

UC Davis

UC Davis Previously Published Works

Title

Veterinary Cooperative Oncology Group-Common Terminology Criteria for Adverse Events (VCOG-CTCAE v2) following investigational therapy in dogs and cats.

Permalink

<https://escholarship.org/uc/item/1jc6g3s3>

Journal

Veterinary and comparative oncology, 19(2)

ISSN

1476-5810

Authors

LeBlanc, Amy K
Atherton, Matthew
Bentley, R Timothy
et al.

Publication Date

2021-06-01

DOI

10.1111/vco.12677







Copyright Information

This work is made available under the terms of a Creative Commons Attribution-NonCommercial-NoDerivatives License, available at <https://creativecommons.org/licenses/by-nc-nd/4.0/>

Peer reviewed

ORIGINAL ARTICLE

Veterinary Cooperative Oncology Group—Common Terminology Criteria for Adverse Events (VCOG-CTCAE v2) following investigational therapy in dogs and cats

Amy K. LeBlanc¹  | Matthew Atherton²  | R. Timothy Bentley^{3,4} |
 C. Elizabeth Boudreau⁵ | Jenna H. Burton⁶  | Kaitlin M. Curran⁷ | Steven Dow⁶ |
 Michelle A. Giuffrida⁸ | Heidi B. Kellihan⁹ | Nicola J. Mason^{10,11,12}  |
 Michelle Oblak¹³  | Laura E. Selmic¹⁴  | Kimberly A. Selting¹⁵  |
 Ameet Singh¹³ | Sonja Tjostheim⁹ | David M. Vail⁹ | Kristen M. Weishaar⁶  |
 Erika P. Berger¹⁶ | John H. Rossmeisl¹⁷ | Christina Mazcko¹

¹National Cancer Institute, National Institutes of Health, Comparative Oncology Program, Center for Cancer Research, Bethesda, Maryland

²Department of Biomedical Sciences, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

³Department of Veterinary Clinical Sciences, Purdue University, West Lafayette, Indiana

⁴Purdue University Center for Cancer Research, Purdue University, West Lafayette, Indiana

⁵Department of Small Animal Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, College Station, Texas

⁶Animal Cancer Center, Department of Clinical Sciences, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Ft. Collins, Colorado

⁷Department of Clinical Sciences, Carlson College of Veterinary Medicine, Oregon State University, Corvallis, Oregon

⁸Department of Surgical and Radiological Sciences, Davis School of Veterinary Medicine, University of California, Davis, California

⁹Department of Medical Sciences, School of Veterinary Medicine, University of Wisconsin, Madison, Wisconsin

¹⁰Department of Clinical Sciences and Advanced Medicine, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

¹¹Department of Pathobiology, School of Veterinary Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

¹²Parker Institute for Cancer Immunotherapy, University of Pennsylvania, Philadelphia, Pennsylvania

¹³Department of Clinical Studies, Ontario Veterinary College, University of Guelph, Guelph, Ontario, Canada

¹⁴Department of Veterinary Clinical Sciences, College of Veterinary Medicine, The Ohio State University, Columbus, Ohio

¹⁵Department of Veterinary Clinical Medicine, College of Veterinary Medicine, University of Illinois at Urbana-Champaign, Urbana, Illinois

¹⁶Frederick National Laboratory for Cancer Research in the Comparative Oncology Program, National Cancer Institute, Bethesda, Maryland

¹⁷Department of Small Animal Clinical Sciences, VA-MD College of Veterinary Medicine, Blacksburg, Virginia

Correspondence

Amy K. LeBlanc, Comparative Oncology Program, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892.
 Email: amy.leblanc@nih.gov

Funding information

This work was also supported (AKL and CM) by the Intramural Program of the National Cancer Institute, NIH (Z01-BC006161). This project has been funded (EPB) in whole or in part with Federal funds from the National Cancer

Abstract

The updated VCOG-CTCAE v2 guidelines contain several important updates and additions since the last update (v1.1) was released in 2011 and published within *Veterinary and Comparative Oncology* in 2016. As the Veterinary Cooperative Oncology Group (VCOG) is no longer an active entity, the original authors and contributors to the VCOG-CTCAE v1.0 and v1.1 were consulted for input, and additional co-authors sought for expansion and refinement of the adverse event (AE) categories. VCOG-CTCAE v2 includes expanded neurology, cardiac and immunologic AE sections, and

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2021 The Authors. *Veterinary and Comparative Oncology* published by John Wiley & Sons Ltd. This article has been contributed to by US Government employees and their work is in the public domain in the USA.

Institute, National Institutes of Health, Grant/
Award Number: HHSN261201800001I

the addition of procedural-specific AEs. It is our intent that, through inclusion of additional authors from ACVIM subspecialties and the American College of Veterinary Surgery, that we can more comprehensively capture AEs that are observed during clinical studies conducted across a variety of disease states, clinical scenarios, and body systems. It is also our intent that these updated veterinary CTCAE guidelines will offer improved application and ease of use within veterinary practice in general, as well as within clinical trials that assess new therapeutic strategies for animals with a variety of diseases. Throughout the revision process, we strived to ensure the grading structure for each AE category was reflective of the decision-making process applied to determination of dose-limiting events. As phase I trial decisions are based on these criteria and ultimately determine the maximally tolerated dose, there is impact on standard dosing recommendations for any new drug registration or application. This document should be updated regularly to reflect ongoing application to clinical studies carried out in veterinary patients.

KEYWORDS

adverse events, clinical trials, comparative oncology, investigational therapy, small animal

Quick Reference : The VCOG-CTCAE is a descriptive terminology, which can be used for adverse event (AE) reporting in dogs and cats. A grading (severity) scale is provided for each AE term.

Components and Organization :

AE and grades apply to both cats and dogs unless otherwise stated.

CATEGORY

A CATEGORY is a broad classification of AEs based on anatomy and/or pathophysiology. Within each CATEGORY, AEs are listed accompanied by their descriptions of severity (Grade).

Adverse Event Terms

An AE is any unfavourable and unintended sign (including an abnormal clinicopathologic finding), clinical sign, or disease temporally associated with the use of a medical treatment that may or may *not* be considered related to the medical treatment (see **ATTRIBUTION** below). An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses. AEs are listed alphabetically within CATEGORIES. For several AEs, a definition is provided and highlighted in grey within the tables.

Grades

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

Grade 1	Mild; asymptomatic or mild symptoms; clinical signs or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; outpatient or non-invasive intervention indicated; moderate limitation of Activities of Daily Living (ADL).
Grade 3	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; significantly limiting Activities of Daily Living (ADL).

Grade 4	Life-threatening consequences; urgent interventions indicated
Grade 5	Death related to AE Death can be defined as either euthanasia or natural death, according to the investigators' discretion.

Further comments

- A Semi-colon indicates “or” within the description of the grade. When items within the description of the grade are separated by a comma, the “;” means “and.” All items separated by a comma are necessary to establish that grade level.
- An “—” 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 (Death) is not appropriate for some AEs and therefore is not listed as an option.
- Dose-limiting toxicities (DLTs) are defined a priori by study investigators on a per-protocol basis
- CTCAE definitions and criteria for hypothermia, fever, cardiac arrhythmias and bradycardia can also be applied to anaesthetized patients as appropriate for recording of events that occur under anaesthesia.

