inflammation involving the skeletal muscles. **Navigational Note:** -					
Neck pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the neck area. **Navigational Note:** -					
Neck soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the neck. **Navigational Note:** -					
Osteonecrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., analgesics or bisphosphonates); limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by necrotic changes in the bone tissue due to interruption of blood supply. Most often affecting the epiphysis of the long bones, the necrotic changes result in the collapse and the destruction of the bone structure. **Navigational Note:** -					
Osteonecrosis of jaw	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., topical agents); limiting instrumental ADL	Severe symptoms; limiting self care ADL; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the bone of the mandible. **Navigational Note:** -					

Musculoskeletal and connective tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Osteoporosis	**Adult:** Radiologic evidence of osteoporosis or Bone Mineral Density (BMD) t-score -1 to -2.5 (osteopenia); **Pediatric:** Radiologic evidence of low BMD with z score of <= -2.0 and no history of significant fractures	**Adult:** BMD t-score < -2.5; loss of height <2 cm; therapy to improve BMD indicated; limiting instrumental ADL; **Pediatric:** Low BMD (z-score <= -2.0) and significant fracture history (defined as a long bone fracture of the lower extremity, vertebral compression, 2 or more long bone fractures of the upper extremities); therapy to improve BMD indicated	**Adult:** Loss of height >=2 cm; hospitalization indicated; limiting self care ADL; **Pediatric:** Limiting self care ADL	-	-
Definition: A disorder characterized by reduced bone mass, with a decrease in cortical thickness and in the number and size of the trabeculae of cancellous bone (but normal chemical composition), resulting in increased fracture incidence. **Navigational Note:** -					
Pain in extremity	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the upper or lower extremities. **Navigational Note:** -					
Pelvic soft tissue necrosis	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the pelvis. **Navigational Note:** -					
Rhabdomyolysis	Asymptomatic, intervention not indicated; laboratory findings only	Non-urgent intervention indicated	Symptomatic, urgent intervention indicated	Life-threatening consequences; dialysis	Death
Definition: A disorder characterized by the breakdown of muscle tissue resulting in the release of muscle fiber contents into the bloodstream. **Navigational Note:** -					

Musculoskeletal and connective tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Rotator cuff injury	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	-	-
Definition: A disorder characterized by an injury of the rotator cuff. **Navigational Note:** -					
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	-	-
Definition: A disorder characterized by a malformed, lateral curvature of the spine. **Navigational Note:** -					
Soft tissue necrosis lower limb	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the lower extremity. **Navigational Note:** -					
Soft tissue necrosis upper limb	-	Local wound care; medical intervention indicated (e.g., dressings or topical medications)	Operative debridement or other invasive intervention indicated (e.g., tissue reconstruction, flap, or grafting)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues of the upper extremity. **Navigational Note:** -					
Superficial soft tissue fibrosis	Mild induration, able to move skin parallel to plane (sliding) and perpendicular to skin (pinching up)	Moderate induration, able to slide skin, unable to pinch skin; limiting instrumental ADL	Severe induration; unable to slide or pinch skin; limiting joint or orifice movement (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death
Definition: A disorder characterized by fibrotic degeneration of the superficial soft tissues. **Navigational Note:** -					

Musculoskeletal and connective tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Trismus	Decreased ROM (range of motion) without impaired eating	Decreased ROM requiring small bites, soft foods or purees	Decreased ROM with inability to adequately aliment or hydrate orally	-	-
Definition: A disorder characterized by lack of ability to open the mouth fully due to a decrease in the range of motion of the muscles of mastication. **Navigational Note:** -					
Unequal limb length	Mild length discrepancy <2 cm	Moderate length discrepancy 2 - 5 cm; shoe lift indicated; limiting instrumental ADL	Severe length discrepancy >5 cm; limiting self care ADL; operative intervention indicated	-	-
Definition: A disorder characterized by a discrepancy between the lengths of the lower or upper extremities. **Navigational Note:** -					
Musculoskeletal and connective tissue disorder - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

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

Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Abducens nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the abducens nerve (sixth cranial nerve). **Navigational Note:** -					
Accessory nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the accessory nerve (eleventh cranial nerve). **Navigational Note:** -					
Acoustic nerve disorder NOS	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the acoustic nerve (eighth cranial nerve). **Navigational Note:** -					
Akathisia	Mild restlessness or increased motor activity	Moderate restlessness or increased motor activity; limiting instrumental ADL	Severe restlessness or increased motor activity; limiting self care ADL	-	-
Definition: A disorder characterized by an uncomfortable feeling of inner restlessness and inability to stay still; this is a side effect of some psychotropic drugs. **Navigational Note:** -					
Amnesia	Mild; transient memory loss	Moderate; short term memory loss; limiting instrumental ADL	Severe; long term memory loss; limiting self care ADL	-	-
Definition: A disorder characterized by systematic and extensive loss of memory. **Navigational Note:** -					
Anosmia	Present	-	-	-	-
Definition: A disorder characterized by a change in the sense of smell. **Navigational Note:** Also consider Olfactory nerve disorder					
Aphonia	-	-	Voicelessness; unable to speak	-	-
Definition: A disorder characterized by the inability to speak. It may result from injuries to the vocal cords or may be functional (psychogenic). **Navigational Note:** -					
Arachnoiditis	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation of the arachnoid membrane and adjacent subarachnoid space. **Navigational Note:** -					

Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Ataxia	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; mechanical assistance indicated	-	-
Definition: A disorder characterized by lack of coordination of muscle movements resulting in the impairment or inability to perform voluntary activities. **Navigational Note:** -					
Brachial plexopathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by regional paresthesia of the brachial plexus, marked discomfort and muscle weakness, and limited movement in the arm or hand. **Navigational Note:** -					
Central nervous system necrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; corticosteroids indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the brain and/or spinal cord. **Navigational Note:** -					
Cerebrospinal fluid leakage	Post-craniotomy: asymptomatic; Post-lumbar puncture: transient headache; postural care indicated	Post-craniotomy: moderate symptoms; medical intervention indicated; Post-lumbar puncture: persistent moderate symptoms; blood patch indicated	Severe symptoms; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by loss of cerebrospinal fluid into the surrounding tissues. **Navigational Note:** -					
Cognitive disturbance	Mild cognitive disability; not interfering with work/school/life performance; specialized educational services/devices not indicated	Moderate cognitive disability; interfering with work/school/life performance but capable of independent living; specialized resources on part time basis indicated	Severe cognitive disability; significant impairment of work/school/life performance	-	-
Definition: A disorder characterized by a conspicuous change in cognitive function. **Navigational Note:** -					
Concentration impairment	Mild inattention or decreased level of concentration	Moderate impairment in attention or decreased level of concentration; limiting instrumental ADL	Severe impairment in attention or decreased level of concentration; limiting self care ADL	-	-
Definition: A disorder characterized by a deterioration in the ability to concentrate. **Navigational Note:** -					

Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Depressed level of consciousness	Decreased level of alertness	Sedation; slow response to stimuli; limiting instrumental ADL	Difficult to arouse	Life-threatening consequences; coma; urgent intervention indicated	Death
Definition: A disorder characterized by a decrease in ability to perceive and respond. **Navigational Note:** -					
Dizziness	Mild unsteadiness or sensation of movement	Moderate unsteadiness or sensation of movement; limiting instrumental ADL	Severe unsteadiness or sensation of movement; limiting self care ADL	-	-
Definition: A disorder characterized by a disturbing sensation of lightheadedness, unsteadiness, giddiness, spinning or rocking. **Navigational Note:** -					
Dysarthria	Mild slurred speech	Moderate impairment of articulation or slurred speech	Severe impairment of articulation or slurred speech	-	-
Definition: A disorder characterized by slow and slurred speech resulting from an inability to coordinate the muscles used in speech. **Navigational Note:** -					
Dysesthesia	Mild sensory alteration	Moderate sensory alteration; limiting instrumental ADL	Severe sensory alteration; limiting self care ADL	-	-
Definition: A disorder characterized by distortion of sensory perception, resulting in an abnormal and unpleasant sensation. **Navigational Note:** -					
Dysgeusia	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	-	-	-
Definition: A disorder characterized by abnormal sensual experience with the taste of foodstuffs; it can be related to a decrease in the sense of smell. **Navigational Note:** -					
Dysphasia	Awareness of receptive or expressive characteristics; not impairing ability to communicate	Moderate receptive or expressive characteristics; impairing ability to communicate spontaneously	Severe receptive or expressive characteristics; impairing ability to read, write or communicate intelligibly	-	-
Definition: A disorder characterized by impairment of verbal communication skills, often resulting from brain damage. **Navigational Note:** -					
Edema cerebral	-	-	New onset; worsening from baseline	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the brain. **Navigational Note:** -					
Encephalopathy	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a pathologic process involving the brain. **Navigational Note:** -					

Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Extrapyramidal disorder	Mild involuntary movements	Moderate involuntary movements; limiting instrumental ADL	Severe involuntary movements or torticollis; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by abnormal, repetitive, involuntary muscle movements, frenzied speech and extreme restlessness. **Navigational Note:** Synonym: Restless legs					
Facial muscle weakness	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by a reduction in the strength of the facial muscles. **Navigational Note:** -					
Facial nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the facial nerve (seventh cranial nerve). **Navigational Note:** -					
Glossopharyngeal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by dysfunction of the glossopharyngeal nerve (ninth cranial nerve). **Navigational Note:** -					
Guillain-Barre syndrome	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated; intubation	Death
Definition: A disorder characterized by the body's immune system attacking the peripheral nervous system causing ascending paralysis. **Navigational Note:** -					
Headache	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in various parts of the head, not confined to the area of distribution of any nerve. **Navigational Note:** -					
Hydrocephalus	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; intervention not indicated	Severe symptoms or neurological deficit; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal increase of cerebrospinal fluid in the ventricles of the brain. **Navigational Note:** -					
Hypersomnia	Mild increased need for sleep	Moderate increased need for sleep	Severe increased need for sleep	-	-
Definition: A disorder characterized by characterized by excessive sleepiness during the daytime. **Navigational Note:** -					

Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hypoglossal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the hypoglossal nerve (twelfth cranial nerve). **Navigational Note:** -					
Intracranial hemorrhage	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; intervention indicated	Ventriculostomy, ICP monitoring, intraventricular thrombolysis, or invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the cranium. **Navigational Note:** -					
Ischemia cerebrovascular	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	-	-	-
Definition: A disorder characterized by a decrease or absence of blood supply to the brain caused by obstruction (thrombosis or embolism) of an artery resulting in neurological damage. **Navigational Note:** Prior to using this term consider Nervous system disorder: TIA or Stroke					
Lethargy	Mild symptoms; reduced alertness and awareness	Moderate symptoms; limiting instrumental ADL	-	-	-
Definition: A disorder characterized by a decrease in consciousness characterized by mental and physical inertness. **Navigational Note:** -					
Leukoencephalopathy	Asymptomatic; small focal T2/FLAIR hyperintensities; involving periventricular white matter or <1/3 of susceptible areas of cerebrum +/- mild increase in subarachnoid space (SAS) and/or mild ventriculomegaly	Moderate symptoms; focal T2/FLAIR hyperintensities, involving periventricular white matter extending into centrum semiovale or involving 1/3 to 2/3 of susceptible areas of cerebrum +/- moderate increase in SAS and/or moderate ventriculomegaly	Severe symptoms; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving 2/3 or more of susceptible areas of cerebrum +/- moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Life-threatening consequences; extensive T2/FLAIR hyperintensities, involving periventricular white matter involving most of susceptible areas of cerebrum +/- moderate to severe increase in SAS and/or moderate to severe ventriculomegaly	Death
Definition: A disorder characterized by diffuse reactive astrocytosis with multiple areas of necrotic foci without inflammation. **Navigational Note:** -					
Memory impairment	Mild memory impairment	Moderate memory impairment; limiting instrumental ADL	Severe memory impairment; limiting self care ADL	-	-
Definition: A disorder characterized by a deterioration in memory function. **Navigational Note:** -					

Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Meningismus	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by neck stiffness, headache, and photophobia resulting from irritation of the cerebral meninges. **Navigational Note:** -					
Movements involuntary	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by uncontrolled and purposeless movements. **Navigational Note:** -					
Muscle weakness left-sided	Symptomatic; perceived by patient but not evident on physical exam	Symptomatic; evident on physical exam; limiting instrumental ADL	Limiting self care ADL	-	-
Definition: A disorder characterized by a reduction in the strength of the muscles on the left side of the body. **Navigational Note:** -					
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	-	-
Definition: A disorder characterized by a reduction in the strength of the muscles on the right side of the body. **Navigational Note:** -					
Myasthenia gravis	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; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by weakness and rapid fatigue of any of the skeletal muscles. **Navigational Note:** -					
Neuralgia	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by intense painful sensation along a nerve or group of nerves. **Navigational Note:** -					
Nystagmus	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by involuntary movements of the eyeballs. **Navigational Note:** -					
Oculomotor nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the oculomotor nerve (third cranial nerve). **Navigational Note:** -					

Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Olfactory nerve disorder	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the olfactory nerve (first cranial nerve). **Navigational Note:** -					
Paresthesia	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and/or warmth. **Navigational Note:** -					
Peripheral motor neuropathy	Asymptomatic; clinical or diagnostic observations only	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by damage or dysfunction of the peripheral motor nerves. **Navigational Note:** Also consider Nervous system disroders: Peripheral sensory neuropathy					
Peripheral sensory neuropathy	Asymptomatic	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by damage or dysfunction of the peripheral sensory nerves. **Navigational Note:** -					
Phantom pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort related to a limb or an organ that is removed from or is not physically part of the body. **Navigational Note:** -					
Presyncope	-	Present (e.g., near fainting)	-	-	-
Definition: A disorder characterized by an episode of lightheadedness and dizziness which may precede an episode of syncope. **Navigational Note:** -					
Pyramidal tract syndrome	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by dysfunction of the corticospinal (pyramidal) tracts of the spinal cord. Symptoms include an increase in the muscle tone in the lower extremities, hyperreflexia, positive Babinski and a decrease in fine motor coordination. **Navigational Note:** -					
Radiculitis	Mild symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation involving a nerve root. Patients experience marked discomfort radiating along a nerve path because of spinal pressure on the connecting nerve root. **Navigational Note:** -					

Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Recurrent laryngeal nerve palsy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms	Severe symptoms; medical intervention indicated (e.g., thyroplasty, vocal cord injection)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by paralysis of the recurrent laryngeal nerve. **Navigational Note:** -					
Reversible posterior leukoencephalopathy syndrome	-	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization	Life-threatening consequences	Death
Definition: A disorder characterized by headaches, mental status changes, visual disturbances, and/or seizures associated with imaging findings of posterior leukoencephalopathy. It has been observed in association with hypertensive encephalopathy, eclampsia, and immunosuppressive and cytotoxic drug treatment. It is an acute or subacute reversible condition. Also known as posterior reversible encephalopathy syndrome (PRES). **Navigational Note:** -					
Seizure	Brief partial seizure and no loss of consciousness	Brief generalized seizure	New onset seizures (partial or generalized); multiple seizures despite medical intervention	Life-threatening consequences; prolonged repetitive seizures	Death
Definition: A disorder characterized by a sudden, involuntary skeletal muscular contractions of cerebral or brain stem origin. **Navigational Note:** -					
Somnolence	Mild but more than usual drowsiness or sleepiness	Moderate sedation; limiting instrumental ADL	Obtundation or stupor	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by characterized by excessive sleepiness and drowsiness. **Navigational Note:** -					
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 consequences; unable to move active or passive range of motion	Death
Definition: A disorder characterized by increased involuntary muscle tone that affects the regions interfering with voluntary movement. It results in gait, movement, and speech disturbances. **Navigational Note:** -					
Spinal cord compression	-	-	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by pressure on the spinal cord. **Navigational Note:** -					

Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Stroke	Incidental radiographic findings only	Mild to moderate neurologic deficit; limiting instrumental ADL	Severe neurologic deficit; limiting self care ADL; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a decrease or absence of blood supply to the brain caused by obstruction (thrombosis or embolism) of an artery resulting in neurological damage. **Navigational Note:** -					
Syncope	-	-	Fainting; orthostatic collapse	-	-
Definition: A disorder characterized by spontaneous loss of consciousness caused by insufficient blood supply to the brain. **Navigational Note:** -					
Tendon reflex decreased	Ankle reflex reduced	Ankle reflex absent; other reflexes reduced	Absence of all reflexes	-	-
Definition: A disorder characterized by less than normal deep tendon reflexes. **Navigational Note:** Also consider Nervous system disorders: Peripheral motor neuropathy or Peripheral sensory neuropathy					
Transient ischemic attacks	Mild neurologic deficit with or without imaging confirmation	Moderate neurologic deficit with or without imaging confirmation	-	-	-
Definition: A disorder characterized by a brief attack (less than 24 hours) of cerebral dysfunction of vascular origin, with no persistent neurological deficit. **Navigational Note:** If >24 hours, Consider Nervous system disorders: Stroke					
Tremor	Mild symptoms	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by the uncontrolled shaking movement of the whole body or individual parts. **Navigational Note:** -					
Trigeminal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the trigeminal nerve (fifth cranial nerve). **Navigational Note:** -					
Trochlear nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by dysfunction of the trochlear nerve (fourth cranial nerve). **Navigational Note:** -					
Vagus nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by dysfunction of the vagus nerve (tenth cranial nerve). **Navigational Note:** -					

Nervous system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Vasovagal reaction	-	-	Present	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a sudden drop of the blood pressure, bradycardia, and peripheral vasodilation that may lead to loss of consciousness. It results from an increase in the stimulation of the vagus nerve. **Navigational Note:** -					
Nervous system disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Pregnancy, puerperium and perinatal conditions					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Fetal growth retardation	-	<10% percentile of weight for gestational age	<5% percentile of weight for gestational age	<1% percentile of weight for gestational age	-
Definition: A disorder characterized by inhibition of fetal growth resulting in the inability of the fetus to achieve its potential weight. **Navigational Note:** -					
Pregnancy loss	-	-	-	Fetal loss at any gestational age	-
Definition: Death in utero. **Navigational Note:** -					
Premature delivery	Delivery of a liveborn infant at >34 to 37 weeks gestation	Delivery of a liveborn infant at >28 to 34 weeks gestation	Delivery of a liveborn infant at 24 to 28 weeks gestation	Delivery of a liveborn infant at 24 weeks of gestation or less	-
Definition: A disorder characterized by delivery of a viable infant before the normal end of gestation. Typically, viability is achievable between the twentieth and thirty-seventh week of gestation. **Navigational Note:** -					
Pregnancy, puerperium and perinatal conditions - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Psychiatric disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Agitation	Mild mood alteration	Moderate mood alteration	Severe agitation; hospitalization not indicated	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by a state of restlessness associated with unpleasant feelings of irritability and tension. **Navigational Note:** -					
Anorgasmia	Inability to achieve orgasm not adversely affecting relationship	Inability to achieve orgasm adversely affecting relationship	-	-	-
Definition: A disorder characterized by an inability to achieve orgasm. **Navigational Note:** -					
Anxiety	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by apprehension of danger and dread accompanied by restlessness, tension, tachycardia, and dyspnea unattached to a clearly identifiable stimulus. **Navigational Note:** -					
Confusion	Mild disorientation	Moderate disorientation; limiting instrumental ADL	Severe disorientation; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by a lack of clear and orderly thought and behavior. **Navigational Note:** -					
Delayed orgasm	Delay in achieving orgasm not adversely affecting relationship	Delay in achieving orgasm adversely affecting relationship	-	-	-
Definition: A disorder characterized by sexual dysfunction characterized by a delay in climax. **Navigational Note:** -					
Delirium	Mild acute confusional state	Moderate and acute confusional state; limiting instrumental ADL	Severe and acute confusional state; limiting self care ADL; urgent intervention indicated; new onset	Life-threatening consequences, threats of harm to self or others; urgent intervention indicated	Death
Definition: A disorder characterized by the acute and sudden development of confusion, illusions, movement changes, inattentiveness, agitation, and hallucinations. Usually, it is a reversible condition. **Navigational Note:** -					
Delusions	-	Moderate delusional symptoms	Severe delusional symptoms; hospitalization not indicated; new onset	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by false personal beliefs held contrary to reality, despite contradictory evidence and common sense. **Navigational Note:** -					

Psychiatric disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Depression	Mild depressive symptoms	Moderate depressive symptoms; limiting instrumental ADL	Severe depressive symptoms; limiting self care ADL; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by melancholic feelings of grief or unhappiness. **Navigational Note:** -					
Euphoria	Mild mood elevation	Moderate mood elevation	Severe mood elevation (e.g., hypomania)	-	-
Definition: A disorder characterized by an exaggerated feeling of well-being which is disproportionate to events and stimuli. **Navigational Note:** -					
Hallucinations	Mild hallucinations (e.g., perceptual distortions)	Moderate hallucinations	Severe hallucinations; hospitalization not indicated	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by a false sensory perception in the absence of an external stimulus. **Navigational Note:** -					
Insomnia	Mild difficulty falling asleep, staying asleep or waking up early	Moderate difficulty falling asleep, staying asleep or waking up early	Severe difficulty in falling asleep, staying asleep or waking up early	-	-
Definition: A disorder characterized by difficulty in falling asleep and/or remaining asleep. **Navigational Note:** -					
Irritability	Mild; easily consolable	Moderate; limiting instrumental ADL; increased attention indicated	Severe abnormal or excessive response; limiting self care ADL; inconsolable; medical or psychiatric intervention indicated	-	-
Definition: A disorder characterized by an abnormal responsiveness to stimuli or physiological arousal; may be in response to pain, fright, a drug, an emotional situation or a medical condition. **Navigational Note:** -					
Libido decreased	Decrease in sexual interest not adversely affecting relationship	Decrease in sexual interest adversely affecting relationship	-	-	-
Definition: A disorder characterized by a decrease in sexual desire. **Navigational Note:** -					
Libido increased	Present	-	-	-	-
Definition: A disorder characterized by an increase in sexual desire. **Navigational Note:** -					

Psychiatric disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
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; new onset	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by excitement of psychotic proportions manifested by mental and physical hyperactivity, disorganization of behavior and elevation of mood. **Navigational Note:** -					
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	-
Definition: A disorder characterized by a conspicuous change in a person's behavior and thinking. **Navigational Note:** -					
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; new onset	Life-threatening consequences, threats of harm to self or others; hospitalization indicated	Death
Definition: A disorder characterized by personality change, impaired functioning, and loss of touch with reality. It may be a manifestation of schizophrenia, bipolar disorder or brain tumor. **Navigational Note:** -					
Restlessness	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by an inability to rest, relax or be still. **Navigational Note:** -					
Suicidal ideation	Increased thoughts of death but no wish to kill oneself	Suicidal ideation with no specific plan or intent	Specific plan to commit suicide without serious intent to die which may not require hospitalization	Specific plan to commit suicide with serious intent to die which requires hospitalization	-
Definition: A disorder characterized by thoughts of taking one's own life. **Navigational Note:** -					
Suicide attempt	-	-	Suicide attempt or gesture without intent to die	Suicide attempt with intent to die which requires hospitalization	Death
Definition: A disorder characterized by self-inflicted harm in an attempt to end one's own life. **Navigational Note:** -					

Psychiatric disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
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; limiting self care ADL	Life-threatening consequences; hospitalization or urgent intervention indicated	Death
Definition: -					
Navigational Note: -					

Renal and urinary disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Acute kidney injury	-	-	Hospitalization indicated	Life-threatening consequences; dialysis indicated	Death
Definition: A disorder characterized by the acute loss of renal function (within 2 weeks) and is traditionally classified as pre-renal (low blood flow into kidney), renal (kidney damage) and post-renal causes (ureteral or bladder outflow obstruction). **Navigational Note:** Also consider Investigations: Creatinine increased					
Bladder perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Definition: A disorder characterized by a rupture in the bladder wall. **Navigational Note:** -					
Bladder spasm	Intervention not indicated	Antispasmodics indicated	Hospitalization indicated	-	-
Definition: A disorder characterized by a sudden and involuntary contraction of the bladder wall. **Navigational Note:** -					
Chronic kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN - 60 ml/min/1.73 m2 or proteinuria 2+ present; urine protein/creatinine >0.5	eGFR or CrCl 59 - 30 ml/min/1.73 m2	eGFR or CrCl 29 - 15 ml/min/1.73 m2	eGFR or CrCl <15 ml/min/1.73 m2; dialysis or renal transplant indicated	Death
Definition: A disorder characterized by gradual and usually permanent loss of kidney function resulting in renal failure. **Navigational Note:** -					
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 invasive intervention indicated	Life-threatening consequences; urgent invasive intervention indicated	Death
Definition: A disorder characterized by inflammation of the bladder which is not caused by an infection of the urinary tract. **Navigational Note:** -					
Dysuria	Present	-	-	-	-
Definition: A disorder characterized by painful urination. **Navigational Note:** If associated with an infection, report the infection. For grades higher than Grade 1, consider Renal and urinary disorders: Bladder spasm or Cystitis noninfective; Infections and infestations: Urinary tract infection.					
Glucosuria	Present	-	-	-	-
Definition: A disorder characterized by laboratory test results that indicate glucose in the urine. **Navigational Note:** -					

Renal and urinary disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
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 invasive intervention indicated; limiting self care ADL	Life-threatening consequences; urgent invasive intervention indicated	Death
Definition: A disorder characterized by laboratory test results that indicate blood in the urine. **Navigational Note:** -					
Hemoglobinuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by laboratory test results that indicate the presence of free hemoglobin in the urine. **Navigational Note:** Report underlying AE if > Grade 1					
Nephrotic syndrome	-	-	Not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by symptoms that include severe edema, proteinuria, and hypoalbuminemia; it is indicative of renal dysfunction. **Navigational Note:** -					
Proteinuria	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs	**Adult:** 2+ and 3+ proteinuria; urinary protein 1.0 - <3.5 g/24 hrs; **Pediatric:** Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	**Adult:** Urinary protein >=3.5 g/24 hrs; 4+ proteinuria; **Pediatric:** Urine P/C (Protein/Creatinine) ratio >1.9	-	-
Definition: A disorder characterized by laboratory test results that indicate the presence of excessive protein in the urine. It is predominantly albumin, but also globulin. **Navigational Note:** 24-hour urine collection takes precedence over dipstick					
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 invasive intervention indicated	Life-threatening consequences; urgent invasive intervention indicated	Death
Definition: A disorder characterized by the formation of crystals/kidney stones in the pelvis of the kidney. **Navigational Note:** -					

Renal and urinary disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Renal colic	Mild pain not interfering with activity; nonprescription medication indicated	Moderate pain; limiting instrumental ADL; prescription medication indicated	Hospitalization indicated; limiting self care ADL	-	-
Definition: A disorder characterized by paroxysmal and severe flank marked discomfort radiating to the inguinal area. Often, the cause is the passage of crystals/kidney stones. **Navigational Note:** -					
Renal hemorrhage	Mild symptoms; intervention not indicated	Analgesics and hematocrit monitoring indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the kidney. **Navigational Note:** -					
Urinary fistula	-	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent invasive intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between any part of the urinary system and another organ or anatomic site. **Navigational Note:** -					
Urinary frequency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Definition: A disorder characterized by urination at short intervals. **Navigational Note:** -					
Urinary incontinence	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated	Spontaneous; pads indicated; limiting instrumental ADL	Intervention indicated (e.g., clamp, collagen injections); operative intervention indicated; limiting self care ADL	-	-
Definition: A disorder characterized by inability to control the flow of urine from the bladder. **Navigational Note:** -					
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 invasive intervention indicated; substantial loss of affected kidney function or mass	Life-threatening consequences; organ failure; urgent operative intervention indicated	Death
Definition: A disorder characterized by accumulation of urine within the bladder because of the inability to urinate. **Navigational Note:** -					

Renal and urinary disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Urinary tract obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic but no hydronephrosis, sepsis, or renal dysfunction; urethral dilation, urinary or suprapubic catheter indicated	Altered organ function (e.g., hydronephrosis or renal dysfunction); invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by blockage of the normal flow of contents of the urinary tract. **Navigational Note:** -					
Urinary tract pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the urinary tract. **Navigational Note:** -					
Urinary urgency	Present	Limiting instrumental ADL; medical management indicated	-	-	-
Definition: A disorder characterized by a sudden compelling urge to urinate. **Navigational Note:** -					
Urine discoloration	Present	-	-	-	-
Definition: A disorder characterized by a change in the color of the urine. **Navigational Note:** -					
Renal and urinary 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; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Reproductive system and breast disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Amenorrhea	-	Present	-	-	-
Definition: A disorder characterized by the abnormal absence of menses for at least three consecutive menstrual cycles. **Navigational Note:** -					
Azoospermia	-	Absence of sperm in ejaculate	-	-	-
Definition: A disorder characterized by laboratory test results that indicate complete absence of spermatozoa in the semen. **Navigational Note:** -					
Breast atrophy	Minimal asymmetry; minimal atrophy	Moderate asymmetry; moderate atrophy	Asymmetry >1/3 of breast volume; severe atrophy	-	-
Definition: A disorder characterized by underdevelopment of the breast. **Navigational Note:** -					
Breast pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the breast region. **Navigational Note:** -					
Dysmenorrhea	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by abnormally painful abdominal cramps during menses. **Navigational Note:** -					
Dyspareunia	Mild discomfort or pain associated with vaginal penetration; discomfort relieved with use of vaginal lubricants or estrogen	Moderate discomfort or pain associated with vaginal penetration; discomfort or pain partially relieved with use of vaginal lubricants or estrogen	Severe discomfort or pain associated with vaginal penetration; discomfort or pain unrelieved by vaginal lubricants or estrogen	-	-
Definition: A disorder characterized by painful or difficult coitus. **Navigational Note:** -					
Ejaculation disorder	Diminished ejaculation	Anejaculation or retrograde ejaculation	-	-	-
Definition: A disorder characterized by problems related to ejaculation. This category includes premature, delayed, retrograde and painful ejaculation. **Navigational Note:** -					

Reproductive system and breast disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Erectile dysfunction	Decrease in erectile function (frequency or rigidity of erections) but intervention not indicated (e.g., medication or use of mechanical device, penile pump)	Decrease in erectile function (frequency/rigidity of erections), erectile intervention indicated, (e.g., medication or mechanical devices such as penile pump)	Decrease in erectile function (frequency/rigidity of erections) but erectile intervention not helpful (e.g., medication or mechanical devices such as penile pump); placement of a permanent penile prosthesis indicated (not previously present)	-	-
Definition: A disorder characterized by the persistent or recurrent inability to achieve or to maintain an erection during sexual activity. **Navigational Note:** -					
Fallopian tube obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; elective intervention indicated	Severe symptoms; invasive intervention indicated	-	-
Definition: A disorder characterized by blockage of the normal flow of the contents in the fallopian tube. **Navigational Note:** -					
Feminization acquired	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by the development of secondary female sex characteristics in males due to extrinsic factors. **Navigational Note:** -					
Genital edema	Mild swelling or obscuration of anatomic architecture on close inspection	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour	Lymphorrhea; gross deviation from normal anatomic contour; limiting self care ADL	-	-
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the genitals. **Navigational Note:** -					
Gynecomastia	Asymptomatic	Symptomatic (e.g., pain or psychosocial impact)	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by excessive development of the breasts in males. **Navigational Note:** -					
Hematosalpinx	Minimal bleeding identified on imaging study or laparoscopy; intervention not indicated	Moderate bleeding; medical intervention indicated	Transfusion indicated; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by the presence of blood in a fallopian tube. **Navigational Note:** -					

Reproductive system and breast disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Irregular menstruation	Intermittent/irregular menses for no more than 3 consecutive menstrual cycles	Intermittent/irregular menses for more than 3 consecutive menstrual cycles	-	-	-
Definition: A disorder characterized by a change in cycle or duration of menses from baseline. **Navigational Note:** Also consider Reproductive system and breast disorders: Premature menopause, Amenorrhea.					
Lactation disorder	Mild changes in lactation, not significantly affecting production or expression of breast milk	Changes in lactation, significantly affecting breast production or expression of breast milk	-	-	-
Definition: A disorder characterized by disturbances of milk secretion. It is not necessarily related to pregnancy that is observed in females and can be observed in males. **Navigational Note:** -					
Menorrhagia	Mild; iron supplements indicated	Moderate symptoms; medical intervention indicated (e.g., hormones)	Severe; transfusion indicated; operative intervention indicated (e.g., hysterectomy)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by abnormally heavy vaginal bleeding during menses. **Navigational Note:** -					
Nipple deformity	Asymptomatic; asymmetry with slight retraction and/or thickening of the nipple areolar complex	Symptomatic; asymmetry of nipple areolar complex with moderate retraction and/or thickening of the nipple areolar complex	-	-	-
Definition: A disorder characterized by a malformation of the nipple. **Navigational Note:** -					
Oligospermia	Sperm concentration > 0 to < 15 million/ml	-	-	-	-
Definition: A disorder characterized by a decrease in the number of spermatozoa in the semen. **Navigational Note:** -					
Ovarian hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the ovary. **Navigational Note:** -					
Ovarian rupture	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Transfusion; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by tearing or disruption of the ovarian tissue. **Navigational Note:** -					

Reproductive system and breast disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Ovulation pain	-	Present	-	-	-
Definition: A disorder characterized by a sensation of marked discomfort in one side of the abdomen between menstrual cycles, around the time of the discharge of the ovum from the ovarian follicle. **Navigational Note:** -					
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	-	-
Definition: A disorder characterized by a reduction in the strength of the muscles of the pelvic floor. **Navigational Note:** -					
Pelvic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the pelvis. **Navigational Note:** -					
Penile pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the penis. **Navigational Note:** -					
Perineal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the area between the genital organs and the anus. **Navigational Note:** -					
Premature menopause	-	Present	-	-	-
Definition: A disorder characterized by premature ovarian failure. Symptoms may include hot flashes, night sweats, mood swings, and a decrease in sex drive. Laboratory findings include elevated luteinizing hormone (LH) and follicle-stimulating hormone (FSH.) **Navigational Note:** -					
Prostatic hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the prostate gland. **Navigational Note:** -					
Prostatic obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; elective intervention indicated	Severe symptoms; invasive intervention indicated	-	-
Definition: A disorder characterized by compression of the urethra secondary to enlargement of the prostate gland. This results in voiding difficulties (straining to void, slow urine stream, and incomplete emptying of the bladder). **Navigational Note:** -					

Reproductive system and breast disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Prostatic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the prostate gland. **Navigational Note:** -					
Scrotal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the scrotal area. **Navigational Note:** -					
Spermatic cord hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the spermatic cord. **Navigational Note:** -					
Spermatic cord obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; elective intervention indicated	Severe symptoms; invasive intervention indicated	-	-
Definition: A disorder characterized by blockage of the normal flow of the contents of the spermatic cord. **Navigational Note:** -					
Testicular disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic but not interfering with sexual function; intervention not indicated; limiting instrumental ADL	Severe symptoms; interfering with sexual function; limiting self care ADL; intervention indicated	Life-threatening consequences; urgent intervention indicated	-
Definition: A disorder characterized by abnormal function or appearance of the testis. **Navigational Note:** Also consider Reproductive system and breast disorders: Genital edema or other AE terms in the Renal and urinary disorders SOC or Reproductive system and breast disorders SOC.					
Testicular hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the testis. **Navigational Note:** -					
Testicular pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the testis. **Navigational Note:** -					
Uterine fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the uterus and another organ or anatomic site. **Navigational Note:** -					

Reproductive system and breast disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Uterine hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the uterus. **Navigational Note:** -					
Uterine obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; elective intervention indicated	Severe symptoms; invasive intervention indicated	-	-
Definition: A disorder characterized by blockage of the uterine outlet. **Navigational Note:** -					
Uterine pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the uterus. **Navigational Note:** -					
Vaginal discharge	Mild vaginal discharge (greater than baseline for patient)	Moderate to heavy vaginal discharge; use of perineal pad or tampon indicated	-	-	-
Definition: A disorder characterized by vaginal secretions. Mucus produced by the cervical glands is discharged from the vagina naturally, especially during the childbearing years. **Navigational Note:** -					
Vaginal dryness	Mild vaginal dryness not interfering with sexual function	Moderate vaginal dryness interfering with sexual function or causing frequent discomfort	Severe vaginal dryness resulting in dyspareunia or severe discomfort	-	-
Definition: A disorder characterized by an uncomfortable feeling of itching and burning in the vagina. **Navigational Note:** -					
Vaginal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the vagina and another organ or anatomic site. **Navigational Note:** -					
Vaginal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the vagina. **Navigational Note:** -					