Abbreviations used

- ADL = activities of daily living (eating, drinking, sleeping, defecating and urinating)
- BSA = body surface area
- CHF = congestive heart failure
- LLN = lower limit of normal

- ULN = upper limit of normal

AE ATTRIBUTION: There exist several potential causes of AEs, including the protocol intervention under assessment, pre-existing conditions (eg, liver disease with associated liver enzyme abnormalities, diabetes), progression of disease being treated, concomitant medications (eg, steroids) and other causes (eg, transfusion reactions, accidental injuries). Documenting and grading an AE simply reports that an event has occurred and the seriousness of the event. To be complete the clinician should assign attribution of the AE, either to the intervention or something else. Attribution of an event can be possibly due to one or more concomitant disease process. Designating an event as treatment related (or not) can be done in two ways:

1. By the treating clinician at the time of clinical evaluation.
2. By Investigators, usually occurring later in aggregate data review and reporting by the Investigators

Attribution standards are divided into 5 categories :

1. Unrelated: The Adverse Event is *clearly not related* to the investigational agent(s)
2. Unlikely: The Adverse Event is *doubtfully related* to the investigational agent(s)
3. Possible: The Adverse Event *may be related* to the investigational agent(s)
4. Probable: The Adverse Event is *likely related* to the investigational agent(s)
5. Definite: The Adverse Event is *clearly related* to the investigational agent(s)

ADMINISTRATION SITE CONDITIONS					
Grade					
Adverse Event	1	2	3	4	5
Infusion site extravasation/ reaction	Swelling including oedema but without erythema or pain	Erythema with associated signs (eg, oedema, pain, swelling induration, phlebitis)	Ulceration or necrosis; severe tissue damage; surgical intervention indicated (such as soft tissue debridement and repair)	Life-threatening consequences (euthanasia will be performed without intervention), primarily wound that shows no evidence of healing or improvement over 2 weeks; urgent and extreme intervention indicated (such as limb amputation)	Death
Definition: A disorder characterized by leakage of a pharmacologic or a biologic substance from the infusion site into the surrounding tissue. Signs include induration, erythema, swelling and marked discomfort at the infusion site.					
Other (specify, -----)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate 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
ALLERGIC/IMMUNOLOGIC EVENT					
Grade					
Adverse Event	1	2	3	4	5
Allergic reaction/ hypersensitivity	Transient urticaria or rash distant from injection/infusion site; drug fever; intervention not indicated	Intervention or infusion interruption indicated; responds promptly to treatment (eg, antihistamines, NSAIDs, narcotics); prophylactic medications indicated	Prolonged (eg, not rapidly responsive to medication and/or brief interruption of infusion); recurrence of signs following initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrates or oedema)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Anaphylaxis	—	—	Bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related oedema/ 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, hypotension, cyanosis and loss of consciousness and may lead to death.					
Autoimmune disorder	Subclinical and serologic or other evidence of autoimmune reaction, with normal organ function and intervention not indicated.	Evidence of autoimmune reaction involving a non-essential organ or function (eg, hypothyroidism)	Reversible reaction involving function of a major organ or other adverse event (eg, transient colitis or anaemia)	Autoimmune reaction with life-threatening consequences	Death
Definition: A disorder resulting from loss of function or tissue destruction of an organ or multiple organs, arising from humoral or cellular immune responses of the individual to their own tissue constituents.					
Cytokine release syndrome	Fever (>39.5°C/103.5°F) with or without constitutional signs	Hospitalization for observation and supportive care without requirement for	Life-threatening consequences; urgent	Life-threatening consequences; urgent	Death

ALLERGIC/IMMUNOLOGIC EVENT

Grade	
Adverse Event	1
	2
	3
	4
	5

pressors or oxygen supplementation; hypotension managed with one pressor; hypoxia requiring non-invasive oxygen support (flow-by/prongs/mask/oxygen cage) intervention required; hypoxia requiring mechanical ventilation

Definition: A disorder characterized by fever, depression, tachypnea, tachycardia, hypotension, rash and/or hypoxia caused by the release of cytokines.

Serum sickness
Clinical or diagnostic observations only; intervention not indicated
Moderate arthralgia; fever, rash, urticaria, or IV fluids 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 6-21 days following the administration of the foreign antigen. Signs include fever, arthralgias, myalgias, skin eruptions, lymphadenopathy and dyspnoea.

Other (specify, -----)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate 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
------------------------	---	---	---	--	-------

BLOOD/BONE MARROW

Grade	
Adverse Event	1
	2
	3
	4
	5

Mildly hypocellular; <25% reduction from normal cellularity for age
Moderately hypocellular; >25-<50% reduction from normal cellularity for age
Severely hypocellular; >50-<75% reduction of cellularity from normal for age
Aplastic persistent for longer than 2 weeks

Definition: A disorder characterized by the inability of the bone marrow to produce haematopoietic elements.

Haemoglobin
Dog: 10 g/dL-<LLN
Cat: 8.0 g/dL-<LLN
Dog: <10-8.0 g/dL
Cat: <8.0-6.5 g/dL
Dog: <8.0-6.5 g/dL
Cat: <6.5-5.0

Haemolysis
Laboratory evidence of haemolysis only (eg, direct antiglobulin test; DAT; Coombs'; schistocytes and/or spherocytes present)
Evidence of haemolysis and ≥2 g decrease in haemoglobin.
Transfusion or medical intervention indicated (eg, steroids)
Life-threatening consequences; urgent intervention indicated
Death

Definition: A disorder characterized by laboratory test results that indicate widespread erythrocyte cell membrane destruction.

Lymphocytosis	>4000/ μ L 20 000/ μ L	>20 000/ μ L	Clinical manifestations of leucostasis; urgent intervention indicated	Death
---------------	-----------------------------------	------------------	---	-------

(Continues)

BLOOD/BONE MARROW	
Adverse Event	Grade
Packed cell volume (PCV)	<p>1 Dog: 30%-<LLN Cat: 25%-<LLN</p> <p>2 Dog: 20-<30% Cat: 20-<25% Transfusion indicated</p> <p>3 Dog: 15-<20% Cat: 15-<20% Transfusion indicated</p> <p>4 Dog: <15% Cat: <15% Life threatening; urgent medical intervention indicated</p> <p>5 Death</p>
Neutropenia	1500/ μ L-<LLN
Neutrophilia	1000-1499/ μ L >100 000/ μ L
Thrombocytopenia (no clinical bleeding)	100 000/ μ L-<LLN 50 000-99 000/ μ L 25 000-49 000/ μ L
Thrombocytopenia— with clinical bleeding	—
Other (specify, _____)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate 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
	Life-threatening bleeding prompting urgent medical intervention
	Death

LLN, lower limit of normal.

BODY CAVITY	
Adverse Event	Grade
Abdominal pain	<p>1 Mild pain</p> <p>2 Moderate pain; limiting ADL</p> <p>3 Severe pain; limiting ADL</p> <p>4 —</p> <p>5 —</p>
Ascites	<p>Definition: A sensation of marked discomfort in the abdominal region.</p> <p>Clinical or diagnostic observations only; intervention not indicated</p> <p>Symptomatic; medical intervention indicated</p> <p>Severe symptoms; invasive intervention indicated</p> <p>Life-threatening consequences; urgent operative intervention indicated</p> <p>Death</p>