Reproductive system and breast disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
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	Life-threatening consequences; widespread areas of mucosal ulceration; urgent intervention indicated	-
Definition: A disorder characterized by inflammation involving the vagina. Symptoms may include redness, edema, marked discomfort and an increase in vaginal discharge. **Navigational Note:** -					
Vaginal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; elective intervention indicated	Severe symptoms; invasive intervention indicated	-	-
Definition: A disorder characterized by blockage of vaginal canal. **Navigational Note:** -					
Vaginal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the vagina. **Navigational Note:** -					
Vaginal perforation	-	Invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the vaginal wall. **Navigational Note:** -					
Vaginal stricture	Asymptomatic; mild vaginal shortening or narrowing	Vaginal narrowing and/or shortening not interfering with physical examination	Vaginal narrowing and/or shortening interfering with the use of tampons, sexual activity or physical examination	-	Death
Definition: A disorder characterized by a narrowing of the vaginal canal. **Navigational Note:** -					
Reproductive system and breast disorders - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Adult respiratory distress syndrome	-	-	Present with radiologic findings; intubation not indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by progressive and life-threatening pulmonary distress in the absence of an underlying pulmonary condition, usually following major trauma or surgery. **Navigational Note:** -					
Allergic rhinitis	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by an inflammation of the nasal mucous membranes caused by an IgE-mediated response to external allergens. The inflammation may also involve the mucous membranes of the sinuses, eyes, middle ear, and pharynx. Symptoms include sneezing, nasal congestion, rhinorrhea and itching. **Navigational Note:** -					
Apnea	-	-	Present; medical intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by cessation of breathing. **Navigational Note:** -					
Aspiration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Altered eating habits; coughing or choking episodes after eating or swallowing; medical intervention indicated (e.g., suction or oxygen)	Dyspnea and pneumonia symptoms (e.g., aspiration pneumonia); hospitalization indicated; unable to aliment orally	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by inhalation of solids or liquids into the lungs. **Navigational Note:** -					
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	Supplemental oxygen indicated; hospitalization or elective operative intervention indicated (e.g., stent, laser)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by the collapse of part or the entire lung. **Navigational Note:** -					
Bronchial fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the bronchus and another organ or anatomic site. **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Bronchial obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., mild wheezing); endoscopic evaluation indicated; radiographic evidence of atelectasis/lobar collapse; medical management indicated (e.g., steroids, bronchodilators)	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by blockage of a bronchus passage, most often by bronchial secretions and exudates. **Navigational Note:** -					
Bronchial stricture	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., rhonchi or wheezing) but without respiratory distress; medical intervention indicated (e.g., steroids, bronchodilators)	Shortness of breath with stridor; endoscopic intervention indicated (e.g., laser, stent placement)	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by a narrowing of the bronchial tube. **Navigational Note:** -					
Bronchopleural fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Hospitalization; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between a bronchus and the pleural cavity. **Navigational Note:** -					
Bronchopulmonary hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; invasive intervention not indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the bronchial wall and/or lung parenchyma. **Navigational Note:** -					
Bronchospasm	Mild symptoms; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Limiting self care ADL; supplemental oxygen indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by a sudden contraction of the smooth muscles of the bronchial wall. **Navigational Note:** -					
Chylothorax	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., fat-restricted diet); thoracentesis or tube drainage indicated	Severe symptoms; elective operative intervention indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by milky pleural effusion (abnormal collection of fluid) resulting from accumulation of lymph fluid in the pleural cavity. **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Cough	Mild symptoms; nonprescription intervention indicated	Moderate symptoms, medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by sudden, often repetitive, spasmodic contraction of the thoracic cavity, resulting in violent release of air from the lungs and usually accompanied by a distinctive sound. **Navigational Note:** -					
Dyspnea	Shortness of breath with moderate exertion	Shortness of breath with minimal exertion; limiting instrumental ADL	Shortness of breath at rest; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an uncomfortable sensation of difficulty breathing. **Navigational Note:** -					
Epistaxis	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated (e.g., nasal packing, cauterization; topical vasoconstrictors)	Transfusion; invasive intervention indicated (e.g., hemostasis of bleeding site)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the nose. **Navigational Note:** -					
Hiccups	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe symptoms; interfering with sleep; limiting self care ADL	-	-
Definition: A disorder characterized by repeated gulp sounds that result from an involuntary opening and closing of the glottis. This is attributed to a spasm of the diaphragm. **Navigational Note:** -					
Hoarseness	Mild or intermittent voice change; fully understandable; self-resolves	Moderate or persistent voice changes; may require occasional repetition but understandable on telephone; medical evaluation indicated	Severe voice changes including predominantly whispered speech	-	-
Definition: A disorder characterized by harsh and raspy voice arising from or spreading to the larynx. **Navigational Note:** -					
Hypoxia	-	Decreased oxygen saturation with exercise (e.g., pulse oximeter <88%); intermittent supplemental oxygen	Decreased oxygen saturation at rest (e.g., pulse oximeter <88% or PaO2 <=55 mm Hg)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a decrease in the level of oxygen in the body. **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Laryngeal edema	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated (e.g., dexamethasone, epinephrine, antihistamines)	Stridor; respiratory distress; hospitalization indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the larynx. **Navigational Note:** -					
Laryngeal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the larynx and another organ or anatomic site. **Navigational Note:** -					
Laryngeal hemorrhage	Mild cough or trace hemoptysis; laryngoscopic findings	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by bleeding from the larynx. **Navigational Note:** -					
Laryngeal inflammation	Mild sore throat; raspy voice	Moderate sore throat; analgesics indicated	Severe throat pain; endoscopic intervention indicated	-	-
Definition: A disorder characterized by an inflammation involving the larynx. **Navigational Note:** -					
Laryngeal mucositis	Endoscopic findings only; mild discomfort with normal intake	Moderate pain, analgesics indicated; altered oral intake; limiting instrumental ADL	Severe pain; severely altered eating/swallowing; medical intervention indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by ulceration or inflammation involving the mucous membrane of the larynx. **Navigational Note:** -					
Laryngeal obstruction	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), no respiratory distress; medical intervention indicated (e.g., steroids); limiting instrumental ADL	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by blockage of the laryngeal airway. **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Laryngeal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), no respiratory distress; medical intervention indicated (e.g., steroids); limiting instrumental ADL	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a narrowing of the laryngeal airway. **Navigational Note:** -					
Laryngopharyngeal dysesthesia	Mild symptoms; no anxiety; intervention not indicated	Moderate symptoms; mild anxiety, but no dyspnea; short duration of observation and/or anxiolytic indicated; limiting instrumental ADL	Severe symptoms; dyspnea and swallowing difficulty; limiting self care ADL	Life-threatening consequences	Death
Definition: A disorder characterized by an uncomfortable persistent sensation in the area of the laryngopharynx. **Navigational Note:** -					
Laryngospasm	-	Transient episode; intervention not indicated	Recurrent episodes; noninvasive intervention indicated (e.g., breathing technique, pressure point massage)	Persistent or severe episodes associated with syncope; urgent intervention indicated (e.g., fiberoptic laryngoscopy, intubation, botox injection)	Death
Definition: A disorder characterized by paroxysmal spasmodic muscular contraction of the vocal cords. **Navigational Note:** -					
Mediastinal hemorrhage	Mild symptoms; intervention not indicated; radiologic evidence only	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the mediastinum. **Navigational Note:** -					
Nasal congestion	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	Associated with bloody nasal discharge or epistaxis	-	-
Definition: A disorder characterized by obstruction of the nasal passage due to mucosal edema. **Navigational Note:** -					
Oropharyngeal pain	Mild pain	Moderate pain; altered oral intake; non-narcotics initiated; topical analgesics initiated	Severe pain; severely altered eating/swallowing; narcotics initiated; requires parenteral nutrition	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the oropharynx. **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Pharyngeal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the pharynx and another organ or anatomic site. **Navigational Note:** -					
Pharyngeal hemorrhage	Mild symptoms; intervention not indicated	Moderate symptoms; intervention indicated	Transfusion indicated; invasive intervention indicated; hospitalization	Life-threatening consequences; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the pharynx. **Navigational Note:** -					
Pharyngeal mucositis	Endoscopic findings only; minimal symptoms with normal oral intake; mild pain but analgesics not indicated	Moderate pain, analgesics indicated; altered oral intake; limiting instrumental ADL	Severe pain; unable to adequately aliment or hydrate orally; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by ulceration or inflammation involving the mucous membrane of the pharynx. **Navigational Note:** -					
Pharyngeal necrosis	-	-	Inability to aliment adequately by GI tract; invasive intervention indicated; tube feeding or TPN indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by a necrotic process occurring in the pharynx. **Navigational Note:** -					
Pharyngeal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), no respiratory distress; medical intervention indicated (e.g., steroids); limiting instrumental ADL	Limiting self care ADL; stridor; endoscopic intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a narrowing of the pharyngeal airway. **Navigational Note:** -					
Pharyngolaryngeal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the pharyngolaryngeal region. **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Pleural effusion	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated (e.g., diuretics or therapeutic thoracentesis)	Symptomatic with respiratory distress and hypoxia; operative intervention including chest tube or pleurodesis indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by an increase in amounts of fluid within the pleural cavity. Symptoms include shortness of breath, cough and marked chest discomfort. **Navigational Note:** -					
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; hospitalization	Life-threatening consequences; intubation or urgent intervention indicated	Death
Definition: A disorder characterized by bleeding from the pleural cavity. **Navigational Note:** -					
Pleuritic pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the pleura. **Navigational Note:** -					
Pneumonitis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated; limiting instrumental ADL	Severe symptoms; limiting self care ADL; oxygen indicated	Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma. **Navigational Note:** -					
Pneumothorax	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated	Sclerosis and/or operative intervention indicated; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by abnormal presence of air in the pleural cavity resulting in the collapse of the lung. **Navigational Note:** -					
Postnasal drip	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by excessive mucous secretion in the back of the nasal cavity or throat, causing sore throat and/or coughing. **Navigational Note:** -					
Productive cough	Occasional/minimal production of sputum with cough	Moderate sputum production; limiting instrumental ADL	Persistent or copious production of sputum; limiting self care ADL	-	-
Definition: A disorder characterized by expectorated secretions upon coughing. **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Pulmonary edema	Radiologic findings only; minimal dyspnea on exertion	Moderate dyspnea on exertion; medical intervention indicated; limiting instrumental ADL	Severe dyspnea or dyspnea at rest; oxygen indicated; limiting self care ADL	Life-threatening respiratory compromise; urgent intervention or intubation with ventilatory support indicated	Death
Definition: A disorder characterized by accumulation of fluid in the lung tissues that causes a disturbance of the gas exchange that may lead to respiratory failure. **Navigational Note:** -					
Pulmonary fibrosis	Radiologic pulmonary fibrosis <25% of lung volume associated with hypoxia	Evidence of pulmonary hypertension; radiographic pulmonary fibrosis 25 - 50% associated with hypoxia	Severe hypoxia; evidence of right-sided heart failure; radiographic pulmonary fibrosis >50 - 75%	Life-threatening consequences (e.g., hemodynamic/pulmonary complications); intubation with ventilatory support indicated; radiographic pulmonary fibrosis >75% with severe honeycombing	Death
Definition: A disorder characterized by the replacement of the lung tissue by connective tissue, leading to progressive dyspnea, respiratory failure or right heart failure. **Navigational Note:** -					
Pulmonary fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the lung and another organ or anatomic site. **Navigational Note:** -					
Pulmonary hypertension	Minimal dyspnea; findings on physical exam or other evaluation	Moderate dyspnea, cough; requiring evaluation by cardiac catheterization and medical intervention	Severe symptoms, associated with hypoxia, right heart failure; oxygen indicated	Life-threatening airway consequences; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by an increase in pressure within the pulmonary circulation due to lung or heart disorder. **Navigational Note:** -					
Respiratory failure	-	-	-	Life-threatening consequences; urgent intervention, intubation, or ventilatory support indicated	Death
Definition: A disorder characterized by impaired gas exchange by the respiratory system resulting in hypoxia and a decrease in oxygenation of the tissues that may be associated with an increase in arterial levels of carbon dioxide. **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Retinoic acid syndrome	Fluid retention; <3 kg of weight gain; intervention with fluid restriction and/or diuretics indicated	Moderate signs or symptoms; steroids indicated	Severe symptoms; hospitalization indicated	Life-threatening consequences; ventilatory support indicated	Death
Definition: A disorder characterized by weight gain, dyspnea, pleural and pericardial effusions, leukocytosis and/or renal failure originally described in patients treated with all-trans retinoic acid. **Navigational Note:** -					
Rhinorrhea	Present	-	-	-	-
Definition: A disorder characterized by excessive mucous secretions draining from the nose. **Navigational Note:** -					
Sinus disorder	Asymptomatic mucosal crusting; blood-tinged secretions	Symptomatic stenosis or edema/narrowing interfering with airflow; limiting instrumental ADL	Stenosis with significant nasal obstruction; limiting self care ADL	Necrosis of soft tissue or bone; urgent operative intervention indicated	Death
Definition: A disorder characterized by involvement of the paranasal sinuses. **Navigational Note:** -					
Sinus pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the face, between the eyes, or upper teeth originating from the sinuses. **Navigational Note:** -					
Sleep apnea	Snoring and nocturnal sleep arousal without apneic periods	Moderate apnea and oxygen desaturation; excessive daytime sleepiness; medical evaluation indicated; limiting instrumental ADL	Oxygen desaturation; associated with pulmonary hypertension; medical intervention indicated; limiting self care ADL	Cardiovascular or neuropsychiatric symptoms; urgent operative intervention indicated	Death
Definition: A disorder characterized by cessation of breathing for short periods during sleep. **Navigational Note:** -					
Sneezing	Mild symptoms; intervention not indicated	Moderate symptoms; medical intervention indicated	-	-	-
Definition: A disorder characterized by the involuntary expulsion of air from the nose. **Navigational Note:** -					
Sore throat	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL; limiting ability to swallow	-	-
Definition: A disorder characterized by marked discomfort in the throat. **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Stridor	-	-	Respiratory distress limiting self care ADL; medical intervention indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a high pitched breathing sound due to laryngeal or upper airway obstruction. **Navigational Note:** -					
Tracheal fistula	Asymptomatic	Symptomatic, invasive intervention not indicated	Invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the trachea and another organ or anatomic site. **Navigational Note:** -					
Tracheal mucositis	Endoscopic findings only; minimal hemoptysis, pain, or respiratory symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe pain; hemorrhage or respiratory symptoms; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an inflammation or ulceration involving the mucous membrane of the trachea. **Navigational Note:** -					
Tracheal stenosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic (e.g., noisy airway breathing), no respiratory distress; medical intervention indicated (e.g., steroids); limiting instrumental ADL	Stridor or respiratory distress limiting self care ADL; invasive intervention indicated (e.g., stent, laser)	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by a narrowing of the trachea. **Navigational Note:** -					
Voice alteration	Mild or intermittent change from normal voice	Moderate or persistent change from normal voice; still understandable	Severe voice changes including predominantly whispered speech; may require frequent repetition or face-to-face contact for understandability; may require assistive technology	-	-
Definition: A disorder characterized by a change in the sound and/or speed of the voice. **Navigational Note:** -					
Wheezing	Detectable airway noise with minimal symptoms	Moderate symptoms; medical intervention indicated; limiting instrumental ADL	Severe respiratory symptoms limiting self care ADL; oxygen therapy or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a high-pitched, whistling sound during breathing. It results from the narrowing or obstruction of the respiratory airways. **Navigational Note:** -					

Respiratory, thoracic and mediastinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
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; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Alopecia	Hair loss of <50% of normal for that individual that is not obvious from a distance but only on close inspection; a different hair style may be required to cover the hair loss but it does not require a wig or hair piece to camouflage	Hair loss of >=50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by a decrease in density of hair compared to normal for a given individual at a given age and body location. **Navigational Note:** -					
Body odor	Mild odor; physician intervention not indicated; self care interventions	Pronounced odor; psychosocial impact; patient seeks medical intervention	-	-	-
Definition: A disorder characterized by an abnormal body smell resulting from the growth of bacteria on the body. **Navigational Note:** -					
Bullous dermatitis	Asymptomatic; blisters covering <10% BSA	Blisters covering 10 - 30% BSA; painful blisters; limiting instrumental ADL	Blisters covering >30% BSA; limiting self care ADL	Blisters covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Definition: A disorder characterized by inflammation of the skin characterized by the presence of bullae which are filled with fluid. **Navigational Note:** If infectious, consider Infections and infestations: Rash pustular or other site-specific Infections and infestations term.					
Dry skin	Covering <10% BSA and no associated erythema or pruritus	Covering 10 - 30% BSA and associated with erythema or pruritus; limiting instrumental ADL	Covering >30% BSA and associated with pruritus; limiting self care ADL	-	-
Definition: A disorder characterized by flaky and dull skin; the pores are generally fine, the texture is a papery thin texture. **Navigational Note:** -					
Eczema	Asymptomatic or mild symptoms; additional medical intervention over baseline not indicated	Moderate; topical or oral intervention indicated; additional medical intervention over baseline indicated	Severe or medically significant but not immediately life-threatening; IV intervention indicated	-	-
Definition: A disorder characterized by skin which becomes itchy, red, inflamed, crusty, thick, scaly, and/or forms blisters. **Navigational Note:** -					
Erythema multiforme	Target lesions covering <10% BSA and not associated with skin tenderness	Target lesions covering 10 - 30% BSA and associated with skin tenderness	Target lesions covering >30% BSA and associated with oral or genital erosions	Target lesions covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Definition: A disorder characterized by target lesions (a pink-red ring around a pale center). **Navigational Note:** -					

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Erythroderma	-	Erythema covering >90% BSA without associated symptoms; limiting instrumental ADL	Erythema covering >90% BSA with associated symptoms (e.g., pruritus or tenderness); limiting self care ADL	Erythema covering >90% BSA with associated fluid or electrolyte abnormalities; ICU care or burn unit indicated	Death
Definition: A disorder characterized by generalized inflammatory erythema and exfoliation. The inflammatory process involves > 90% of the body surface area. **Navigational Note:** -					
Fat atrophy	Covering <10% BSA and asymptomatic	Covering 10 - 30% BSA and associated with erythema or tenderness; limiting instrumental ADL	Covering >30% BSA; associated with erythema or tenderness; limiting self-care ADL	-	-
Definition: A disorder characterized by shrinking of adipose tissue. **Navigational Note:** -					
Hair color changes	Present	-	-	-	-
Definition: A disorder characterized by change in hair color or loss of normal pigmentation. **Navigational Note:** -					
Hair texture abnormal	Present	-	-	-	-
Definition: A disorder characterized by a change in the way the hair feels. **Navigational Note:** -					
Hirsutism	In women, increase in length, thickness or density of hair in a male distribution that the patient is able to camouflage by periodic shaving, bleaching, or removal of hair	In women, increase in length, thickness or density of hair in a male distribution that requires daily shaving or consistent destructive means of hair removal to camouflage; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by the presence of excess hair growth in women in anatomic sites where growth is considered to be a secondary male characteristic and under androgen control (beard, moustache, chest, abdomen). **Navigational Note:** -					
Hyperhidrosis	Limited to one site (palms, soles, or axillae); self care interventions	Involving >1 site; patient seeks medical intervention; associated with psychosocial impact	Associated with electrolyte/hemodynamic imbalance	-	-
Definition: A disorder characterized by excessive sweating. **Navigational Note:** Synonym: Night sweats, diaphoresis					
Hyperkeratosis	Present	-	Limiting self-care ADLs	-	-
Definition: A disorder characterized by a thickening of the outer layer of the skin. **Navigational Note:** -					

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hypertrichosis	Increase in length, thickness or density of hair that the patient is either able to camouflage by periodic shaving or removal of hairs or is not concerned enough about the overgrowth to use any form of hair removal	Increase in length, thickness or density of hair at least on the usual exposed areas of the body [face (not limited to beard/moustache area) plus/minus arms] that requires frequent shaving or use of destructive means of hair removal to camouflage; associated with psychosocial impact	-	-	-
Definition: A disorder characterized by hair density or length beyond the accepted limits of normal in a particular body region, for a particular age or race. **Navigational Note:** -					
Hypohidrosis	-	Symptomatic; limiting instrumental ADL	Increase in body temperature; limiting self care ADL	Heat stroke	Death
Definition: A disorder characterized by reduced sweating. **Navigational Note:** -					
Lipohypertrophy	Asymptomatic and covering <10% BSA	Covering 10 - 30% BSA and associated tenderness; limiting instrumental ADL	Covering >30% BSA and associated tenderness and narcotics or NSAIDs indicated; lipohypertrophy; limiting self care ADL	-	-
Definition: A disorder characterized by hypertrophy of the subcutaneous adipose tissue at the site of multiple subcutaneous injections of insulin. **Navigational Note:** -					
Nail changes	Present	-	-	-	-
Definition: A disorder characterized by a change in the nails. **Navigational Note:** -					
Nail discoloration	Asymptomatic; clinical or diagnostic observations only	-	-	-	-
Definition: A disorder characterized by a change in the color of the nail plate. **Navigational Note:** -					
Nail loss	Asymptomatic separation of the nail bed from the nail plate or nail loss	Symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental ADL	-	-	-
Definition: A disorder characterized by loss of all or a portion of the nail. **Navigational Note:** -					

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Nail ridging	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	-	-	-	-
Definition: A disorder characterized by vertical or horizontal ridges on the nails. **Navigational Note:** -					
Pain of skin	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the skin. **Navigational Note:** -					
Palmar-plantar erythrodysesthesia syndrome	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Severe skin changes (e.g., peeling, blisters, bleeding, fissures, edema, or hyperkeratosis) with pain; limiting self care ADL	-	-
Definition: A disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet. Also known as Hand-Foot Syndrome. **Navigational Note:** -					
Photosensitivity	Painless erythema and erythema covering <10% BSA	Tender erythema covering 10 - 30% BSA	Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an increase in sensitivity of the skin to light. **Navigational Note:** -					
Pruritus	Mild or localized; topical intervention indicated	Widespread and intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Widespread and constant; limiting self care ADL or sleep; systemic corticosteroid or immunosuppressive therapy indicated	-	-
Definition: A disorder characterized by an intense itching sensation. **Navigational Note:** -					

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Purpura	Combined area of lesions covering <10% BSA	Combined area of lesions covering 10 - 30% BSA; bleeding with trauma	Combined area of lesions covering >30% BSA; spontaneous bleeding	-	-
Definition: A disorder characterized by hemorrhagic areas of the skin and mucous membrane. Newer lesions appear reddish in color. Older lesions are usually a darker purple color and eventually become a brownish-yellow color. **Navigational Note:** -					
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 with or without mild symptoms	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Life-threatening consequences; 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	Death
Definition: A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back. **Navigational Note:** -					
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; rash covering > 30% BSA with or without mild symptoms	Macules/papules covering >30% BSA with moderate or severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbillform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritis. **Navigational Note:** -					
Scalp pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the skin covering the top and the back of the head. **Navigational Note:** -					
Skin atrophy	Covering <10% BSA; associated with telangiectasias or changes in skin color	Covering 10 - 30% BSA; associated with striae or adnexal structure loss	Covering >30% BSA; associated with ulceration	-	-
Definition: A disorder characterized by the degeneration and thinning of the epidermis and dermis. **Navigational Note:** -					

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Skin hyperpigmentation	Hyperpigmentation covering <10% BSA; no psychosocial impact	Hyperpigmentation covering >10% BSA; associated psychosocial impact	-	-	-
Definition: A disorder characterized by darkening of the skin due to excessive melanin deposition. **Navigational Note:** -					
Skin hypopigmentation	Hypopigmentation or depigmentation covering <10% BSA; no psychosocial impact	Hypopigmentation or depigmentation covering >10% BSA; associated psychosocial impact	-	-	-
Definition: A disorder characterized by loss of skin pigment (e.g., vitiligo). **Navigational Note:** -					
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 or orifice movement (e.g., mouth, anus); limiting self care ADL	Generalized; associated with signs or symptoms of impaired breathing or feeding	Death
Definition: A disorder characterized by an area of hardness in the skin. **Navigational Note:** -					
Skin ulceration	Combined area of ulcers <1 cm; nonblanchable erythema of intact skin with associated warmth or edema	Combined area of ulcers 1 - 2 cm; partial thickness skin loss involving skin or subcutaneous fat	Combined area of ulcers >2 cm; full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia	Any size ulcer with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures with or without full thickness skin loss	Death
Definition: A disorder characterized by a circumscribed, erosive lesion on the skin. **Navigational Note:** -					
Stevens-Johnson syndrome	-	-	Skin sloughing covering <10% BSA with associated signs (e.g., erythema, purpura, epidermal detachment, and mucous membrane detachment)	Skin sloughing covering 10 - 30% BSA with associated signs (e.g., erythema, purpura, epidermal detachment and mucous membrane detachment)	Death
Definition: A disorder characterized by less than 10% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes. **Navigational Note:** -					

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

Social circumstances					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Social circumstances - Other, specify	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

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

Vascular disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Arterial thromboembolism	-	-	Urgent intervention indicated	Life-threatening consequences; hemodynamic or neurologic instability; organ damage; loss of extremity(ies)	Death
Definition: A disorder characterized by occlusion of an arterial vessel by a blood clot that develops in an artery. **Navigational Note:** Consider Nervous system disorders: TIA or Stroke for CNS-related events or Cardiac disorders: Myocardial infarction					
Capillary leak syndrome	Asymptomatic	Symptomatic; medical intervention indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by leakage of intravascular fluids into the extravascular space. This syndrome is observed in patients who demonstrate a state of generalized leaky capillaries following shock syndromes, low-flow states, ischemia-reperfusion injuries, toxemias, medications, or poisoning. It can lead to generalized edema and multiple organ failure. **Navigational Note:** -					
Flushing	Asymptomatic; clinical or diagnostic observations only	Moderate symptoms; limiting instrumental ADL	Symptomatic, associated with hypotension and/or tachycardia; limiting self care ADL	-	-
Definition: A disorder characterized by episodic reddening of the skin, especially face, neck, or chest. **Navigational Note:** -					
Hematoma	Mild symptoms; intervention not indicated	Minimally invasive evacuation or aspiration indicated	Transfusion; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a localized collection of blood, usually clotted, in an organ, space, or tissue, due to a break in the wall of a blood vessel. **Navigational Note:** -					
Hot flashes	Mild symptoms; intervention not indicated	Moderate symptoms; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by an uncomfortable and temporary sensation of intense body warmth, flushing, sometimes accompanied by sweating upon cooling. **Navigational Note:** -					

Vascular disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Hypertension	**Adult:** Systolic BP 120 - 139 mm Hg or diastolic BP 80 - 89 mm Hg; **Pediatric:** Systolic/diastolic BP >90th percentile but< 95th percentile; **Adolescent:** BP ≥120/80 even if < 95th percentile	**Adult:** Systolic BP 140 - 159 mm Hg or diastolic BP 90 - 99 mm Hg if previously WNL; change in baseline medical intervention indicated; recurrent or persistent (>=24 hrs); symptomatic increase by >20 mm Hg (diastolic) or to >140/90 mm Hg; monotherapy indicated initiated; **Pediatric and adolescent:** Recurrent or persistent (>=24 hrs) BP >ULN; monotherapy indicated; systolic and /or diastolic BP between the 95th percentile and 5 mmHg above the 99th percentile; A**dolescent:** Systolic between 130-139 or diastolic between 80-89 even if < 95th percentile	**Adult:** Systolic BP >=160 mm Hg or diastolic BP >=100 mm Hg; medical intervention indicated; more than one drug or more intensive therapy than previously used indicated; **Pediatric and adolescent:** Systolic and/or diastolic > 5 mmHg above the 99th percentile	**Adult and Pediatric:** Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurologic deficit, hypertensive crisis); urgent intervention indicated	Death
Definition: A disorder characterized by a pathological increase in blood pressure. **Navigational Note:** -					
Hypotension	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Medical intervention indicated; hospitalization indicated	Life-threatening consequences and urgent intervention indicated	Death
Definition: A disorder characterized by a blood pressure that is below the normal expected for an individual in a given environment. **Navigational Note:** -					
Lymph leakage	-	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the loss of lymph fluid into the surrounding tissue or body cavity. **Navigational Note:** -					

Vascular disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Lymphedema	Trace thickening or faint discoloration	Marked discoloration; leathery skin texture; papillary formation; limiting instrumental ADL	Severe symptoms; limiting self care ADL	-	-
Definition: A disorder characterized by excessive fluid collection in tissues that causes swelling. **Navigational Note:** -					
Lymphocele	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	-	-
Definition: A disorder characterized by a cystic lesion containing lymph. **Navigational Note:** -					
Peripheral ischemia	-	Brief (<24 hrs) episode of ischemia managed medically and without permanent deficit	Prolonged (>=24 hrs) or recurring symptoms and/or invasive intervention indicated	Life-threatening consequences; evidence of end organ damage; urgent operative intervention indicated	Death
Definition: A disorder characterized by impaired circulation to an extremity. **Navigational Note:** -					
Phlebitis	-	Present	-	-	-
Definition: A disorder characterized by inflammation of the wall of a vein. **Navigational Note:** -					
Superficial thrombophlebitis	-	Present	-	-	-
Definition: A disorder characterized by a blood clot and inflammation involving a superficial vein of the extremities. **Navigational Note:** -					
Superior vena cava syndrome	Asymptomatic; incidental finding of SVC thrombosis	Symptomatic; medical intervention indicated (e.g., anticoagulation, radiation or chemotherapy)	Severe symptoms; multi-modality intervention indicated (e.g., anticoagulation, chemotherapy, radiation, stenting)	Life-threatening consequences; urgent multi-modality intervention indicated (e.g., lysis, thrombectomy, surgery)	Death
Definition: A disorder characterized by obstruction of the blood flow in the superior vena cava. Signs and symptoms include swelling and cyanosis of the face, neck, and upper arms, cough, orthopnea and headache. **Navigational Note:** -					
Thromboembolic event	Medical intervention not indicated (e.g., superficial thrombosis)	Medical intervention indicated	Urgent medical intervention indicated (e.g., pulmonary embolism or intracardiac thrombus)	Life-threatening consequences with hemodynamic or neurologic instability	Death
Definition: A disorder characterized by occlusion of a vessel by a thrombus that has migrated from a distal site via the blood stream. **Navigational Note:** Consider Nervous system disorders: TIA or Stroke for CNS-related events. Use Vascular disorders: Arterial thromboembolism for arterial thrombi.					

Vascular disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Vasculitis	Asymptomatic, intervention not indicated	Moderate symptoms, medical intervention indicated	Severe symptoms, medical intervention indicated (e.g., steroids)	Life-threatening consequences; evidence of peripheral or visceral ischemia; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation involving the wall of a vessel. **Navigational Note:** -					
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; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: - **Navigational Note:** -					

GENERAL INFORMATION	
S-number & study acronym:	S65525 Acronym: VIPIDO
Protocol version & date	1-2 – 30-06-2021
Sponsor:	University Hospitals Leuven
Number of research sites:	One
Expected number of participants:	40
Coordinating/Principal Investigator:	Toon Van Gorp, MD, PhD Gynaecological Oncology Department of Gynaecology & Obstetrics toon.vangorp@uzleuven.be
DMP prepared/revised by:	Sander Dumont, MD Resident Department of Gynaecology & Obstetrics sander.dumont@uzleuven.be
Study Statistician:	N/A
Study Safety Coordinator/Reviewer:	N/A

Table of Contents

1. Purpose

This Data Management Plan serves to describe all study-specific clinical trial-related data management tasks and deliverables. This includes how the data are collected, how data quality and integrity is assured, how data is handled, transformed, and processed, etc.

2. Scope

This DMP was developed for clinical trials for which KUL-UZ Leuven is Sponsor and/or for which data management tasks are contracted to KUL-UZL, and is governed by CTC DM-SOP-001

Out of scope:

Development and content of the Statistical Analysis Plan (SAP) and Monitoring Plan (MP)

3. Scope of data management activities

A. DATA COLLECTION				
A.1 What data will be collected or re-used and where does it have its origin?				
Data point	**Collect**	**Re-use**	**Recording**	**Comments**
Eligibility criteria	☒	☒	KWS, CRF	
Demographics	☒	☒	KWS, CRF	
Medical history	☒	☒	KWS, CRF	
Concomitant medication	☒	☒	KWS, CRF	
Physical examination	☒	☒	KWS, CRF	
Adverse events	☒	☐	KWS, CRF	
Biochemical analysis	☐	☒	KWS, CRF	
Radiological examinations	☐	☒	KWS, CRF	
Topographic map during surgery	☒	☐	CRF	First on paper, afterwards registration in the eCRF
Surgical report	☒	☐	KWS, CRF	
Imaging during surgery	☒	☐	CRF	
Pathology report	☒	☐	KWS, CRF	
Time stamps during surgery	☒	☐	KWS, CRF	
Additional standard-of-care reports	☐	☒	KWS, CRF	
A.2 Was UZL GDPR questionnaire?		☒ Yes ☐ No		
A.3 Expected recruitment start date		September 2021		
A.4 Name and version of (e)CRF platform or relational database used to capture study-specific data		REDCap™ Production version 9.5.13		
A.5 Party responsible for (e)CRF development		Sander Dumont, MD sander.dumont@uzleuven.be		
B. DATA ACCESS AND SECURITY				
B.1 Physical location of CRF database		REDCap is hosted on dedicated KU Leuven data servers at Campus Heverlee.		

B.2 System Administrator	For UZL REDCap the System Administrator is Gert Goos: gert.goos@kuleuven.be
B.3 How will physical data access be restricted?	Physical access to the data centres is logged and restricted to authorized KU Leuven Information Technology (IT) personnel, using badge identification. At the clinical database level only study team members, monitors and auditors/inspectors for whom the Coordinating or Principal Investigator (as applicable) has requested project-specific eCRF access, are granted data access. Upon successful training completion each user is centrally assigned a user role, associated with predefined system/data privileges, in accordance with CTC DM-WI-001. The gatekeeper for UZL REDCap is UZL CTC (ctc.datamanagement@uzleuven.be).
B.4 Will data be shared outside UZL during and/or following completion of the clinical research trial?	☒ Yes ☐ No
Data will be shared upon request following completion of the Trial. This will be done in accordance with the FAIR data principles and all data will be anonymised before sharing.	
B.5 Describe the use and format of required data exports	For the purpose of statistical analysis and results reporting, data exports out of REDCap will be exported in SPSS format. For SUSAR reporting, safety data reports will be exported in CSV or SPSS format.
C. DATA STANDARDS & CODING	
C.1 Which medical coding dictionary/dictionaries will be used?	Medical Dictionary for Regulatory Activities Terminology (MedDRA), version 23.1.
C.2 What measures will be taken to prevent collection and sharing of personal data from trial participants?	All participant data will be pseudonymized using a unique study-specific identifier for each trial participant, in compliance with applicable data protection regulations.
D. DATA CLEANING AND VALIDATION	
D.1 Describe the type, level and frequency of quality control (QC) activities.	Data quality will be checked through biweekly reviews of comprehensive data discrepancy reports, including information about missing and unreviewed/unvalidated data fields.
D.2 Will the study be monitored by a qualified, trained individual, who is independent from the study team?	☐ Yes ☒ No
In accordance with EMA guideline on Data Monitoring Commitees (Doc. Ref. EMEA/CHMP/EWP/5872/03 Corr), this study does not require an independent monitor. This study is a clinical study in a non-critical indication with a very short (one day) treatment time. Furthermore, the IMP is well characterized and known for not harming patients. A risk analysis was performed by the UZ Leuven Clinical Trial Center, classifying this Trial as "intermediate risk". As such, and as permitted by ICH-GCP (r2) section 5.0.4, the Sponsor of the trial accepts the minimal risks associated with this trial and determines that monitoring activities (as defined by ICH-GCP E6(r2) §1.38) by a qualified individual, independent of the study team, is not necessary as it will provide little or no added value in protecting the safety of trial participants and assuring the integrity of collected trial data.	
D.3 Name of monitoring party	None
D.4 Data cleaning strategy, i.e. query process	Following periodic data reviews, the data will be cleaned using an interactive query workflow whereby the Data Manager and/or Safety Reviewer and/or Monitor will open a query when identifying missing and/or discrepant and/or unsubstantiated data, prompting the Investigator and/or designated study team members to address the issue. Upon verification of response/actions taken by the study team, the query generator will close the query.

D.5 Describe how protocol deviations and/or violations will be documented and/or reported.	All possible protocol deviations and/or violations will be reported to the P.I. as soon as possible. These deviations and/or violations will be reported in the CRF. Should this participant be excluded from the trial, this participant will be accounted for in the statistical analysis with an intention-to-treat analysis.
E. RANDOMISATION / TREATMENT ALLOCATION	
E.1 Is the study randomized?	☐ Yes ☒ No
F. DATA INTEGRITY	
F.1 How will the integrity of the data be assured during data transfer and processing?	Imports/exports and/or transfers of any kind of partial or complete data sets will be systematically encrypted. During transfer and processing all data will be protected with a strong password, two-step authentication or a specialised application (e.g. 7-Zip, AES Crypt, …). All data transfers will happen via the Belnet FileSender which fully encrypt all data.
F.2 Which measures are taken to allow verification of data integrity throughout the entire data lifecycle?	A comprehensive audit trail is maintained within the eCRF allowing to demonstrate the validity of collected trial data. This includes historical records of original data entries, by whom the data was entered and when it was entered, as well as detailed records of who, when, which and why corrections to the original data entry were made. This also includes records pertaining to managing user access and data privileges.
F.3 What measures will be taken to assure the integrity of blinded treatment allocation/information?	N/A, no blinding will be used in this Trial.
F.4 What measures will be taken to avoid bias of independent raters? (as applicable)	By using UZL REDCap, data privileges can be customized to restrict specific users from viewing certain information or study data to which other users do have access to.
G. SAFETY REVIEW / REPORTING	
G.1 How will study participant safety be assured?	The CI/PI will be notified via email whenever an SAE is recorded in the (e)CRF. In addition, comprehensive safety reports will be reviewed on a weekly basis, including the following parameters: - Potential data breaches - Lost or incomplete data
G.2 Party responsible for safety reviews	Sander Dumont, MD sander.dumont@uzleuven.be
G.3 Party responsible for safety reporting, per applicable regulations, protocol and study-specific agreements	UZ Leuven Clinical Trial Center ctc.safety@uzleuven.be
H. DATABASE LOCK	
H.1 Will an interim database lock be executed?	☐ Yes ☒ No
H.2 When and under which conditions/at what point in time will the final database lock be executed?	Final database lock will occur when both Trial arms have included 20 participants and each individual participant has fully completed follow-up (i.e., definitive pathological report has been obtained and no adverse events have been registered).

H.3 Expected data/timing for final DB lock	We expect final DB lock within 12-18 months of the start of recruitment.
H.4 Party responsible for interim/final database lock	Toon Van Gorp, MD, PhD toon.vangorp@uzleuven.be
I. DATA RETENTION, CONTINGENCY & DISASTER RECOVERY	
I.1 Describe contingency procedures and data backup schedule	Data is backed up as follows: ▪ The web server backup regime is specified below: - An hourly backup, the last 6 versions of which are saved - A daily backup, the last 7 versions of which are saved - A weekly backup, the last 6 versions of which are saved ▪ The database backup regime is specified below: - A nightly cold backup of all databases - One month's storage of the nightly cold backups ▪ Data restore, upon request
I.2 Provide reference to relevant system disaster recovery procedures	The following KU Leuven procedures for system recovery apply: ▪ Systems are proactively monitored 24 hours a day, 7 days a week. ▪ An emergency on-call service guarantees constant monitoring of the technical equipment, also outside office hours, but not at night. The on-call service is notified automatically in case of problems (between 7.00 - 23.00 hrs). ▪ There are no fixed maintenance windows: a timely email is sent to inform the local IT Administrator of any planned maintenance or upgrades. ▪ Any service unavailability, scheduled or unscheduled, is announced on the ICTS status page. ▪ The web space is designed redundantly: in the event of system problems on one back-end server, all traffic is automatically diverted to another back-end server. The database platform is also designed redundantly.
J. END OF TRIAL DATA ARCHIVING	
J.1 Describe how (format and media) data will be archived at the end of the study	All data will be exported in open file formats (such as .csv or .odt) or widely readable data (such as .jpeg or .png).
J.2 How long will data be the study database be archived?	25 years
J.3 Please provide archiving location following the end of the study	Password protected personal file storage from UZ Leuven.
K. THIRD PARTY DATA HANDLERS	
K.1 Are any third parties involved with any aspects of data management?	☐ Yes ☒ No
L. INDEPENDENT DATA SAFETY MONITORING BOARD (DSMB)	
L.1 Will a DSMB be used?	☐ Yes ☒ No
L.2 Frequency of DSMB meetings?	N/A
L.3 Scope and objectives of DSMB activities?	N/A

4. Archiving

Final versions of this DMP will be filed in the appropriate section of the study-specific TMF.

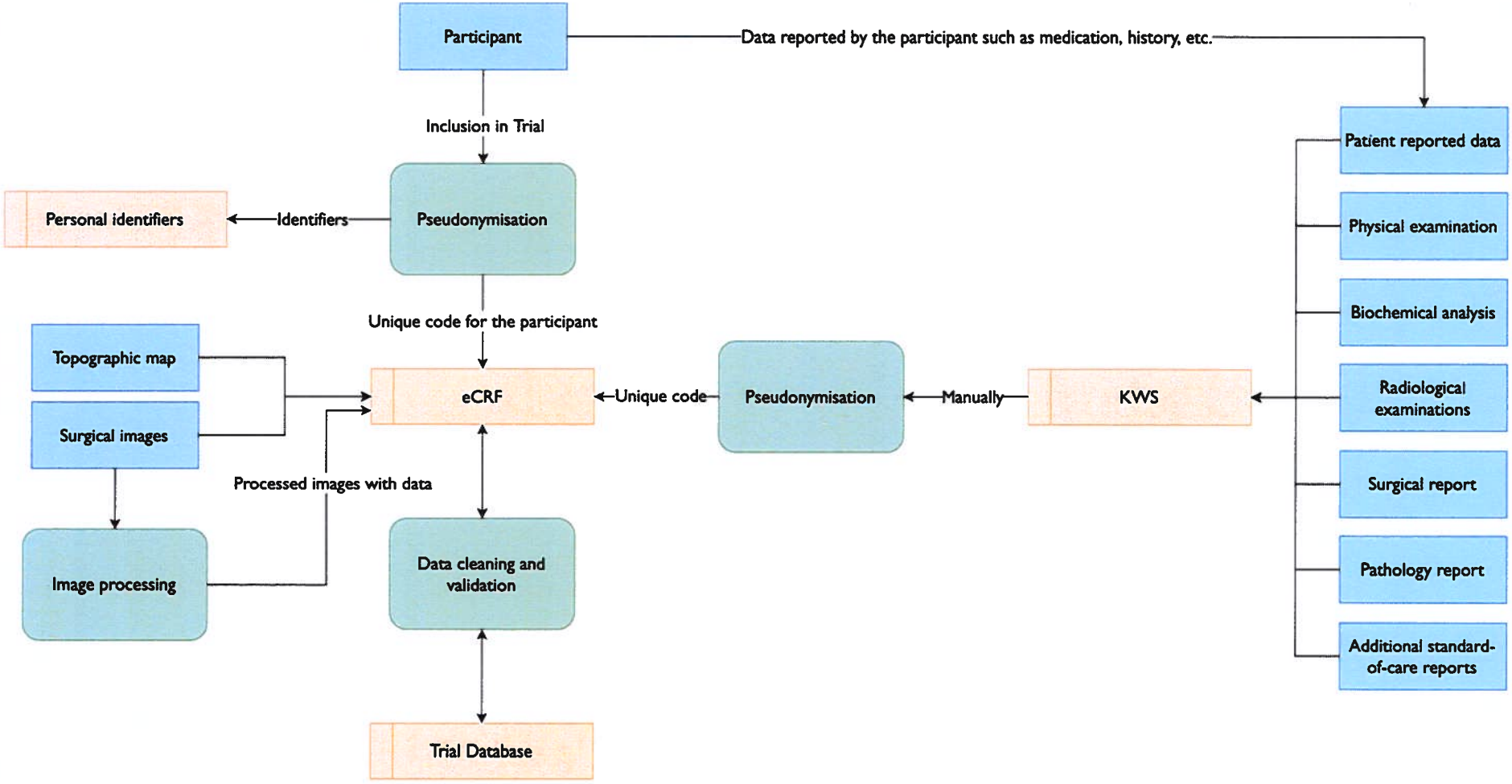
5. Version history

Version	Reason for change
1-0_29-04-2021	New document
1-1_07-05-2021	Updated with S number
1-2_30-06-2021	Removed monitoring party (D.3) and referenced the advice from CTC monitoring (D.2).

6. Approvals

Author	Reviewer/Approver
Toon Van Gorp, MD, PhD Date: 30-06-2021	Date:

7. APPENDIX 1: Data Flow Diagram (DFD)



SPONSOR STATEMENT ON USE OF ICF MODEL FOR INTERVENTIONAL TRIALS WITH IMP ON ADULT PATIENTS

EU number: 2021-002449-13

Trial number: S65525

Sponsor of the trial: University Hospitals Leuven (UZ Leuven), Herestraat 49, 3000 Leuven

I, the undersigned representative of the sponsor in the member state, hereby confirm that for the above-mentioned clinical trial application:

☐ No informed consent forms are submitted.

☒ Informed consent forms are submitted and the Belgian ICF template for adult patients, version **1-3**, publication date **28-07-2021** has been used,

- ☐ without changes to the mandatory text.
- ☒ with the following adaptations to the mandatory text, and because of the following reasons:

Adaptation to section	Reason
§ 6.1.	Since the IMP has already obtained market authorisation, the statement this IMP is still under investigation is not valid. As such additional adverse effects outside the SmPC are not expected.