BODY CAVITY					
Grade					
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by accumulation of serous or haemorrhagic fluid in the peritoneal cavity.					
Hernia, non-diaphragmatic	Clinical or diagnostic observation only; intervention not indicated	Reducible, non-strangulating; elective intervention indicated	Incarcerated, symptomatic; operative intervention indicated	Life-threatening consequences; strangulating or necrotic; urgent intervention indicated	Death
Definition: Organ or tissue displacement through an opening in muscle or fascia of the body wall, scrotum, or inguinal, femoral or pelvic canals					
Hernia, hiatal	Clinical or diagnostic observation only; intervention not indicated	Symptomatic; medical management indicated	Symptomatic; operative intervention indicated	Severe symptoms; urgent intervention indicated	Death
Definition: Displacement of abdominal contents into the thorax through the oesophageal hiatus					
Hernia, diaphragmatic	—	Clinical or diagnostic observation with minimal or absent symptoms; incidental finding without recent history of trauma; elective intervention indicated	Symptomatic; operative intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: Displacement of abdominal contents into the thorax through an abnormal opening in the diaphragm muscle, fascia, or attachments to the body wall.					
Peritonitis (septic)	—	Symptomatic; medical management indicated	Hospitalization, IV antimicrobials indicated; invasive intervention indicated (eg, tube feeding, abdominal drainage, surgery)	Life-threatening consequences including organ system dysfunction; urgent operative intervention indicated	Death
Definition: Focal or generalized inflammation of the peritoneum attributed to microbial contamination.					
Peritonitis (non-septic)	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical management indicated	Hospitalization, invasive intervention indicated (eg, tube feeding, abdominal drainage, surgery)	Life-threatening consequences including organ system dysfunction; urgent intervention indicated	Death
Definition: Focal of generalized inflammation of the peritoneum attributed to non-microbial (sterile) aetiologies.					
Pleural effusion (non-malignant)	Asymptomatic	Symptomatic, intervention with diuretics or single thoracocentesis indicated	Symptomatic and supplemental oxygen, >1 thoracocenteses, continuous tube drainage or pleurodesis indicated	Life-threatening (eg, haemodynamic instability or ventilatory support)	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.					
Pleuritis (septic)	—	Symptomatic; medical management indicated	Hospitalization, IV antimicrobials indicated; invasive intervention indicated (eg, thoracic drainage or lavage, surgery)	Life-threatening consequences including organ system dysfunction; urgent operative intervention indicated	Death
Definition: Focal or generalized inflammation of the pleural cavity attributed to microbial contamination.					
Pneumothorax	Asymptomatic, radiographic findings only	Symptomatic, non-operative intervention indicated	Sclerosis and/or operative intervention indicated	Life-threatening, haemodynamic instability; ventilatory support	Death

(Continues)

BODY CAVITY		Grade				
Adverse Event	1	2	3	4	5	
Definition: A disorder characterized by abnormal presence of air in the pleural cavity resulting in the collapse of the lung.						
Other (specify, _____)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate 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	
CARDIAC ARRHYTHMIA						
Grade						
Adverse Event	1	2	3	4	5	
Supraventricular and junctional arrhythmias. <u>Select:</u>	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Incompletely controlled medically or controlled with device (eg, pacemaker)	Life-threatening (eg, arrhythmia associated with CHF [congestive heart failure], hypotension, syncope, shock)	Death	
- Sinus tachycardia						
- Atrial premature complexes (APCs)						
- APCs patterns (atrial bigeminy/trigeminy)						
- Focal atrial tachycardia						
- Multi-focal atrial tachycardia						
- Atrioventricular tachycardia mediated by accessory pathways (OAVRT [orthodromic atrioventricular reciprocating tachycardia], PJRT [persistent or permanent junctional reciprocating tachycardia])						
- Atrial flutter						
- Atrial fibrillation						
- Atrial parasystole						
- Junctional premature complexes (JPCs)						
- Junctional tachycardia						
- Other (specify, _____)						
Bradyarrhythmias. <u>Select:</u>	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Incompletely controlled medically or controlled with device (eg, pacemaker)	Life-threatening (eg, arrhythmia associated with CHF, hypotension, syncope, shock)	Death	
- Sinus bradycardia						
- Sinus arrest						
- Sinus node dysfunction (sick sinus syndrome)						
- Atrial standstill						
- Sino-ventricular rhythm						
- Ventricular asystole/arrest						
- Pulseless electrical activity; electromechanical dissociation						
Conduction abnormality/atrioventricular heart block. <u>Select:</u>	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Incompletely controlled medically or controlled with device (eg, pacemaker)	Life-threatening (eg, arrhythmia associated with CHF, hypotension, syncope, shock)	Death	
- AV block-first degree						
- AV block-second degree Mobitz I						
- AV block-second degree Mobitz II						

CARDIAC ARRHYTHMIA					
Grade					
Adverse Event	1	2	3	4	5
- AV block-second degree (2:1 conduction) - AV block-second degree (advanced) - AV block-third degree (complete) - Interventricular conduction disturbance (IVCD) - Bundle branch block (BBB) - Phasic (rate-dependent) aberrant conduction - Other (specify _____)					
Ventricular arrhythmias. <u>Select:</u> - VPCs (ventricular premature complexes)/uniform VPCs/multiform - VPC patterns (ventricular bigeminy/trigeminy) - Accelerated idioventricular rhythm - Monomorphic ventricular tachycardia - Polymorphic ventricular tachycardia - R on T ventricular tachycardia - Torsade de pointes - Ventricular fibrillation - Ventricular parasystole - Other (specify, _____)	Asymptomatic, intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (eg, pacemaker)	Life-threatening (eg, arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Other (specify, _____)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate 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
CARDIAC GENERAL					
Grade					
Adverse Event	1	2	3	4	5
Acquired valvular heart disease	Valvular thickening with or without mild valvular regurgitation or stenosis, treatment not indicated	Moderate regurgitation or stenosis by imaging, treatment not indicated	Severe regurgitation or stenosis controlled with medical therapy	Life-threatening; disabling; poorly responsive to medical therapy	Death
Cardiopulmonary arrest	—	—	—	Life-threatening	Death
Infective vegetative endocarditis	—	—	CHF or arrhythmia responsive to intervention	Severe or refractory CHF or life-threatening arrhythmia (eg, 3rd degree AV block, ventricular tachycardia)	Death
Left ventricular diastolic dysfunction	Asymptomatic diagnostic finding without associated signs; intervention not indicated	Asymptomatic, intervention indicated (eg, LAE [left atrial enlargement] and dlopidogrel indicated)	Symptomatic CHF responsive to intervention	Refractory CHF, poorly controlled with intervention	Death

(Continues)

CARDIAC GENERAL						
Adverse Event	Grade	1	2	3	4	5
Left ventricular systolic dysfunction		Asymptomatic, resting ejection fraction (EF) 45%-50%	Asymptomatic, resting EF 40%-45%	Symptomatic CHF responsive to intervention; EF 20%-40%	Symptomatic CHF or poorly controlled; EF < 20%	Death
Mycarditis	—	—	—	CHF responsive to intervention	Severe or refractory CHF	Death
Pericardial effusion (non-malignant)	—	Effusion without associated clinical signs	Effusion without associated clinical signs	Physiologic consequences (eg, tamponade)	Life-threatening; emergency intervention indicated	Death
Pulmonary hypertension	—	No associated clinical signs without therapy	No associated clinical signs without therapy	Clinical signs present (eg, syncope, ascites, exercise intolerance) present, responsive to intervention	Clinical signs present (eg, syncope, ascites, exercise intolerance) and refractory to intervention, poorly controlled	Death
Sinus bradycardia		Dog: <60 bpm Cat: <140 bpm	Dog: <40 bpm Cat: <120 bpm	Dog: <30 bpm Cat: <100 bpm	Dog: <20 bpm Cat: <80 bpm	Death
Sinus tachycardia		Dog: >140 bpm Cat: >220 bpm	Dog: >180 bpm Cat: >230 bpm	Dog: >200 bpm Cat: >240 bpm	Dog: >240 bpm Cat: >260 bpm	Death
Systemic hypertension (systolic BP > 160 mm Hg)		Asymptomatic, transient (<24 h) increase, intervention not indicated	Recurrent or persistent (>24 h); monotherapy may be indicated	Requiring more than one drug or more intensive therapy	Life-threatening consequences (eg, hypertensive crisis)	Death
Systemic hypotension (systolic BP < 100 mm Hg)		Asymptomatic, transient (<24 h), intervention not indicated	Brief (<24 h) fluid replacement or other therapy; no physiologic consequences	Sustained therapy, resolves without persisting physiologic consequences	Shock (eg, impairment of vital organ function)	Death
Other (specify, -----)		Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate 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

COAGULATION						
Adverse Event	Grade	1	2	3	4	5
DIC (disseminated intravascular coagulation)	—	Laboratory findings, no haemorrhage detected.	Laboratory findings, evidence of haemorrhage, non-disabling	Laboratory findings, evidence of haemorrhage, non-disabling	Laboratory findings, life-threatening or disabling consequences (eg, CNS haemorrhage, organ damage, or haemodynamically significant blood loss); 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 haemorrhage as the body is depleted of platelets and coagulation factors.