☐ Informed consent forms are submitted and the Belgian ICF template for adult patients has <u>not</u> been used, because of the following reason: N/A

Surname and first name: VAN GORP Toon, MD, PhD
Date: 28-07-2021
Signature:

Eligibility & ICF

Participant identifier

eCRF version 1.3 / Date: 21-10-2021
Protocol version 1.3

Internal ref. Nbr: S65525

EudraCT Nbr: 2021-002449-13

ClinicalTrials.gov Nbr: NCT04891185

Date of recruitment

INFORMED CONSENT

Has informed consent been obtained?
- ◯ Yes
- ◯ No

(DO NOT PROCEED if informed consent has not been obtained!)

Date informed consent signed

Have all inclusion criteria been met and are none of the exclusion criteria met?
- ◯ Yes
- ◯ No

(DO NOT ENROLL subject if all eligibility criteria have not been met!)

Please enter the response about information concerning incidental findings
- ◯ No
- ◯ Yes
- ◯ No response (= Yes)

SCREEN FAILURE

Did the subject fail screening for any reason other than not meeting eligibility criteria?
- ◯ Yes
- ◯ No

Demographics & History

Date demographics data collected

Participant's age

Has the participants any allergies?

◯ Yes
◯ No

Patient history

[redacted]

Please add patient history in a structured method below

Diabetes	Yes No
Chronic kidney disease	Yes No
Thyroid disease	Yes No
Major abdominal surgery	Yes No
Previous tumour	Yes No

PREOPERATIVE TUMOUR INFORMATION

The patient was diagnosed with HGSOC?	Yes No
FIGO stage of ovarian cancer	IIIb IIIc IV Other

TRIAL ARM

Select arm of Trial	Primary debulking Interval debulking
Select reason for interval debulking	Unfit patient High intra-abdominal tumour load Extra-abdominal tumour load Unresectable lesions Time issues Other
Pre-operative chemotherapy regimen	[redacted]

Pre-operative

Date of physical examination and vital signs [redacted]

Relevant physical examination

_____

Most recent body weight (kg) [redacted]

Body height (cm) [redacted]

BMI (kg/m2) [redacted]

Most recent systolic blood pressure [redacted]

Most recent diastolic blood pressure [redacted]

Most recent heart rate [redacted]

Most recent body temperature [redacted]
(1 number after comma)

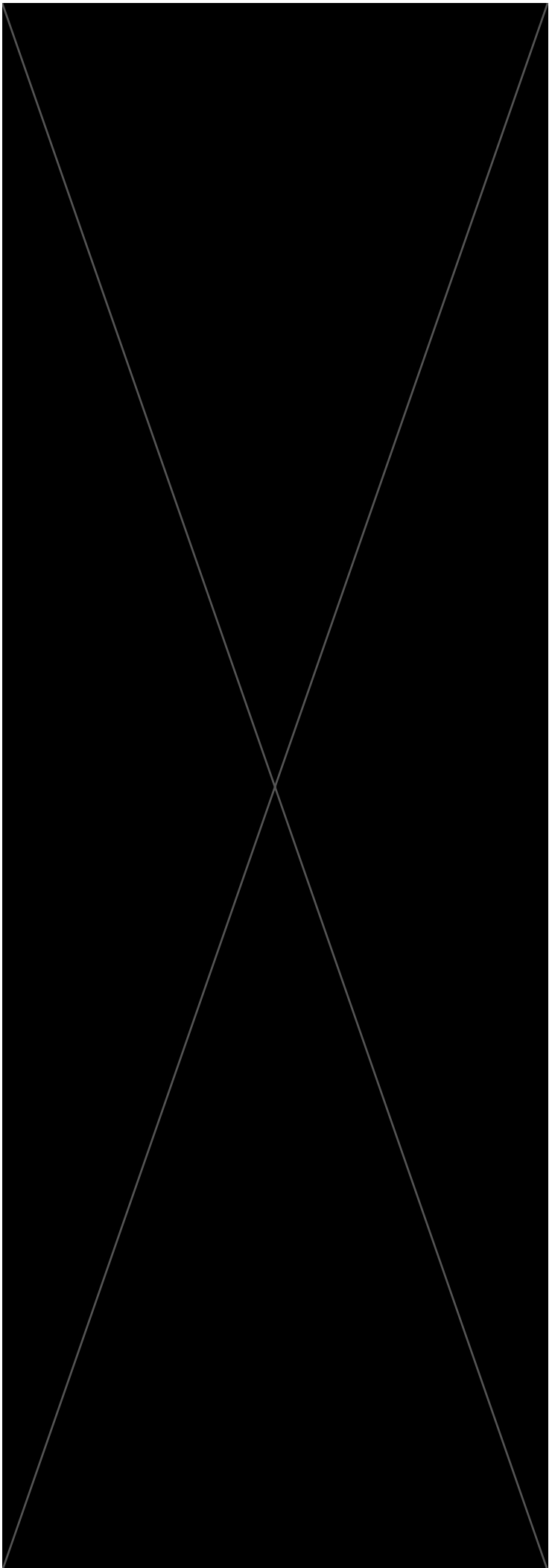
Eastern Cooperative Oncology Group (ECOG) performance status [redacted]
0: Fully active, able to carry on all pre-disease performance without restriction
1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2: Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3: Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4: Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5: Dead

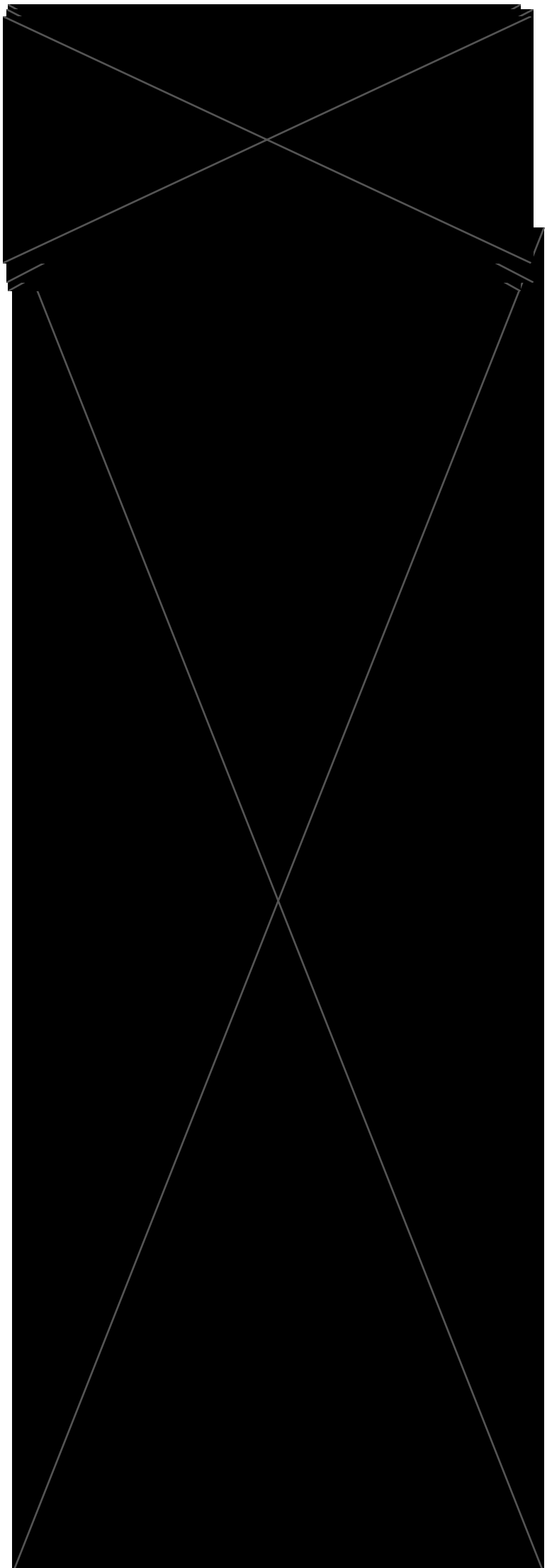
PREOPERATIVE IMAGING

	Completed	Planned	Only external hospital	Not performed
CT abdomen	[redacted]			
CT thorax				
CT thorax-abdomen				
PET-CT				
MRI pelvis				
MRI whole body				

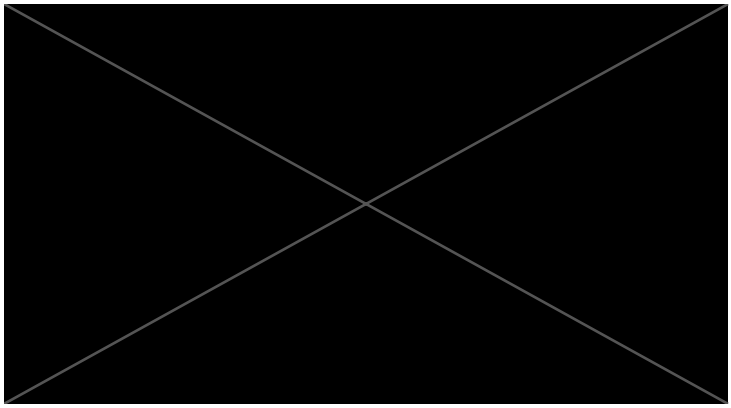
Expert ultrasound [redacted]

Validated imaging report of MRI whole body





Additional validated imaging reports of other studies



LAB TESTS

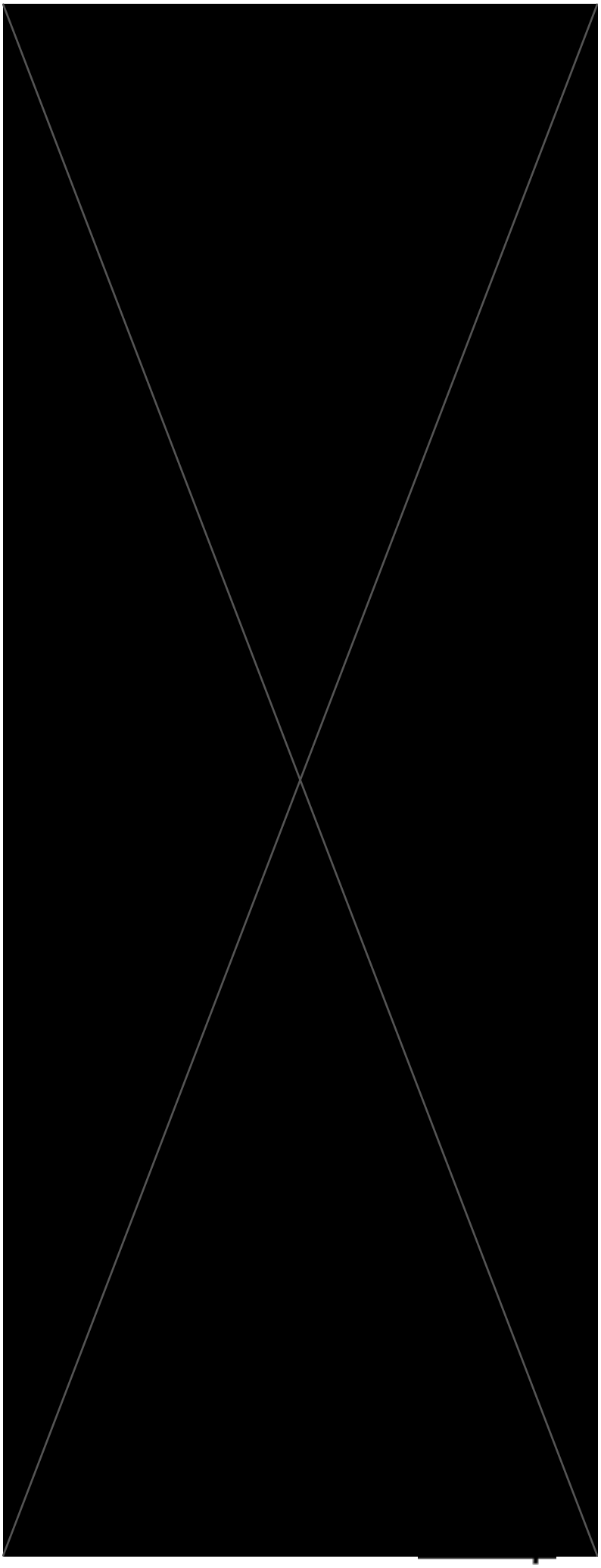
Most recent renal function (eGFR, in ml/min/1,73m2)

Most recent CA-125 biomaker (kU/L)

Most recent hemoglobin (g/dl)

(1 number after comma)

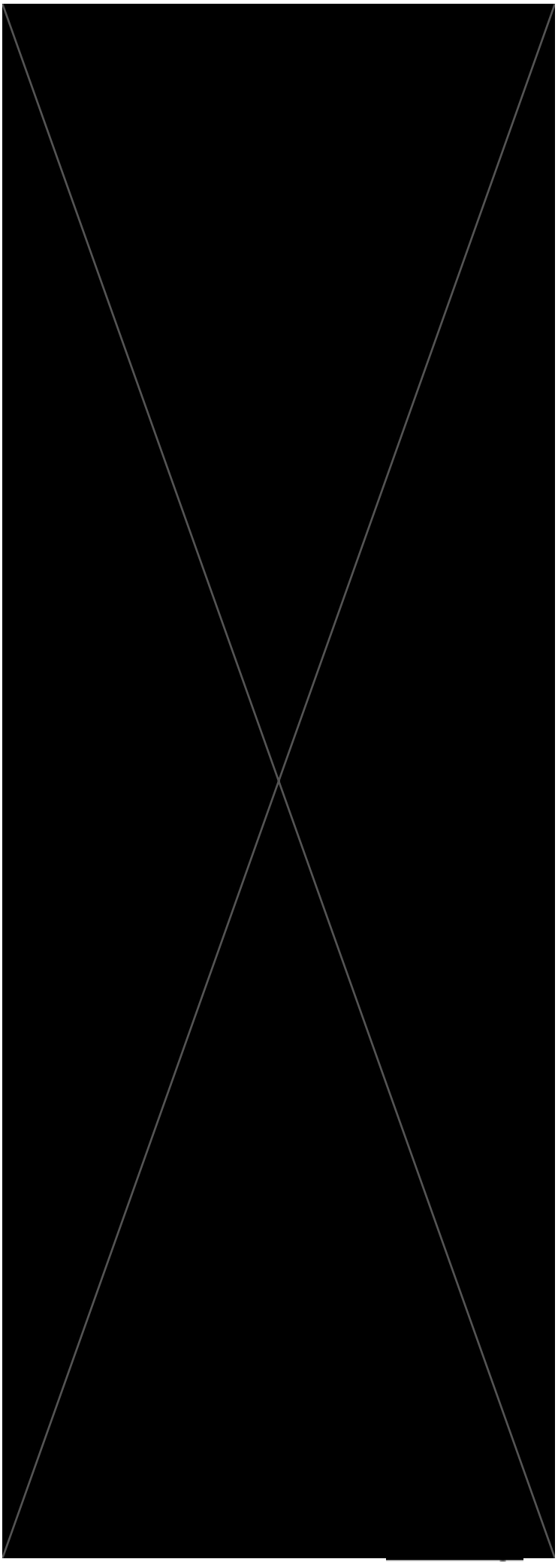
Please add relevant recent lab tests

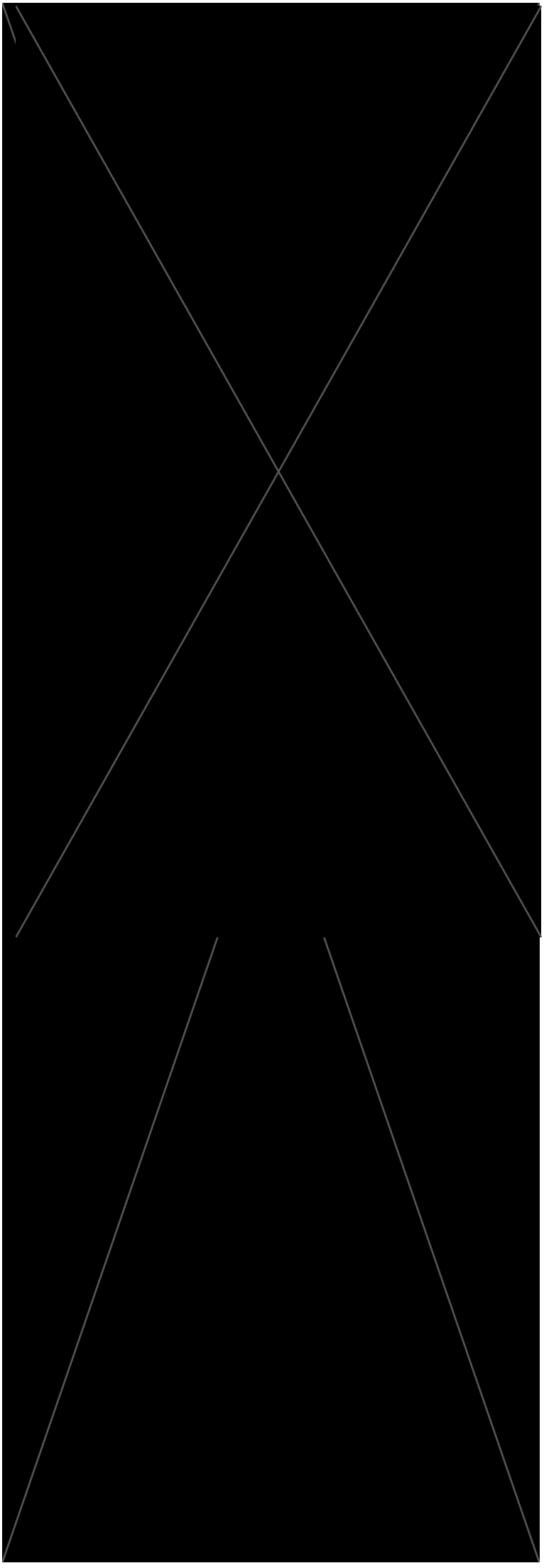


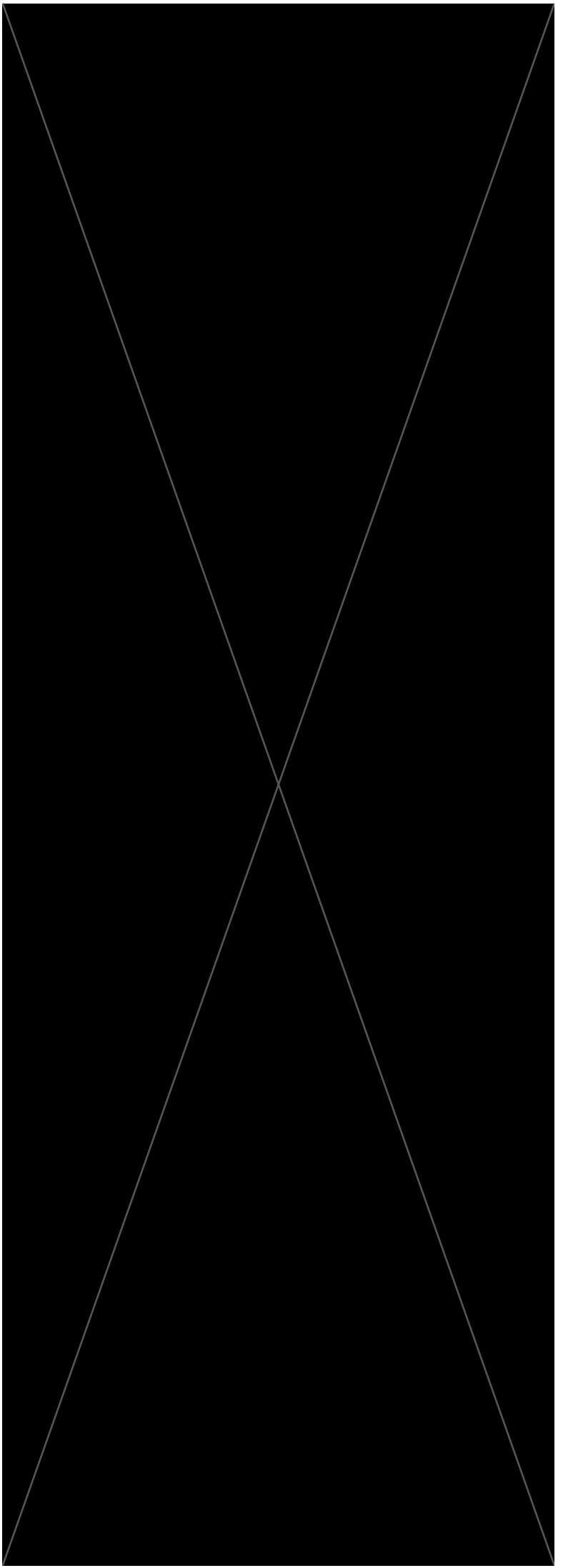
Surgery

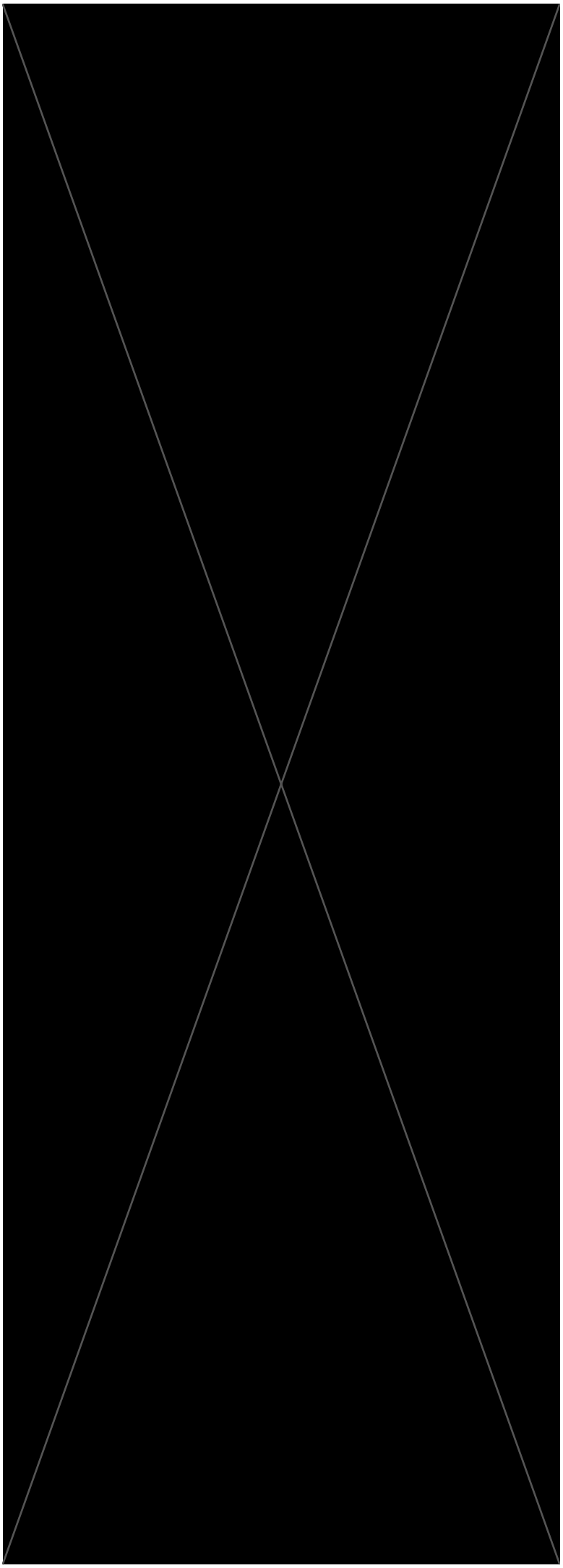
Date of surgery [redacted]