PT (prothrombin time)	>1-1.5 × ULN	>1.5-2.5 × ULN	>2.5 × ULN; bleeding	–	–
PTT (partial thromboplastin time)	>1-1.5 × ULN	>1.5-2.5 × ULN	>2.5 × ULN; bleeding	–	–
Other (specify, _____)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate 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

ULN, upper limit of normal.

CONSTITUTIONAL CLINICAL SIGNS

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Lethargy/fatigue	Mild lethargy over baseline; diminished activity from pre-disease level, but able to function as an acceptable pet	Moderate lethargy causing some difficulty with performing ADL; ambulatory only to the point of eating, sleeping, and consistently defecating and urinating in acceptable area; Decreased grooming habits	Compromised, severely restricted in ADL; will ambulate if assisted; unable to confine urinations and defecation to acceptable areas unless assisted; absent grooming habits	Disabled, fully recumbent posture; reliant on urinary catheter and/or bladder expression; has no control over bowel movements	Death
Definition: Disorders characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities.					
Fever	39.5-40.0°C (103.5-104°F)	>40.0-40.8°C (>104-105.5°F)	>40.9-41.7°C (>105.6-107.6°F)	>41.8°C (>107.6°F)	Death
Hypothermia	–	36.1->34.4°C (97.0->94.0°F)	34.4->32.2°C (93.9->90.0°F)	<32.1°C (<89.9°F) or life-threatening consequences (eg, coma, hypotension, pulmonary oedema)	Death
Weight loss	>5% but <10% from baseline	10%-15% from baseline	>15% but <20% of baseline	>20% of baseline	Death
Other (specify, _____)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate 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

ADL, activities of daily living (eating, drinking, sleeping, defecating and urinating; in cats, also includes adequate grooming).

DERMATOLOGIC/SKIN						
Adverse Event	Grade	1	2	3	4	5
Alopecia		Transient sparse thinning or denuding of hair at localized site, patchy alopecia (regrows but takes longer than 4 weeks)	Transient generalized thinning of hair coat, generalized alopecia (regrows but takes longer than 4 weeks)	Permanent sparse or generalized thinning of hair at localized site, or permanent patchy or generalized alopecia	—	—
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.						
Bruising (in absence of Grade 3 or 4 thrombocytopenia)		Localized or in a dependent area	Generalized/multi-focal	—	—	—
Definition: A finding of injury of the soft tissues or bone characterized by leakage of blood into surrounding tissues.						
Oedema, limbs		5%-10% inter-limb discrepancy in volume or circumference at point of greatest difference; readily apparent obscuration of swelling or obscuration of anatomic architecture on close inspection	>10%-30% inter-limb discrepancy in volume or circumference at point of greatest difference; readily apparent obscuration of anatomic architecture, deviation from normal anatomic contour	>30% inter-limb discrepancy in volume; gross deviation from normal anatomic contour; limiting ADL	—	—
Definition: Swelling due to excessive fluid accumulation in the upper or lower extremities.						
Oedema, localized		Localized to dependent areas; no disability or functional impairment	Moderate localized oedema; intervention indicated	Severe localized oedema limiting ADL; intervention indicated	—	—
Definition: Swelling due to excessive fluid accumulation at a specific anatomic site.						
Erythema		Limited to localized site	Generalized	—	—	—
Definition: Superficial reddening of the skin, usually in patches, as a result of injury or irritation causing dilatation of the blood capillaries.						
Erythema multifforme		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, or any number of lesions associated with oral or genital erosions	Target lesions covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care indicated	Death
Definition: A disorder characterized by target lesions (a pink-red ring around a pale centre).						
Hyperpigmentation		Slight or moderate and confined to fewer than moderate generalized changes (more than 3 sites)	Marked localized (<3 sites), or moderate generalized changes (more than 3 sites)	Marked generalized changes	—	—

DERMATOLOGIC/SKIN						
Adverse Event	Grade	1	2	3	4	5
		3 sites (localized), or slight generalized changes				
Hypopigmentation	Slight or moderate and confined to fewer than 3 sites (localized), or slight generalized changes		Marked generalized changes	—	—	—
Nail/nailbed/claw changes	Discoloration, pitting, any number of nail(s)/claw(s)	Weakening (friable, breaks easily), no pain or changes in gait; any number of nail(s)/claw(s)	Partial or complete loss of nail(s)/claw(s) on any number of paws/feet; pain; lameness	Partial or complete loss of nail(s)/claw (s) on at least two paws/feet and significantly interfering with ADL—unwilling to ambulate	Partial or complete loss of nail(s)/claw changes that result in a decision for euthanasia	Nail/nailbed/claw changes that result in a decision for euthanasia
Palmar-plantar erythrodysesthesia syndrome	Minimal changes or pododermatitis (eg, erythema) without pain	Skin or paw pad changes (eg, peeling/flaking, blisters, bleeding, oedema) or pain, not interfering with function, easily managed medically, resolves significantly within 1 week of drug withdrawal	Skin or paw pad changes that are painful and interfere with function (lameness, excessive licking) and include moist, ulcerative dermatitis, and return to function within 1 week of drug withdrawal	Skin or paw pad changes that are painful, interfere with function and change in function persists longer than 1 week	Skin or paw pad changes that result in a decision for euthanasia	Skin or paw pad changes that result in a decision for euthanasia
Definition: A disorder characterized by redness, marked discomfort, swelling and possible ulceration of the palmar/plantar surfaces of the paws.						
Photosensitivity	Painless erythema	Painful erythema	Erythema with dry desquamation	Erythema with moist desquamation or ulceration, life-threatening (would result in euthanasia if not treated); disabling	Erythema with moist desquamation or ulceration, life-threatening (would result in euthanasia if not treated); disabling	Complications of photosensitivity that result in death or euthanasia
Definition: A disorder characterized by an increase in sensitivity of the skin to light.						
Pruritus	Mild or localized, does not result in lesions because of self-trauma	Moderate or widespread and occurs regularly; may occur at night but not when eating or playing; would result in lesions due to self-trauma if restraint (e-collar or covering of affected area) is not used when unsupervised.	Licking or scratching continuously, requires restraint (e-collar or covering of affected area) at all times to prevent self-trauma, oral corticosteroid or immunosuppressive therapy usually prescribed unless contraindicated	Severe and prolonged; continues when eating, playing, exercising, limits sleeping and eating; oral corticosteroid or immunosuppressive therapy indicated	Severe and prolonged; continues when eating, playing, exercising, limits sleeping and eating; oral corticosteroid or immunosuppressive therapy indicated	—
Definition: A disorder characterized by intense itching.						
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	—	—	—

(Continues)