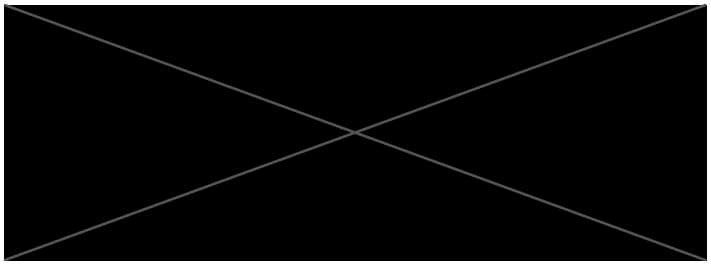
Validated surgical report











INFORMATION ABOUT DEBULKING

Primary debulking
Yes
No

Indication for debulking is HGSOC?
Yes
No

FIGO stage PREoperatively?
IIIb
IIIc
IV

ANESTHESIA

General anesthesia
Yes
No

Locoregional anesthesia
Yes
No

Time between administration and start of visualisation of IMP utilising NIR fluorescence camera? (in minutes)

APPROACH

Midline laparotomy
Yes
No

Adequate abdominal exposure?
Yes
No

Excluded because of inadequate intra-abdominal exposure?
Yes
No

IMP ADMINISTRATION

Was the IMP administered?
Yes
No

Was a direct allergic reaction apparant during or shortly after administration of the IMP?
Yes
No

NIR FLUORESCENCE CAMERA

Any problems with NIR fluorescence camera equipement?
[redacted] Yes
No

Was the Karl Storz Image1 S TH 121 4K camera utilised?
[redacted] Yes
No

Additional notes concerning surgery
[redacted]

LYMPH NODES

Were lymph nodes resected?
[redacted] Yes
No

Provide the anatomical region(s) the lymph nodes were resected
[redacted]

IMP handling, administration and accountability

The paper Drug Accountability log has been filled in completely	[X] Yes [ ] No

DURING IMP ADMINISTRATION

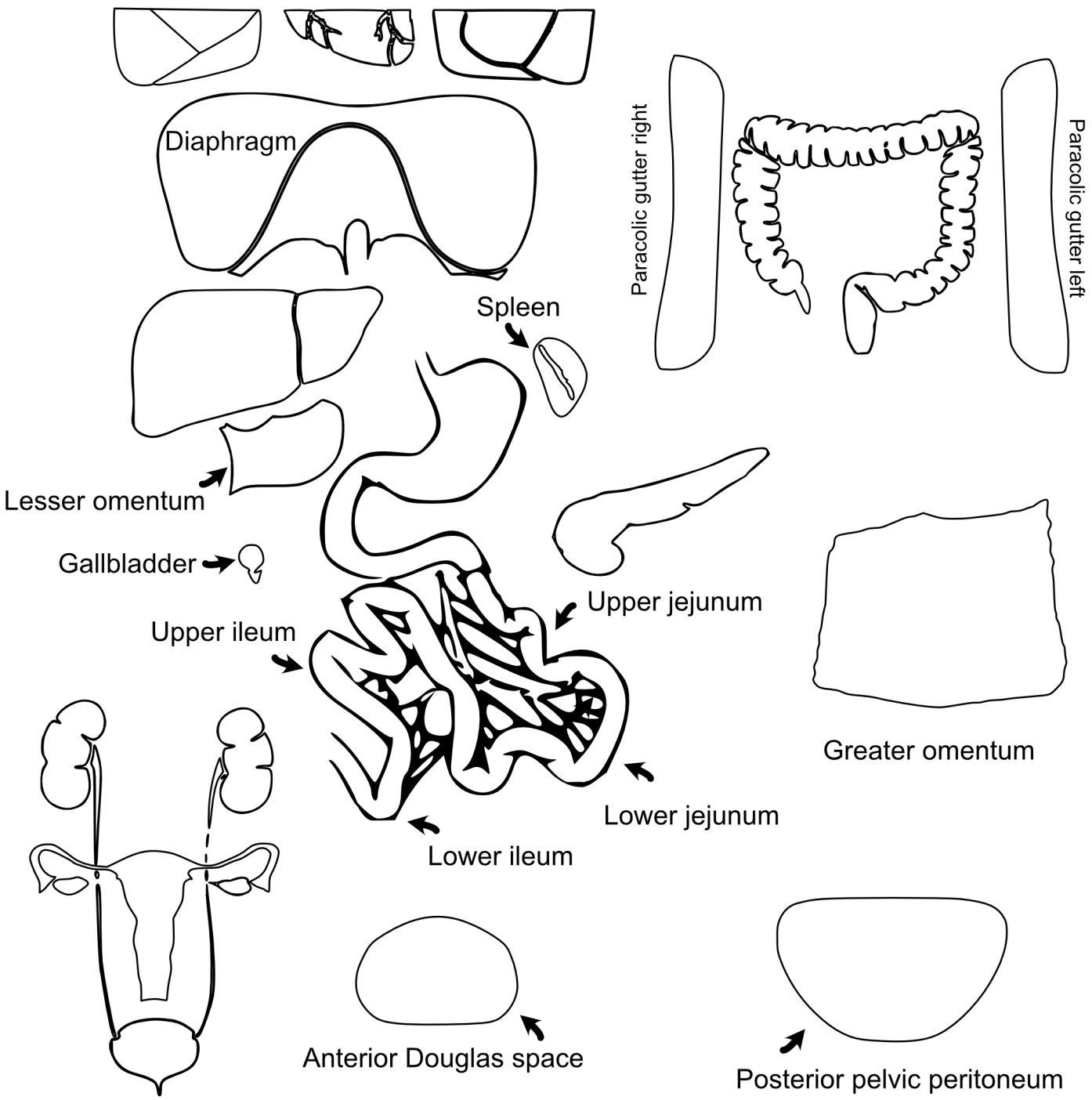
Most recent body weight	[redacted]
Calculated optimal dose (mg)	[redacted]
Any abnormalities during administration of the IMP?	[X] Yes [ ] No
Administered dose of the IMP (in mg)	[redacted]
Correct dose according to body weight?	[redacted]

Locked by sdumon3 (Sander Dumont) on 2021-11-17 11:09

Paper CRF

STEP 1: LESIONS

If macroscopically suspicious for malignancy: draw X
If fluorescence signal is positive: draw O
If both: draw ⊗



Lesion number 1

Location

- ◯ Lung/Thorax R (including pleura)
- ◯ Lung/Thorax L (including pleura)
- ◯ Heart and pericardium
- ◯ Diaphragm R
- ◯ Diaphragm center
- ◯ Diaphragm L
- ◯ Liver R
- ◯ Liver L
- ◯ Gallbladder
- ◯ Spleen
- ◯ Lesser omentum
- ◯ Greater omentum
- ◯ Paracolic gutter R (upper half)
- ◯ Paracolic gutter R (lower half)
- ◯ Paracolic gutter L (upper half)
- ◯ Paracolic gutter L (lower half)
- ◯ Oesophagus
- ◯ Stomach
- ◯ Duodenum
- ◯ Upper jejunum
- ◯ Lower jejunum
- ◯ Upper lieum
- ◯ Lower ileum
- ◯ Caecum
- ◯ Ascending colon
- ◯ Transverse colon
- ◯ Descending colon
- ◯ Sigmoid
- ◯ Rectum
- ◯ Pancreatic head
- ◯ Pancreatic tail
- ◯ Anterior Douglas space
- ◯ Posterior pelvic peritoneum R
- ◯ Posterior pelvic peritoneum center
- ◯ Posterior pelvic peritoneum L
- ◯ Kidney (capsula) R
- ◯ Kidney (capsula) L
- ◯ Proximal ureter R
- ◯ Distal ureter R
- ◯ Proximal ureter L
- ◯ Distal ureter L
- ◯ Bladder R
- ◯ Bladder center
- ◯ Bladder L
- ◯ Urethra
- ◯ Ovary R
- ◯ Ovary L
- ◯ Fallopian tube R
- ◯ Fallopian tube L
- ◯ Corpus uteri
- ◯ Cervix
- ◯ Vagina
- ◯ Other

BEFORE fluorescence

- ◯ Malignant / Certain
- ◯ Malignant / Probably
- ◯ Malignant / Uncertain
- ◯ Benign / Uncertain
- ◯ Benign / Probably
- ◯ Benign / Certain

AFTER fluorescence

- ◯ Malignant / Certain
- ◯ Malignant / Probably
- ◯ Malignant / Uncertain
- ◯ Benign / Uncertain
- ◯ Benign / Probably
- ◯ Benign / Certain

A photograph was taken?

- ◯ Yes
- ◯ No

Lesion number 2

Location

◯ Lung/Thorax R (including pleura)
◯ Lung/Thorax L (including pleura)
◯ Heart and pericardium
◯ Diaphragm R
◯ Diaphragm center
◯ Diaphragm L
◯ Liver R
◯ Liver L
◯ Gallbladder
◯ Spleen
◯ Lesser omentum
◯ Greater omentum
◯ Paracolic gutter R (upper half)
◯ Paracolic gutter R (lower half)
◯ Paracolic gutter L (upper half)
◯ Paracolic gutter L (lower half)
◯ Oesophagus
◯ Stomach
◯ Duodenum
◯ Upper jejunum
◯ Lower jejunum
◯ Upper lieum
◯ Lower ileum
◯ Caecum
◯ Ascending colon
◯ Transverse colon
◯ Descending colon
◯ Sigmoid
◯ Rectum
◯ Pancreatic head
◯ Pancreatic tail
◯ Anterior Douglas space
◯ Posterior pelvic peritoneum R
◯ Posterior pelvic peritoneum center
◯ Posterior pelvic peritoneum L
◯ Kidney (capsula) R
◯ Kidney (capsula) L
◯ Proximal ureter R
◯ Distal ureter R
◯ Proximal ureter L
◯ Distal ureter L
◯ Bladder R
◯ Bladder center
◯ Bladder L
◯ Urethra
◯ Ovary R
◯ Ovary L
◯ Fallopian tube R
◯ Fallopian tube L
◯ Corpus uteri
◯ Cervix
◯ Vagina
◯ Other

AFTER fluorescence

◯ Malignant / Certain
◯ Malignant / Probably
◯ Malignant / Uncertain
◯ Benign / Uncertain
◯ Benign / Probably
◯ Benign / Certain

BEFORE fluorescence	◯ Malignant / Certain ◯ Malignant / Probably ◯ Malignant / Uncertain ◯ Benign / Uncertain ◯ Benign / Probably ◯ Benign / Certain
A photograph was taken?	◯ Yes ◯ No

Lesion number 3

Location

- ◯ Lung/Thorax R (including pleura)
- ◯ Lung/Thorax L (including pleura)
- ◯ Heart and pericardium
- ◯ Diaphragm R
- ◯ Diaphragm center
- ◯ Diaphragm L
- ◯ Liver R
- ◯ Liver L
- ◯ Gallbladder
- ◯ Spleen
- ◯ Lesser omentum
- ◯ Greater omentum
- ◯ Paracolic gutter R (upper half)
- ◯ Paracolic gutter R (lower half)
- ◯ Paracolic gutter L (upper half)
- ◯ Paracolic gutter L (lower half)
- ◯ Oesophagus
- ◯ Stomach
- ◯ Duodenum
- ◯ Upper jejunum
- ◯ Lower jejunum
- ◯ Upper lieum
- ◯ Lower ileum
- ◯ Caecum
- ◯ Ascending colon
- ◯ Transverse colon
- ◯ Descending colon
- ◯ Sigmoid
- ◯ Rectum
- ◯ Pancreatic head
- ◯ Pancreatic tail
- ◯ Anterior Douglas space
- ◯ Posterior pelvic peritoneum R
- ◯ Posterior pelvic peritoneum center
- ◯ Posterior pelvic peritoneum L
- ◯ Kidney (capsula) R
- ◯ Kidney (capsula) L
- ◯ Proximal ureter R
- ◯ Distal ureter R
- ◯ Proximal ureter L
- ◯ Distal ureter L
- ◯ Bladder R
- ◯ Bladder center
- ◯ Bladder L
- ◯ Urethra
- ◯ Ovary R
- ◯ Ovary L
- ◯ Fallopian tube R
- ◯ Fallopian tube L
- ◯ Corpus uteri
- ◯ Cervix
- ◯ Vagina
- ◯ Other

BEFORE fluorescence

- ◯ Malignant / Certain
- ◯ Malignant / Probably
- ◯ Malignant / Uncertain
- ◯ Benign / Uncertain
- ◯ Benign / Probably
- ◯ Benign / Certain

AFTER fluorescence	◯ Malignant / Certain ◯ Malignant / Probably ◯ Malignant / Uncertain ◯ Benign / Uncertain ◯ Benign / Probably ◯ Benign / Certain
A photograph was taken?	◯ Yes ◯ No

Lesion number 4

Location

- ◯ Lung/Thorax R (including pleura)
- ◯ Lung/Thorax L (including pleura)
- ◯ Heart and pericardium
- ◯ Diaphragm R
- ◯ Diaphragm center
- ◯ Diaphragm L
- ◯ Liver R
- ◯ Liver L
- ◯ Gallbladder
- ◯ Spleen
- ◯ Lesser omentum
- ◯ Greater omentum
- ◯ Paracolic gutter R (upper half)
- ◯ Paracolic gutter R (lower half)
- ◯ Paracolic gutter L (upper half)
- ◯ Paracolic gutter L (lower half)
- ◯ Oesophagus
- ◯ Stomach
- ◯ Duodenum
- ◯ Upper jejunum
- ◯ Lower jejunum
- ◯ Upper lieum
- ◯ Lower ileum
- ◯ Caecum
- ◯ Ascending colon
- ◯ Transverse colon
- ◯ Descending colon
- ◯ Sigmoid
- ◯ Rectum
- ◯ Pancreatic head
- ◯ Pancreatic tail
- ◯ Anterior Douglas space
- ◯ Posterior pelvic peritoneum R
- ◯ Posterior pelvic peritoneum center
- ◯ Posterior pelvic peritoneum L
- ◯ Kidney (capsula) R
- ◯ Kidney (capsula) L
- ◯ Proximal ureter R
- ◯ Distal ureter R
- ◯ Proximal ureter L
- ◯ Distal ureter L
- ◯ Bladder R
- ◯ Bladder center
- ◯ Bladder L
- ◯ Urethra
- ◯ Ovary R
- ◯ Ovary L
- ◯ Fallopian tube R
- ◯ Fallopian tube L
- ◯ Corpus uteri
- ◯ Cervix
- ◯ Vagina
- ◯ Other

BEFORE fluorescence

- ◯ Malignant / Certain
- ◯ Malignant / Probably
- ◯ Malignant / Uncertain
- ◯ Benign / Uncertain
- ◯ Benign / Probably
- ◯ Benign / Certain

AFTER fluorescence

- ◯ Malignant / Certain
- ◯ Malignant / Probably
- ◯ Malignant / Uncertain
- ◯ Benign / Uncertain
- ◯ Benign / Probably
- ◯ Benign / Certain

A photograph was taken?

- ◯ Yes
- ◯ No

Lesion number 5

Location

◯ Lung/Thorax R (including pleura)
◯ Lung/Thorax L (including pleura)
◯ Heart and pericardium
◯ Diaphragm R
◯ Diaphragm center
◯ Diaphragm L
◯ Liver R
◯ Liver L
◯ Gallbladder
◯ Spleen
◯ Lesser omentum
◯ Greater omentum
◯ Paracolic gutter R (upper half)
◯ Paracolic gutter R (lower half)
◯ Paracolic gutter L (upper half)
◯ Paracolic gutter L (lower half)
◯ Oesophagus
◯ Stomach
◯ Duodenum
◯ Upper jejunum
◯ Lower jejunum
◯ Upper lieum
◯ Lower ileum
◯ Caecum
◯ Ascending colon
◯ Transverse colon
◯ Descending colon
◯ Sigmoid
◯ Rectum
◯ Pancreatic head
◯ Pancreatic tail
◯ Anterior Douglas space
◯ Posterior pelvic peritoneum R
◯ Posterior pelvic peritoneum center
◯ Posterior pelvic peritoneum L
◯ Kidney (capsula) R
◯ Kidney (capsula) L
◯ Proximal ureter R
◯ Distal ureter R
◯ Proximal ureter L
◯ Distal ureter L
◯ Bladder R
◯ Bladder center
◯ Bladder L
◯ Urethra
◯ Ovary R
◯ Ovary L
◯ Fallopian tube R
◯ Fallopian tube L
◯ Corpus uteri
◯ Cervix
◯ Vagina
◯ Other

BEFORE fluorescence

◯ Malignant / Certain
◯ Malignant / Probably
◯ Malignant / Uncertain
◯ Benign / Uncertain
◯ Benign / Probably
◯ Benign / Certain

AFTER fluorescence

- ◯ Malignant / Certain
- ◯ Malignant / Probably
- ◯ Malignant / Uncertain
- ◯ Benign / Uncertain
- ◯ Benign / Probably
- ◯ Benign / Certain

A photograph was taken?

- ◯ Yes
- ◯ No

Lesion number 6

Location

- ◯ Lung/Thorax R (including pleura)
- ◯ Lung/Thorax L (including pleura)
- ◯ Heart and pericardium
- ◯ Diaphragm R
- ◯ Diaphragm center
- ◯ Diaphragm L
- ◯ Liver R
- ◯ Liver L
- ◯ Gallbladder
- ◯ Spleen
- ◯ Lesser omentum
- ◯ Greater omentum
- ◯ Paracolic gutter R (upper half)
- ◯ Paracolic gutter R (lower half)
- ◯ Paracolic gutter L (upper half)
- ◯ Paracolic gutter L (lower half)
- ◯ Oesophagus
- ◯ Stomach
- ◯ Duodenum
- ◯ Upper jejunum
- ◯ Lower jejunum
- ◯ Upper lieum
- ◯ Lower ileum
- ◯ Caecum
- ◯ Ascending colon
- ◯ Transverse colon
- ◯ Descending colon
- ◯ Sigmoid
- ◯ Rectum
- ◯ Pancreatic head
- ◯ Pancreatic tail
- ◯ Anterior Douglas space
- ◯ Posterior pelvic peritoneum R
- ◯ Posterior pelvic peritoneum center
- ◯ Posterior pelvic peritoneum L
- ◯ Kidney (capsula) R
- ◯ Kidney (capsula) L
- ◯ Proximal ureter R
- ◯ Distal ureter R
- ◯ Proximal ureter L
- ◯ Distal ureter L
- ◯ Bladder R
- ◯ Bladder center
- ◯ Bladder L
- ◯ Urethra
- ◯ Ovary R
- ◯ Ovary L
- ◯ Fallopian tube R
- ◯ Fallopian tube L
- ◯ Corpus uteri
- ◯ Cervix
- ◯ Vagina
- ◯ Other

BEFORE fluorescence

- ◯ Malignant / Certain
- ◯ Malignant / Probably
- ◯ Malignant / Uncertain
- ◯ Benign / Uncertain
- ◯ Benign / Probably
- ◯ Benign / Certain

AFTER fluorescence

- ◯ Malignant / Certain
- ◯ Malignant / Probably
- ◯ Malignant / Uncertain
- ◯ Benign / Uncertain
- ◯ Benign / Probably
- ◯ Benign / Certain

A photograph was taken?

- ◯ Yes
- ◯ No

Lesion number 7

Location

◯ Lung/Thorax R (including pleura)
◯ Lung/Thorax L (including pleura)
◯ Heart and pericardium
◯ Diaphragm R
◯ Diaphragm center
◯ Diaphragm L
◯ Liver R
◯ Liver L
◯ Gallbladder
◯ Spleen
◯ Lesser omentum
◯ Greater omentum
◯ Paracolic gutter R (upper half)
◯ Paracolic gutter R (lower half)
◯ Paracolic gutter L (upper half)
◯ Paracolic gutter L (lower half)
◯ Oesophagus
◯ Stomach
◯ Duodenum
◯ Upper jejunum
◯ Lower jejunum
◯ Upper lieum
◯ Lower ileum
◯ Caecum
◯ Ascending colon
◯ Transverse colon
◯ Descending colon
◯ Sigmoid
◯ Rectum
◯ Pancreatic head
◯ Pancreatic tail
◯ Anterior Douglas space
◯ Posterior pelvic peritoneum R
◯ Posterior pelvic peritoneum center
◯ Posterior pelvic peritoneum L
◯ Kidney (capsula) R
◯ Kidney (capsula) L
◯ Proximal ureter R
◯ Distal ureter R
◯ Proximal ureter L
◯ Distal ureter L
◯ Bladder R
◯ Bladder center
◯ Bladder L
◯ Urethra
◯ Ovary R
◯ Ovary L
◯ Fallopian tube R
◯ Fallopian tube L
◯ Corpus uteri
◯ Cervix
◯ Vagina
◯ Other

BEFORE fluorescence

◯ Malignant / Certain
◯ Malignant / Probably
◯ Malignant / Uncertain
◯ Benign / Uncertain
◯ Benign / Probably
◯ Benign / Certain

AFTER fluorescence

- ◯ Malignant / Certain
- ◯ Malignant / Probably
- ◯ Malignant / Uncertain
- ◯ Benign / Uncertain
- ◯ Benign / Probably
- ◯ Benign / Certain

A photograph was taken?

- ◯ Yes
- ◯ No

Lesion number 8

Location

◯ Lung/Thorax R (including pleura)
◯ Lung/Thorax L (including pleura)
◯ Heart and pericardium
◯ Diaphragm R
◯ Diaphragm center
◯ Diaphragm L
◯ Liver R
◯ Liver L
◯ Gallbladder
◯ Spleen
◯ Lesser omentum
◯ Greater omentum
◯ Paracolic gutter R (upper half)
◯ Paracolic gutter R (lower half)
◯ Paracolic gutter L (upper half)
◯ Paracolic gutter L (lower half)
◯ Oesophagus
◯ Stomach
◯ Duodenum
◯ Upper jejunum
◯ Lower jejunum
◯ Upper lieum
◯ Lower ileum
◯ Caecum
◯ Ascending colon
◯ Transverse colon
◯ Descending colon
◯ Sigmoid
◯ Rectum
◯ Pancreatic head
◯ Pancreatic tail
◯ Anterior Douglas space
◯ Posterior pelvic peritoneum R
◯ Posterior pelvic peritoneum center
◯ Posterior pelvic peritoneum L
◯ Kidney (capsula) R
◯ Kidney (capsula) L
◯ Proximal ureter R
◯ Distal ureter R
◯ Proximal ureter L
◯ Distal ureter L
◯ Bladder R
◯ Bladder center
◯ Bladder L
◯ Urethra
◯ Ovary R
◯ Ovary L
◯ Fallopian tube R
◯ Fallopian tube L
◯ Corpus uteri
◯ Cervix
◯ Vagina
◯ Other

BEFORE fluorescence

◯ Malignant / Certain
◯ Malignant / Probably
◯ Malignant / Uncertain
◯ Benign / Uncertain
◯ Benign / Probably
◯ Benign / Certain

AFTER fluorescence

- ◯ Malignant / Certain
- ◯ Malignant / Probably
- ◯ Malignant / Uncertain
- ◯ Benign / Uncertain
- ◯ Benign / Probably
- ◯ Benign / Certain

A photograph was taken?

- ◯ Yes
- ◯ No

Lesion number 9

Location

- ◯ Lung/Thorax R (including pleura)
- ◯ Lung/Thorax L (including pleura)
- ◯ Heart and pericardium
- ◯ Diaphragm R
- ◯ Diaphragm center
- ◯ Diaphragm L
- ◯ Liver R
- ◯ Liver L
- ◯ Gallbladder
- ◯ Spleen
- ◯ Lesser omentum
- ◯ Greater omentum
- ◯ Paracolic gutter R (upper half)
- ◯ Paracolic gutter R (lower half)
- ◯ Paracolic gutter L (upper half)
- ◯ Paracolic gutter L (lower half)
- ◯ Oesophagus
- ◯ Stomach
- ◯ Duodenum
- ◯ Upper jejunum
- ◯ Lower jejunum
- ◯ Upper lieum
- ◯ Lower ileum
- ◯ Caecum
- ◯ Ascending colon
- ◯ Transverse colon
- ◯ Descending colon
- ◯ Sigmoid
- ◯ Rectum
- ◯ Pancreatic head
- ◯ Pancreatic tail
- ◯ Anterior Douglas space
- ◯ Posterior pelvic peritoneum R
- ◯ Posterior pelvic peritoneum center
- ◯ Posterior pelvic peritoneum L
- ◯ Kidney (capsula) R
- ◯ Kidney (capsula) L
- ◯ Proximal ureter R
- ◯ Distal ureter R
- ◯ Proximal ureter L
- ◯ Distal ureter L
- ◯ Bladder R
- ◯ Bladder center
- ◯ Bladder L
- ◯ Urethra
- ◯ Ovary R
- ◯ Ovary L
- ◯ Fallopian tube R
- ◯ Fallopian tube L
- ◯ Corpus uteri
- ◯ Cervix
- ◯ Vagina
- ◯ Other

BEFORE fluorescence

- ◯ Malignant / Certain
- ◯ Malignant / Probably
- ◯ Malignant / Uncertain
- ◯ Benign / Uncertain
- ◯ Benign / Probably
- ◯ Benign / Certain

AFTER fluorescence

- ◯ Malignant / Certain
- ◯ Malignant / Probably
- ◯ Malignant / Uncertain
- ◯ Benign / Uncertain
- ◯ Benign / Probably
- ◯ Benign / Certain

A photograph was taken?

- ◯ Yes
- ◯ No

Lesion number 10

Location

◯ Lung/Thorax R (including pleura)
◯ Lung/Thorax L (including pleura)
◯ Heart and pericardium
◯ Diaphragm R
◯ Diaphragm center
◯ Diaphragm L
◯ Liver R
◯ Liver L
◯ Gallbladder
◯ Spleen
◯ Lesser omentum
◯ Greater omentum
◯ Paracolic gutter R (upper half)
◯ Paracolic gutter R (lower half)
◯ Paracolic gutter L (upper half)
◯ Paracolic gutter L (lower half)
◯ Oesophagus
◯ Stomach
◯ Duodenum
◯ Upper jejunum
◯ Lower jejunum
◯ Upper lieum
◯ Lower ileum
◯ Caecum
◯ Ascending colon
◯ Transverse colon
◯ Descending colon
◯ Sigmoid
◯ Rectum
◯ Pancreatic head
◯ Pancreatic tail
◯ Anterior Douglas space
◯ Posterior pelvic peritoneum R
◯ Posterior pelvic peritoneum center
◯ Posterior pelvic peritoneum L
◯ Kidney (capsula) R
◯ Kidney (capsula) L
◯ Proximal ureter R
◯ Distal ureter R
◯ Proximal ureter L
◯ Distal ureter L
◯ Bladder R
◯ Bladder center
◯ Bladder L
◯ Urethra
◯ Ovary R
◯ Ovary L
◯ Fallopian tube R
◯ Fallopian tube L
◯ Corpus uteri
◯ Cervix
◯ Vagina
◯ Other

BEFORE fluorescence

◯ Malignant / Certain
◯ Malignant / Probably
◯ Malignant / Uncertain
◯ Benign / Uncertain
◯ Benign / Probably
◯ Benign / Certain

AFTER fluorescence

- ◯ Malignant / Certain
- ◯ Malignant / Probably
- ◯ Malignant / Uncertain
- ◯ Benign / Uncertain
- ◯ Benign / Probably
- ◯ Benign / Certain

A photograph was taken?

- ◯ Yes
- ◯ No

STEP 2: TOPOGRAPHIC MAP ABDOMEN

Was the topographic map used?

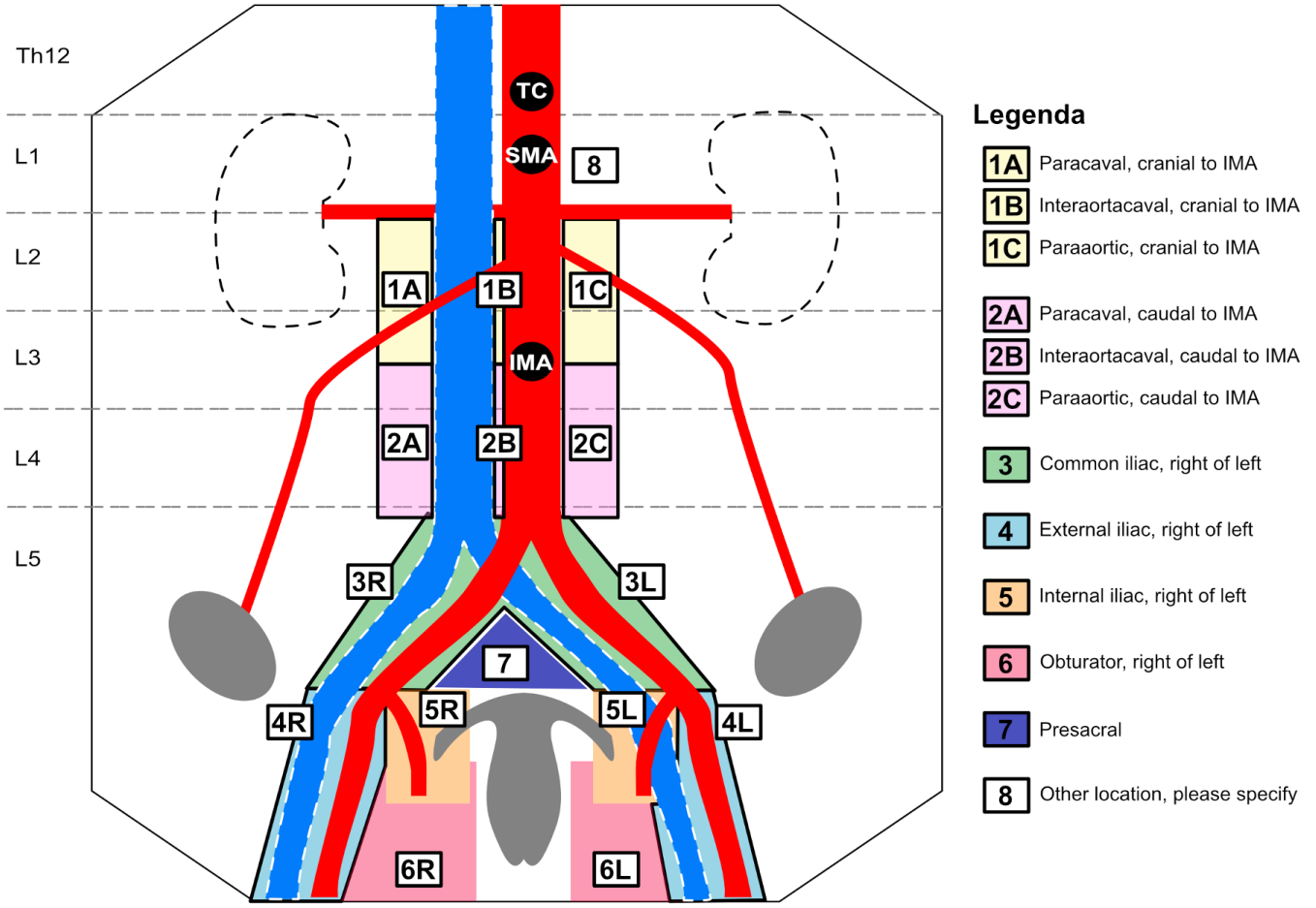
- ◯ Yes
- ◯ No

STEP 3: EXPLORE THE ABDOMEN

	Without fluorescence	With fluorescence
Pelvis	☐	☐
Omentum	☐	☐
Mesentery	☐	☐
Right paracolic gutter	☐	☐
Right-sided diaphragm	☐	☐

STEP 4: EXPLORE PELVIC AND PARA-AORTIC RETROPERITONEAL SPACE

Please indicate the lymph nodes with the number correlating with the lymph node localiser



	Macroscopically suspicious	Fluorescence positive	Both macroscopically suspicious and fluorescence positive	Not indicated
1A				
1B				
1C				
2A				
2B				
2C				
3R				
3L				
4R				
4L				