DERMATOLOGIC/SKIN

Grade		1	2	3	4	5
Adverse Event						
Definition: A disorder characterized by haemorrhagic areas of the skin and mucous membrane. Newer lesions appear reddish in colour. Older lesions are usually a darker purple colour and eventually become a brownish-yellow colour.						
Rash: acne/acneiform	Macules, papules apules and/or pustules covering <10% BSA, which may not be associated with symptoms of pruritus or tenderness	Macules, papules apules and/or pustules covering 10%-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Macules, papules apules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting ADL; associated with local superinfection with oral antibiotics indicated	Macules, papules apules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences		Death
Definition: A disorder characterized by an eruption of papules and pustules or a disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbilliform rash.						
Scaling	Fine scaling, noticeable only upon close examination	Scaling easily visible but not exfoliation in clumps; minimal crusting	Easily visible generalized scaling and crusting with generalized exfoliation upon examination			
Definition: A disorder characterized by flaky and dull skin.						
Skin atrophy	Covering <10% BSA; associated with telangiectasia or changes in skin colour	Covering 10%-30% BSA; associated with striae or adnexal structure loss	Covering >30% BSA; associated with ulceration			
Definition: A disorder characterized by the degeneration and thinning of the epidermis and dermis.						
Skin ulceration	Non-blanchable erythema of only superficially eroded intact skin with associated warmth or oedema	Combined area of ulcers ≤2 cm and partial thickness skin loss involving skin or subcutaneous fat	Combined area of ulcers >2 cm with partial thickness skin loss or full-thickness skin loss (any size) involving damage to or necrosis of subcutaneous tissue that may extend down to fascia	Any size ulcer (full thickness) with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures with or without full thickness skin loss		Death
Definition: A disorder characterized by circumscribed, inflammatory and necrotic erosive lesion on the skin. If depth and size are discrepant, grade is assigned based on depth of ulceration and not size.						
Toxic epidermal necrolysis	—	—	—	—	Skin sloughing covering ≥30% body surface area with associated symptoms (eg, erythema, purpura or epidermal detachment)	Death
Definition: A disorder characterized by greater than 30% total body skin area separation of dermis. The syndrome is thought to be a hypersensitivity complex affecting the skin and the mucous membranes.						
Urticaria (hives, welts, wheals)	Transient, resolves without treatment	Some discomfort; intervention indicated for <48 h	Moderate to marked discomfort; Intervention indicated for >48 h			

DERMATOLOGIC/SKIN

Grade		1	2	3	4	5
Adverse Event						

Definition: A disorder characterized by a pruritic skin eruption characterized by wheals with pale interiors and well-defined red margins.

Other (specify, _____)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate 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
------------------------	---	---	---	--	-------

EAR and LABRYNTH DISORDERS

Grade		1	2	3	4	5
Adverse Event						

Ear pain

Mild pain

Moderate pain; not limiting ADL

Severe pain; limiting ADL

Urgent operative intervention indicated

Death

Definition: A disorder characterized by a sensation of marked discomfort in any part of the ear.

External ear inflammation	External otitis with erythema or dry desquamation	External otitis with moist, desquamation, oedema, enhanced cerumen or discharge; tympanic membrane perforation; tympanostomy indicated	External otitis with mastoiditis; stenosis or osteomyelitis; necrosis of soft tissue or bone	Urgent operative intervention indicated	Death
---------------------------	---	--	--	---	-------

Definition: A disorder characterized by inflammation, swelling and redness to the outer ear and ear canal.

Hearing impaired	Slow to respond to auditory stimuli; mild BAER abnormalities such as prolonged peak latencies and decreased wave amplitudes	Only responsive to loud auditory stimuli; moderate BAER abnormalities such as isoelectric air conducted BAER with normal or abnormal bone conducted BAER	Clinically deaf; severe BAER abnormalities such as isoelectric air and bone conducted BAER	—	—
------------------	---	--	--	---	---

Definition: A disorder characterized by partial or complete loss of the ability to detect or understand sounds resulting from damage to ear structures. BAER = brainstem auditory evoked potentials

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, swelling and redness to the middle ear.

Vertigo	—	Symptomatic; not limiting ADL	Severe symptoms; limiting ADL	—	—
---------	---	-------------------------------	-------------------------------	---	---

Definition: A disorder characterized by dizziness, imbalance, nausea and vision problems.

Other (specify, _____)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate 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
------------------------	---	---	---	--	-------

ENDOCRINE		Grade			
Adverse Event	1	2	3	4	5
Adrenal insufficiency	Asymptomatic, intervention not indicated	Symptomatic, out-patient intervention indicated	Symptomatic, hospitalization indicated	Life-threatening; disabling	Death
Definition: A disorder that occurs when the adrenal cortex does not produce enough of the hormone cortisol and in some cases, the hormone aldosterone. It may be due to a disorder of the adrenal cortex as in Addison's disease or primary adrenal insufficiency.					
Hyperadrenocorticism (Cushing syndrome)	—	Symptomatic, out-patient medical intervention indicated	Symptomatic, in-patient medical intervention indicated	—	—
Definition: A disorder characterized by elevated cortisol concentrations. It may be due to exogenous (iatrogenic) or endogenous (pituitary-dependent, adrenal-dependent) causes.					
Pancreatic endocrine: transient glucose intolerance, diabetes mellitus	Blood glucose <200 mg/dL, no intervention needed	Symptomatic, dietary modification or oral agent or short-term insulin indicated	Symptoms interfering with ADL (eg, anorexia); insulin indicated; hospitalization could be considered	Life-threatening consequences (eg, ketoacidosis, hyperosmolality); hospitalization indicated	Death
Definition: A disorder characterized by insufficient production of pancreatic insulin leading to glucose intolerance and/or diabetes mellitus.					
Pancreatic exocrine: maldigestion	Asymptomatic, intervention not indicated	Symptomatic, dietary modification or oral agents indicated	Symptoms interfering with ADL; Grade 3 weight loss	Life-threatening consequences; cachexia	Death
Definition: A disorder characterized by insufficient production of pancreatic exocrine enzymes leading to maldigestion.					
Parathyroid function (hyperparathyroidism)	Asymptomatic, diagnostic observations only; intervention not indicated	Symptomatic, intervention indicated	—	—	Death
Definition: A disorder characterized by an increase in production of parathyroid hormone by the parathyroid glands. This results in hypercalcaemia.					
Parathyroid function (hypoparathyroidism)	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate symptoms; medical intervention indicated	Severe symptoms; medical 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.					
Thyroid function (hyperthyroidism)	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid suppression therapy indicated; limiting ADL	Severe symptoms; thyroid 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.					
Thyroid function (hypothyroidism)	Asymptomatic, diagnostic observations only; intervention not indicated	Symptomatic, not interfering with ADL, thyroid replacement indicated	Symptoms interfering with ADL, hospitalization indicated	Life-threatening myxedema; coma	Death
Definition: A disorder characterized by a decrease in production of thyroid hormone by the thyroid gland.					
Other (specify, -----)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of	Life-threatening consequences; urgent intervention indicated	Death

indicated; limiting age appropriate ADL

existing hospitalization indicated; limiting self care ADL

GASTROINTESTINAL		Grade				
Adverse Event	1	2	3	4	5	
Abdominal distention	Clinical or diagnostic observations only; intervention not indicated	Clinical signs present; outpatient medical management indicated	Severe discomfort; limiting ADL; inpatient management indicated.	—	—	
Definition: A disorder characterized by swelling of the abdomen.						
Appetite, altered	Decreased appetite lasting ≤ 1 week	Decreased appetite lasting 1-2 weeks	Decreased appetite lasting > 2 weeks	—	—	
Definition: A disorder characterized by a loss of appetite/decreased interest in food.						
Anorexia	Complete anorexia lasting < 48 h	Complete anorexia lasting 2-3 days	Anorexia of 3-5 days duration; associated with significant weight loss ($\geq 10\%$) or malnutrition; IV fluids, tube feeding or force feeding indicated	Life-threatening consequences; TPN indicated; complete anorexia of > 5 days duration	Death	
Definition: A disorder characterized by a complete lack of food intake.						
Colitis	Asymptomatic, pathologic or radiologic findings only	Abdominal cramping/pain; mucus or blood in stool; outpatient medical intervention indicated; ≤ 5 days duration	Abdominal pain, fever, change in bowel habits, ileus, peritoneal signs; hospitalization indicated; > 5 days duration	Life-threatening consequences (eg, perforation, bleeding, ischaemia, necrosis)	Death	
Definition: A disorder characterized by inflammation of the colon.						
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with ADL; obstipation with manual evacuation indicated	Life-threatening consequences (eg, obstruction, megacolon)	Death	
Definition: A disorder characterized by irregular and infrequent or difficult evacuation of the bowels.						
Dehydration	Increased oral fluids indicated; dry mucous membranes; decreased skin turgor	Parenteral (IV or SC) fluids indicated < 48 h	IV fluids indicated > 48 h	Life-threatening (eg, haemodynamic collapse)	Death	
Definition: A disorder characterized by excessive loss of water from the body.						
Diarrhoea	Decreased stool consistency or mild diarrhoea lasting ≤ 24 h that resolves with or without the use of medication and/or parenteral (IV or SC) fluids	Diarrhoea lasting longer than 24 h	Diarrhoea that requires hospitalization; interfering with ADL	Life-threatening (eg, haemodynamic collapse)	Death	
Definition: A disorder characterized by frequent and watery bowel movements.						
Dysphagia	Symptomatic but able to eat regular diet	Symptomatic and altered eating/swallowing (eg, altered dietary habits, food consistency); parenteral (IV or SC) fluids indicated < 48 h	Symptomatic and severely altered eating/swallowing (eg, inadequate oral caloric or fluid intake); IV fluids > 48 h, tube feeding or PPN/TPN indicated	Life-threatening (eg, obstruction, perforation)	Death	

(Continues)

GASTROINTESTINAL		1	2	3	4	5
Grade						
Adverse Event	1	Definition: A disorder characterized by difficulty in swallowing.				
Enteritis	Asymptomatic, pathologic or radiologic findings only	Abdominal pain/cramping; mucus or blood in stool; medical management indicated; Hospitalization ≤ 48 h indicated	Abdominal pain/cramping, fever, change in bowel habits with ileus; peritoneal signs; hospitalization >48 h indicated	Life-threatening (eg, perforation, bleeding, ischaemia, necrosis)	Death	Death
Definition: A disorder characterized by inflammation of the small intestine.						
Esophagitis	Clinical or diagnostic observation only; ≤ 2 episodes of regurgitation in a 48-h period; intervention not indicated	>2 episodes of regurgitation in a 48-h period; medical management indicated	Severe, recurrent symptoms; invasive intervention indicated (eg, endoscopy, luminal dilation, gastrostomy tube feeding)	Life-threatening consequences; urgent intervention indicated	Death	Death
Definition: inflammation of the oesophagus, including sequelae such as stricture; typically due to gastroesophageal reflux.						
Flatulence	Mild	Moderate	Severe	–	–	–
Definition: A disorder characterized by a state of excessive gas in the intestinal tract.						
Gastric dilatation, volvulus	–	Symptomatic; gastric dilatation without volvulus or malposition	Symptomatic; gastric dilatation and malposition; non-surgical intervention indicated	Life threatening consequences; urgent operative intervention indicated	Death	Death
Definition: Pathologic accumulation of gas and ingesta within gastric lumen, with or without gastric torsion or other malposition.						
Gastric ulceration	Clinical or diagnostic observations only; intervention not indicated	Altered GI function; medical intervention indicated	Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated; gastric perforation	Death	Death
Definition: A disorder characterized by a circumscribed, inflammatory and necrotic erosive lesion on the mucosal surface of the stomach.						
Ileus, GI	Asymptomatic, radiologic finding only	Symptomatic; altered GI function (eg, altered dietary habits); parenteral (IV or SC) fluids indicated ≤ 48 h	Symptomatic and severely altered GI function; IV fluids, tube feedings or PPN/TPN indicated >48 h	Life-threatening consequences	Death	Death
Definition: A disorder characterized by failure of the ileum to transport intestinal contents.						
Incontinence, anal	Occasional	Daily	Interfering with ADL; operative intervention indicated	Permanent	Complications of anal incontinence that result in euthanasia	Death
Definition: A disorder characterized by inability to consciously control rectal evacuation.						
Megasophagus	Clinical or diagnostic observation only; secondary to gastric dilatation; intervention not indicated except for underlying gastric complaint	Mild symptoms; minimal weight loss; medical management indicated	Symptomatic; clinically apparent weight loss; intervention such as gastrostomy tube feeding or hospitalization indicated	Severe symptoms; urgent intervention indicated	Death	Death

GASTROINTESTINAL					
Grade					
Adverse Event	1	2	3	4	5
Definition: Generalized dilation and hypomotility of the oesophagus.					
Mucositis/stomatitis	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding; life-threatening	Death
Definition: A disorder characterized by inflammation of the oral mucosa.					
Nausea/ptyalism	Salivation or "smacking of lips" not required intervention	Salivation or "smacking of lips" required intervention	–	–	–
Definition: A disorder characterized by hypersalivation and sensation or urge to vomit—difficult to assess in companion species.					
Vomiting	Vomiting lasting ≤ 24 h that resolves with or without the use of medication and/or parenteral (IV or SC) fluids	Vomiting lasting longer than 24 h	Vomiting that requires hospitalization; interfering with ADL	Life-threatening (eg, haemodynamic collapse)	Death
Definition: A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth.					
Other (specify, _____)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate 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
HAEMORRHAGE/BLEEDING					
Grade					
Adverse Event	1	2	3	4	5
Haematoma	Minimal signs, invasive intervention not indicated	Minimally invasive evacuation or aspiration indicated	–	–	–
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.					
Haemorrhage/bleeding	Minimal: Intervention not indicated	Managed with corrective action and/or fluid therapy but without further consequences or blood product administration	Further non-life-threatening consequences and/or blood product administration	Life-threatening consequences; urgent intervention indicated	Death
Definition: Uncontrolled bleeding.					
Other (specify, _____)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate 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

HEPATOBILIARY/PANCREAS					
Grade					
Adverse Event	1	2	3	4	5
Cholecystitis	Asymptomatic, radiologic (inclusive of radiography, ultrasonography and computed tomography) findings only	Symptomatic, medical intervention indicated	Operative or endoscopic intervention required	Life-threatening (eg, sepsis or perforation)	Death
Definition: A disorder characterized by inflammation involving the gallbladder. It may be associated with the presence of gallstones.					
Liver dysfunction/ failure (clinical signs only)	—	—	Jaundice	Encephalopathy or 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 and alkaline phosphatase.					
Pancreatic exocrine insufficiency	—	Increase in stool frequency, bulk or odour; steatorrhea	Sequelae of absorption deficiency (eg, weight loss)	Life-threatening	Death
Definition: A disorder characterized by insufficient production of pancreatic exocrine enzymes leading to maldigestion.					
Pancreatitis	Pancreatic lipase enzyme elevation; imaging findings only	Grade 1 or 2 vomiting and or/hyporexia; medical intervention indicated (eg, anti-emetics analgesia, parenteral hydration, nutritional support)	Grade 3 or higher vomiting; coagulopathy; Grade 1 or 2 hyperbilirubinemia; evidence of SIRS (systemic inflammatory response syndrome) or MODS (multiple organ dysfunction syndrome); plasma transfusion indicated	Life-threatening consequences; urgent intervention indicated; Uihresponive hypotension; Grade 3/4 hyperbilirubinemia with evidence of extrahepatic biliary obstruction; suppurative abdominal exudate; may require surgical intervention	Death
Definition: A disorder characterized by inflammation of the pancreas.					
Other (specify, _____)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate 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
METABOLIC/LABORATORY					
Grade					
Adverse Event	1	2	3	4	5
Acidosis	pH < normal, but ≥ 7.3	—	pH < 7.3	Life-threatening consequences	Death
Albumin, low	<LLN-2.0 g/dL Dog: >ULN-2.5 \times ULN	<2.0-1.5 g/dL Dog: >2.5-5.0 \times ULN	<1.5 g/dL Dog: >5.0-20 \times ULN	— Dog: >20 \times ULN	—