5R

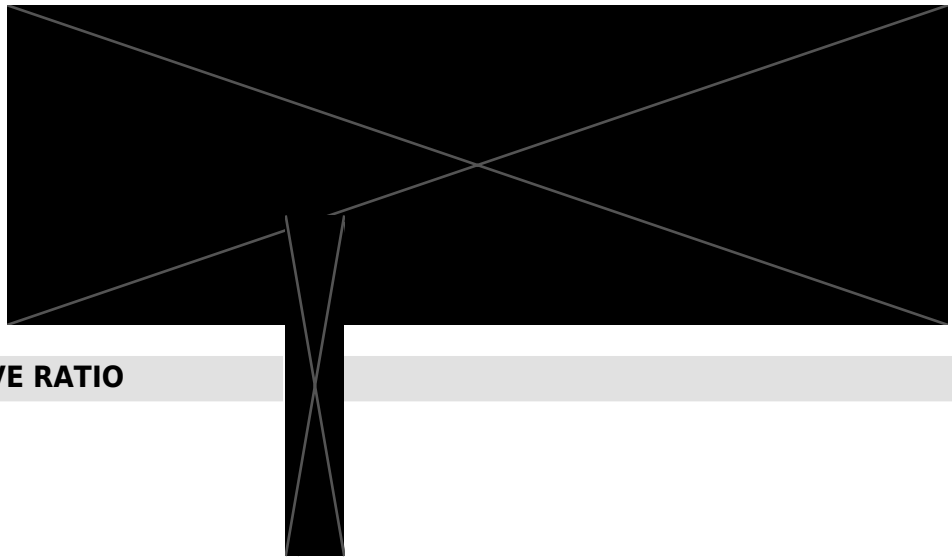
5L

6R

6L

7

8



STEP 5: FLUORESCENCE POSITIVE RATIO

Fluorescence positive ratio

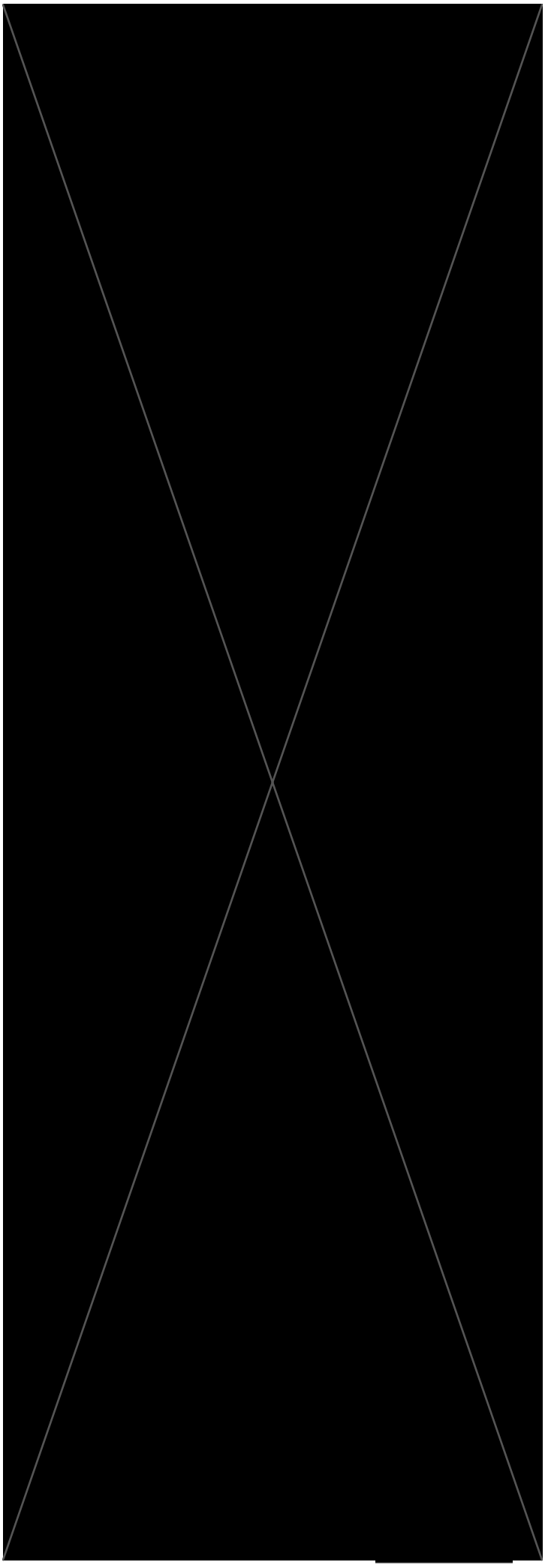
Postoperative

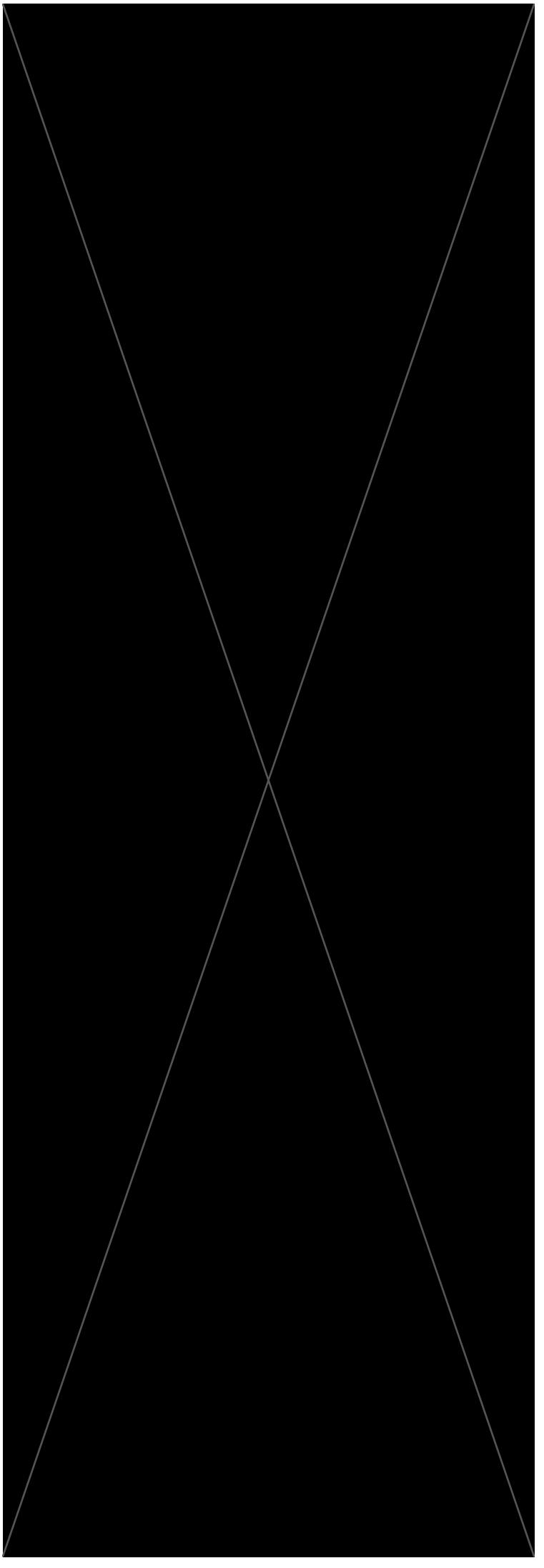
POSTOPERATIVE DIAGNOSIS

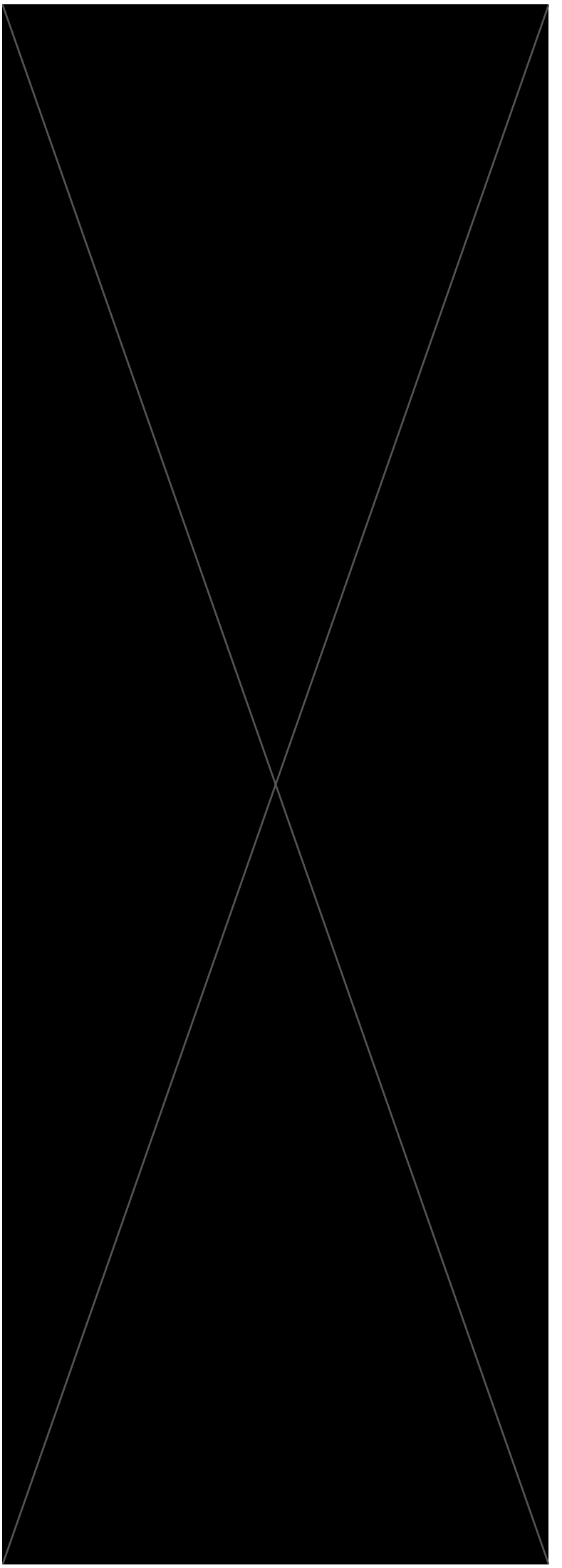
Did the final pathology show HGSOC?	[redacted] es No
FIGO stage postoperatively?	[redacted] IIIb IIIc IV
Was the preoperative FIGO stage correct comparing to the postoperative one?	[redacted] es No
Reason for incorrect preoperative staging?	[redacted]

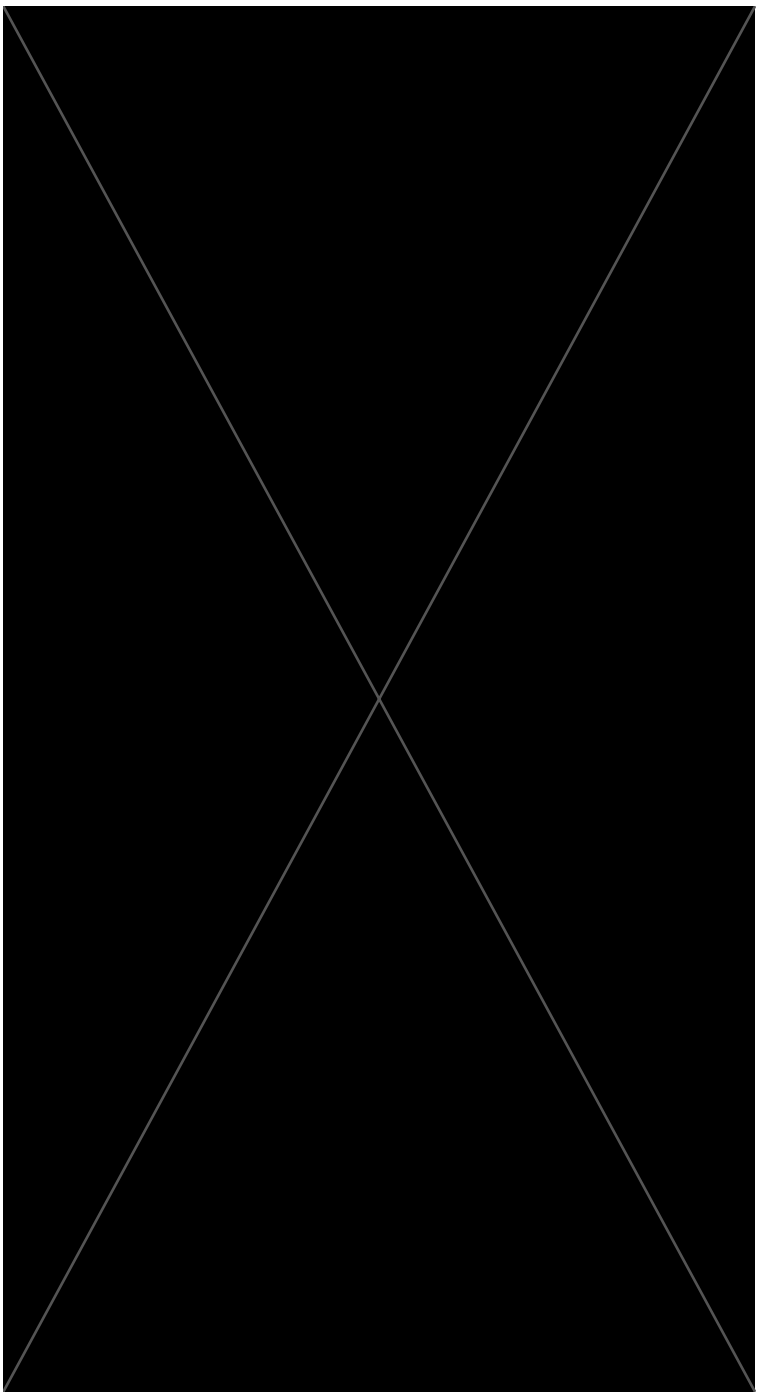
PATHOLOGY

Validated pathology report









Lesion number 1: Paracolic gutter L (lower half)

Did pathology report of LESION 1 show malignancy?

- ◯ Yes
- ◯ No

Correct assement of the lesion BEFORE fluorescence? 0

Correct assement of the lesion AFTER fluorescence? 0

What did the pathology report of LESION 1 show?

- ◯ Fibrotic tissue
- ◯ No clear malignancy proven
- ◯ Normal peritoneal tissue
- ◯ N/A, not peritoneal tissue
- ◯ Other

Lesion number 2: Paracolic gutter R (lower half)

Did pathology report of LESION 2 show malignancy?
- ◯ Yes
- ◯ No

Correct assement of the lesion BEFORE fluorescence? 1

Correct assement of the lesion AFTER fluorescence? 0

What did the pathology report of LESION 2 show?
- ◯ Fibrotic tissue
- ◯ No clear malignancy proven
- ◯ Normal peritoneal tissue
- ◯ N/A, not peritoneal tissue
- ◯ Other

Lesion number 3: Greater omentum

Did pathology report of LESION 3 show malignancy?
- ◯ Yes
- ◯ No

Correct assement of the lesion BEFORE fluorescence? 1

Correct assement of the lesion AFTER fluorescence? 1

Lesion number 4: Diaphragm R

Did pathology report of LESION 4 show malignancy?
- ◯ Yes
- ◯ No

Correct assement of the lesion BEFORE fluorescence? 1

Correct assement of the lesion AFTER fluorescence? 1

What did the pathology report of LESION 4 show?
- ◯ Fibrotic tissue
- ◯ No clear malignancy proven
- ◯ Normal peritoneal tissue
- ◯ N/A, not peritoneal tissue
- ◯ Other

Please add details concerning pathology report of LESION 4 [redacted]

Lesion number 5: Lesser omentum

Did pathology report of LESION 5 show malignancy?
- ◯ Yes
- ◯ No

Correct assement of the lesion BEFORE fluorescence? 0

Correct assement of the lesion AFTER fluorescence? 0

What did the pathology report of LESION 5 show?

- ◯ Fibrotic tissue
- ◯ No clear malignancy proven
- ◯ Normal peritoneal tissue
- ◯ N/A, not peritoneal tissue
- ◯ Other

Please add details concerning pathology report of LESION 5

[redacted]

Lesion number 6: Transverse colon

Did pathology report of LESION 6 show malignancy?

- ◯ Yes
- ◯ No

Correct assement of the lesion BEFORE fluorescence? 1

Correct assement of the lesion AFTER fluorescence? 1

Lesion number 7: Lesser omentum

Did pathology report of LESION 7 show malignancy?

- ◯ Yes
- ◯ No

Correct assement of the lesion BEFORE fluorescence? 1

Correct assement of the lesion AFTER fluorescence? 1

What did the pathology report of LESION 7 show?

- ◯ Fibrotic tissue
- ◯ No clear malignancy proven
- ◯ Normal peritoneal tissue
- ◯ N/A, not peritoneal tissue
- ◯ Other

Please add details concerning pathology report of LESION 7

[redacted]

Lesion number 8: Caecum

Did pathology report of LESION 8 show malignancy?

- ◯ Yes
- ◯ No

Correct assement of the lesion BEFORE fluorescence? 1

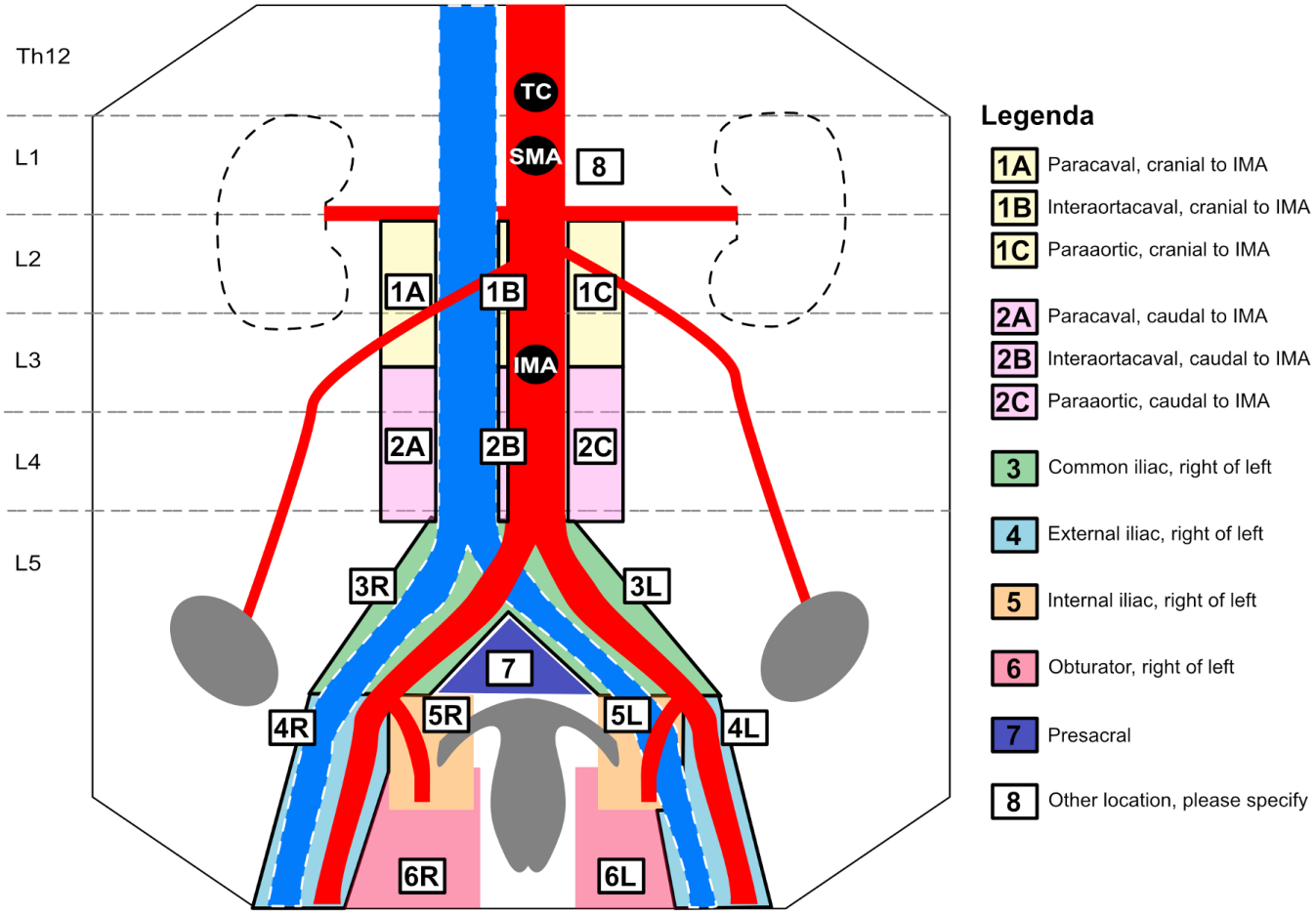
Correct assement of the lesion AFTER fluorescence? 1

Lesion number 9: Lower jejunum

Did pathology report of LESION 9 show malignancy?	◯ Yes ◯ No
Correct assement of the lesion BEFORE fluorescence?	0
Correct assement of the lesion AFTER fluorescence?	0
What did the pathology report of LESION 9 show?	◯ Fibrotic tissue ◯ No clear malignancy proven ◯ Normal peritoneal tissue ◯ N/A, not peritoneal tissue ◯ Other

Lesion number 10: Other

Did pathology report of LESION 10 show malignancy?	◯ Yes ◯ No
Correct assement of the lesion BEFORE fluorescence?	0
Correct assement of the lesion AFTER fluorescence?	0
What did the pathology report of LESION 10 show?	◯ Fibrotic tissue ◯ No clear malignancy proven ◯ Normal peritoneal tissue ◯ N/A, not peritoneal tissue ◯ Other



LYMPH NODES

Did pathology report show malignancy?

	No	Yes
1A	○	○
1B	○	○
1C	○	○
2A	○	○
2B	○	○
2C	○	○
3R	○	○
3L	○	○
4R	○	○
4L	○	○

5R	◯	◯
5L	◯	◯
6R	◯	◯
6L	◯	◯
7	◯	◯
8	◯	◯

End of Trial

END OF TRIAL

Date End of Trial study visit [redacted]

Primary reason for trial participation termination

- ◯ Subject completed study as per protocol
- ◯ Physician decision
- ◯ Subject decision (withdrew consent)
- ◯ Lost contact with subject
- ◯ Adverse Event
- ◯ Death
- ◯ Protocol violation(s)
- ◯ IMP not administered
- ◯ Participant was recruited but never enrolled in trial (failed recruitment)
- ◯ Other

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Concomitant Therapy

Total number of pages 1

By selecting "True", the concomitant medication of the Participant has been checked AT THIS MOMENT IN TIME and no changes were made in comparison with last concomitant medication log
◯ True
◯ False

IMPORTANT: Please, list all medication / non-drug therapy taken by the subject while participating in the study

When adding NEW drug, please fill in all fields
When CHANGING existing drug, please only fill in name and changed fields
When REMOVING drug, please only fill in name

Generic medication name

_____
(ATC code)

If no ATC code is avaiable, please fill in drug name

_____

Reason for concomitant therapy
◯ Pre-existing condition
◯ Adverse event
◯ Other

Start date

_____

Stop date

_____

☐ ongoing

Dose per administration

_____

Dose unit
◯ mg
◯ g
◯ ml
◯ cl
◯ IU
◯ Appl
◯ dr
◯ %
◯ Other

Frequency (times per x)

_____

Frequency unit

◯ /day
◯ /2 days
◯ /3 days
◯ /4 days
◯ /5 days
◯ /6 days
◯ /week
◯ /10 days
◯ /2 weeks
◯ /3 weeks
◯ /4 weeks
◯ /21 days
◯ /28 days
◯ /month
◯ /2 months
◯ /3 months
◯ /4 months
◯ /5 months
◯ /half year
◯ /year
◯ /1.5 year
◯ /2 years
◯ /only occasionally
◯ /only when indicated
◯ other

Concomitant Therapy

Total number of pages 1

By selecting "True", the concomitant medication of the Participant has been checked AT THIS MOMENT IN TIME and no changes were made in comparison with last concomitant medication log
◯ True
◯ False

IMPORTANT: Please, list all medication / non-drug therapy taken by the subject while participating in the study

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_____
(ATC code)

If no ATC code is avaiable, please fill in drug name

_____

Reason for concomitant therapy
◯ Pre-existing condition
◯ Adverse event
◯ Other

Start date

_____

Stop date

_____

☐ ongoing

Dose per administration

_____

Dose unit
◯ mg
◯ g
◯ ml
◯ cl
◯ IU
◯ Appl
◯ dr
◯ %
◯ Other

Frequency (times per x)

_____

Frequency unit

- ◯ /day
- ◯ /2 days
- ◯ /3 days
- ◯ /4 days
- ◯ /5 days
- ◯ /6 days
- ◯ /week
- ◯ /10 days
- ◯ /2 weeks
- ◯ /3 weeks
- ◯ /4 weeks
- ◯ /21 days
- ◯ /28 days
- ◯ /month
- ◯ /2 months
- ◯ /3 months
- ◯ /4 months
- ◯ /5 months
- ◯ /half year
- ◯ /year
- ◯ /1.5 year
- ◯ /2 years
- ◯ /only occasionally
- ◯ /only when indicated
- ◯ other

Adverse Events

Number of pages 1

ADVERSE EVENTS
Definition of 'ADVERSE EVENT' (AE): any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relation with this treatment.

Any SERIOUS adverse event (SAE) must be reported within 24 hours of awareness.

Definition of 'SERIOUS adverse event':
A serious adverse event (SAE) is any event that:

Results in death Is life-threatening Requires inpatient hospitalisation or prolongation of existing hospitalisation Results in persistent or significant disability or incapacity Is a congenital anomaly or birth defect Is an important medical event

Legend for severity of AE :

- Mild: aware of symptom but easily tolerated
- Moderate: discomfort causing interference with usual activity
- Severe: incapacitating with inability to work or to do usual activity

Did ANY adverse event occur?
◯ Yes
◯ No

Describe Event
_____

Was the event a surgical complication?
◯ Yes
◯ No

Enter the CTCAE term
_____

Please enter CTCAE grade

- 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 Activities of Daily Living (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.

◯ Grade 1
◯ Grade 2
◯ Grade 3
◯ Grade 4
◯ Grade 5

MedDRA LLT

_____
(Most recent version of MedDRA dictionary is uploaded automatically during routine system updates)

Start date

_____

Stop date

_____

Outcome

◯ Recovered
◯ Recovered with sequelae
◯ Not yet recovered
◯ Fatal

Action taken

☐ No action taken
☐ Medication
☐ Non-drug therapy
☐ Further investigation performed
☐ Stop study participation due to AE
☐ Other

Action taken regarding study treatment

☐ No action taken
☐ Temporarily interrupted
☐ Stopped permanently, not administered
☐ Other
☐ N/a (study treatment not started yet)

Investigator's assessment

Seriousness

Serious AE?

◯ Yes
◯ No

Severity

Severity

◯ Mild
◯ Moderate
◯ Severe

Causality to study treatment/IMP

Dose of the IMP (in mg)

_____

Causality

◯ Not Related
◯ Unlikely
◯ Possibly
◯ Probably
◯ Definitely
◯ Unknown

Causality to study procedure

Causality to study procedure?

◯ Yes
◯ No
◯ Unknown
(Study procedure = a procedure performed specifically for the study, outside the standard of care)

Any other comments

_____

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