METABOLIC/LABORATORY					
Grade					
Adverse Event	1	2	3	4	5
Alkaline phosphatase (ALP), high	Cat: >ULN-1.25 × ULN	Cat: >1.25-1.5 × ULN	Cat: >1.5-2.0 × ULN	Cat: >2 × ULN	
Alkalosis	pH > normal, but ≤7.5	—	pH > 7.5	Life-threatening consequences	Death
Alanine aminotransferase (ALT), high	Dog: >ULN-1.5 × ULN Cat: >ULN-1.25 × ULN	Dog: >1.5-4.0 × ULN Cat: >1.25-1.5 × ULN	Dog: >4.0-10 × ULN Cat: >1.5-2.0 × ULN	Dog: >10 × ULN Cat: >2 × ULN	—
Amylase	>ULN-1.5 × ULN	>1.5-2.0 × ULN	>2.0-5 × ULN	>5 × ULN	—
Aspartate aminotransferase (AST), high	>ULN-1.5 × ULN	>1.5-2.0 × ULN	>2.0-10 × ULN	>10 × ULN	—
Bile acids, fasting (with normal bilirubin)	—	Values reported above normal reference interval	—	—	—
Bilirubin	>ULN-1.5 × ULN	>1.5-3.0 × ULN	>3.0-10 × ULN	>10 × ULN	—
BUN	>1-1.5 × baseline; >ULN-1.5 × ULN	>1.5-3 × baseline; >1.5-2.0 × ULN	>3 × baseline; >2.0-3 × ULN	>3 × ULN	—
Calcium, low	<LLN-8.0 mg/dL Ionized dog: <LLN-1.1 nmol/L Ionized cat: <LLN-0.9 nmol/L	<8.0-7.0 mg/dL Ionized dog: <1.1-1.0 nmol/L Ionized cat: <0.9-0.8 nmol/L	<7.0-6.0 mg/dL Ionized dog: <1.0-0.9 nmol/L Ionized cat: <0.8-0.7 nmol/L	<6.0 mg/dL Ionized dog: <0.9 nmol/L Ionized cat: <0.7 nmol/L	Death
Calcium, high	>ULN-12.0 mg/dL Ionized: >ULN-1.5 nmol/L	≥12.0-13.0 mg/dL Ionized: >1.5-1.6 nmol/L, mild clinical signs not requiring immediate intervention	>13.0 mg/dL Ionized: >1.6-1.8 nmol/L with clinical signs and/or sequela requiring medical intervention; hospitalization indicated	Life-threatening, require immediate patient intervention	Death
Creatine phosphokinase (CPK), high	>ULN-2.5 × ULN	>2.5-5 × ULN	>5-10 × ULN	>10 × ULN	—
Creatinine, high	>1-1.5 × baseline; >ULN-1.5 × ULN	>1.5-3 × baseline; >1.5-2.0 × ULN	>3 × baseline; >2.0-3 × ULN	>3 × ULN	—
Glucose, high	Dog: >ULN-160 mg/dL Cat: >ULN-200 mg/dL abnormal glucose above normal with no medical intervention needed	Dog: >160-250 mg/dL Cat: >200-250 mg/dL	Dog: >250-500 mg/dL Cat: >250-500 mg/dL	Dog: >500 mg/dL Cat: >500 mg/dL	—
Glucose, low	<LLN-55 mg/dL	<55-40 mg/dL	<40-30 mg/dL	<30 mg/dL	Death
Potassium, high	>ULN-5.5 mmol/L	>5.5-6.0 mmol/L	>6.0-7.0 mmol/L	>7.0 mmol/L	Death

(Continues)

METABOLIC/LABORATORY					
Grade					
Adverse Event	1	2	3	4	5
Potassium, low	<LLN-3.0 mmol/L	–	<3.0-2.5	<2.5	Death
Phosphorous, high	>ULN-8.9 mg/dL	9.0-12.9 mg/dL	13.0-18.9 mg/dL	>19.0 mg/dL	Death
Phosphorous, low	<LLN	<LLN with evidence of haemolysis	–	–	–
Sodium, high	≤5 mEq/L above ULN	6-10 mEq/L above ULN; intervention indicated	11-15 mEq/L above ULN; hospitalization indicated	>15 mEq/L above ULN; life-threatening consequences; urgent intervention indicated	Death
Sodium, low	<LLN-130 mEq/L	125-129 mEq/L, asymptomatic	125-129 mEq/L, symptomatic; 120-124 mEq/L regardless of symptoms	<120 mEq/L; life-threatening consequences	Death
Tumour lysis syndrome	Asymptomatic, clinicopathologic finding	Mild-moderate clinical signs, medical intervention indicated ≤48 h	Medical intervention, hospitalization >48 h indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by metabolic abnormalities that result from a spontaneous or therapy-related cytotoxicity of tumour cells.					
Other (specify _____)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate 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
MUSCULOSKELETAL/SOFT TISSUE					
Grade					
Adverse Event	1	2	3	4	5
Arthritis, non-septic	Imaging or clinicopathologic finding only	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	–	–
Definition: A disorder characterized by inflammation involving a joint.					
Extremity (gait/ambulation) lameness	Clinical signs not interfering with ADL	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	–	–
Definition: Inability to walk normally because of an injury or illness affecting the limbs.					
Joint effusion	Imaging or clinicopathologic finding only	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	–	–
Definition: A disorder characterized by excessive fluid in a joint.					
Muscle weakness, generalized or specific area	Observation only	Clinical signs evident on examination; limiting ADL	Clinical signs evident on examination; severely restricted in ADL	Life-threatening consequences; urgent intervention indicated	Death

MUSCULOSKELETAL/SOFT TISSUE					
Grade					
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by a reduction in the strength of the muscles.					
Myositis (inflammation of muscle)	Imaging or clinicopathologic finding only	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation involving the skeletal muscles.					
Seroma	Clinical or diagnostic observation only; intervention not indicated	Symptomatic; simple aspiration indicated	Symptomatic; invasive intervention indicated	–	–
Definition: Sterile localized collection of fluid at a site of tissue removal or other surgical manipulation.					
Soft tissue necrosis	Minor signs of soft tissue damage, no intervention indicated	Local wound care; medical intervention indicated	Operative debridement or other invasive intervention indicated	Life-threatening; major invasive intervention indicated (eg, reconstruction, graft)	Death
Definition: A disorder characterized by a necrotic process occurring in the soft tissues.					
Other (specify, _____)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate 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
NEUROLOGY					
Grade					
Adverse Event	1	2	3	4	5
Abducens nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	–	–
Definition: A disorder characterized by dysfunction of the abducens nerve (6th cranial nerve).					
Accessory nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	–	–
Definition: A disorder characterized by dysfunction of the accessory nerve (11th cranial nerve).					
Apnoea	–	–	Present	Intubation indicated	Death
Definition: A disorder characterized by cessation of breathing.					
Ataxia	Clinical signs not interfering with ADL	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	–	–

(Continues)

NEUROLOGY		Grade				
Adverse Event	1	2	3	4	5	
Definition: A disorder characterized by lack of coordination of muscle movements resulting in the impairment or inability to perform voluntary activities.						
Brachial plexopathy	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	—	—	
Definition: A disorder characterized by regional motor or sensory dysfunction referable to the brachial plexus.						
Central nervous system necrosis	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characterized by a necrotic process affecting the brain or spinal cord.						
Cerebral oedema	—	New onset; worsening from baseline; affects ADL; outpatient therapy indicated	New onset; worsening from baseline; significantly affects ADL; hospitalization or prolongation of hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the brain.						
Cerebrospinal fluid leakage	Post-procedural; asymptomatic	Post-surgical; moderate clinical signs; medical intervention indicated	Post-surgical; severe clinical signs; medical or surgical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characterized by loss of cerebrospinal fluid into or through surrounding tissues.						
Cochlear nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated; mild BAER abnormalities such as prolonged peak latencies and decreased wave amplitudes	Moderate clinical signs, causing some difficulty with performing ADL; moderate BAER abnormalities such as isoelectric air conducted BAER with normal or abnormal bone conducted BAER	Severe clinical signs, severely restricted in ADL; severe BAER abnormalities such as isoelectric air and bone conducted BAER	—	—	
Definition: A disorder characterized by dysfunction of the cochlear component of the vestibulocochlear nerve (8th cranial nerve).						
Cognitive disturbance	Mild cognitive disability; treatment not indicated	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	—	Euthanized due to cognitive disability	
Definition: A disorder characterized by a conspicuous change in cognitive functions.						
Depressed level of consciousness	Decreased level of alertness	Sedate, slow responses to stimuli; Moderate clinical signs, causing some difficulty with performing ADL	Difficult to arouse; Severe clinical signs, severely restricted in ADL	Life-threatening consequences; urgent intervention indicated	Death	

NEUROLOGY		1	2	3	4	5
Adverse Event	Grade					
Definition: A disorder characterized by a decrease in the ability to receive or respond to stimuli.						
Dizziness	Mild unsteadiness	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	—	—	—
Definition: Nausea/motion sickness due to vestibular dysfunction.						
Dysphonia	Dysphonia	—	Aphonia	—	—	—
Definition: A disorder characterized by a reduced ability to vocalize.						
Encephalitis	Mild signs or symptoms with ADL	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	Life-threatening consequences; urgent intervention indicated	Death	Death
Definition: A disorder characterized by inflammation of the brain; may be infectious or non-infectious aetiology.						
Encephalopathy	—	Mild signs or symptoms; not interfering with ADL	Signs or symptoms interfering with ADL; hospitalization indicated	Life-threatening; disabling	Death	Death
Definition: A disorder characterized by any pathological process involving the brain.						
Facial nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate clinical signs, causing some difficulty with performing ADL (includes neurogenic dry eye syndrome)	Severe clinical signs, severely restricted in ADL	—	—	—
Definition: A disorder characterized by dysfunction of the facial nerve (7th cranial nerve).						
Glossopharyngeal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	Life-threatening	Death	Death
Definition: A disorder characterized by dysfunction of the glossopharyngeal nerve (9th cranial nerve).						
Head pain	Mild pain	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	—	—	—
Definition: A disorder manifested by discomfort in various parts of the cranium/head.						
Hydrocephalus	Clinical or diagnostic observation only; Mild signs or symptoms; not interfering with ADL	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	Life-threatening consequences; urgent intervention indicated	Death	Death
Definition: A disorder characterized by abnormal increase of cerebrospinal fluid in the ventricles (internal), subarachnoid space (external) or ex vacuo.						
Hypertensive encephalopathy	—	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	Life-threatening consequences; urgent intervention indicated	Death	Death

(Continues)

NEUROLOGY		Grade				
Adverse Event	1	2	3	4	5	
Definition: A disorder characterized by the presence of encephalopathic clinical signs observed in association with systemic hypertension.						
Hypoglossal nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	–	–	
Definition: A disorder characterized by dysfunction of the hypoglossal nerve (12th cranial nerve).						
Intracranial haemorrhage	Clinical or diagnostic observations only; Mild signs or symptoms; not interfering with ADL	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characterized by bleeding within the cranium.						
Ischaemic cerebrovascular accident	Imaging finding only	Moderate clinical signs, causing some difficulty with performing ADL; intervention indicated	Severe clinical signs, severely restricted in ADL; invasive intervention indicated	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 of an artery.						
Laryngeal nerve dysfunction	Asymptomatic; clinical exam finding	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characterized by abnormal laryngeal function.						
Leukoencephalopathy	Mild signs or symptoms; not interfering with ADL	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characterized by T2/FLAIR hyperintensities involving the periventricular white matter, +/- ventriculomegaly or enlargement of the subarachnoid space.						
Meningitis	Asymptomatic or mild signs; not interfering with ADL	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characterized by inflammation of the meninges; may be infectious or non-infectious aetiology.						
Movements involuntary	Mild signs or symptoms; not interfering with ADL	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	–	–	

NEUROLOGY		Grade				
Adverse Event	1	2	3	4	5	
Definition: A disorder characterized by uncontrollable and purposeless movements.						
Muscle weakness left-sided	Observation only; no clinical signs present	Clinical signs evident on examination; causing some difficulty with performing ADL	Clinical signs evident on examination; severely restricted in ADL	—	—	
Definition: A disorder characterized by a reduction in the strength of the muscles on the left side of the body.						
Muscle weakness right-sided	Observation only; no clinical signs present	Clinical signs evident on examination; causing some difficulty with performing ADL	Clinical signs evident on examination; severely restricted in ADL	—	—	
Definition: A disorder characterized by a reduction in the strength of the muscles on the right side of the body.						
Myasthenia gravis	—	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characterized by weakness and rapid fatigue of any of the skeletal muscles.						
Myelitis	Asymptomatic or mild signs; not interfering with ADL	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characterized by inflammation of the spinal cord; may be infectious or non-infectious aetiology.						
Oculomotor nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	—	—	
Definition: A disorder characterized by dysfunction of the oculomotor nerve (3rd cranial nerve).						
Olfactory nerve disorder	—	Hyposmia/microsmia	Anosmia	—	—	
Definition: A disorder characterized by dysfunction of the olfactory nerve (1st cranial nerve).						
Optic nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	—	—	
Definition: A disorder characterized by dysfunction of the optic nerve (2nd cranial nerve).						
Peripheral neuropathy-motor (including sensorimotor)	Mild signs or symptoms with ADL	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	Life-threatening consequences; urgent intervention indicated	Death	

(Continues)

NEUROLOGY		Grade				
Adverse Event	1	2	3	4	5	
Definition: A disorder characterized by damage or dysfunction of peripheral sensory nerves.						
Peripheral neuropathy-sensory	Mild signs or symptoms; not interfering with ADL	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	Life-threatening consequences; urgent intervention indicated	—	
Definition: A disorder characterized by damage or dysfunction of peripheral motor nerves.						
Personality/behaviour	Change noticed but not adversely affecting patient or family	Change, adversely affecting patient or family	Change is harmful to others or self; affects ADL	—	Complications that result in death or euthanasia	
Definition: A change in personality or behaviour regardless of aetiology (structural, functional, etc).						
Proprioceptive deficit	Mild signs or symptoms; not interfering with ADL	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	—	—	
Definition: A deficit in proprioception with or without proprioceptive ataxia.						
Seizure	Single focal seizure	Single generalized seizure; anti-convulsant medication indicated	New onset seizures (focal or generalized); multiple seizures despite medical intervention; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.						
Spasticity	Mild increase in muscle tone: not interfering with ADL	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characterized by increased involuntary muscle tone that affects regions interfering with voluntary movement.						
Spinal cord compression	Imaging finding only	Moderate clinical signs, causing some difficulty with performing ADL; intervention indicated	Severe clinical signs, severely restricted in ADL; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characterized by pressure on the spinal cord.						
Transient ischaemic attack	Neurologic deficit with or without imaging confirmation	Neurological deficit with or without imaging confirmation; limiting ADL	Hospitalization or prolongation of hospitalization indicated	—	—	

NEUROLOGY		1	2	3	4	5
Adverse Event	Grade					
Definition: A disorder characterized by a brief attack (<24 h) of brain dysfunction of vascular origin, with no persistent neurological deficits.						
Tremor	Mild signs or symptoms; not interfering with ADL	Moderate clinical signs, causing some difficulty with performing ADL; intervention indicated	Severe clinical signs, severely restricted in ADL; hyperthermia (use same temp as Grade 3 fever, ie, > 104 F)	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characterized by the uncontrolled shaking movement of the whole body or individual parts.						
Trigeminal nerve disorder	Mild signs or symptoms; not interfering with ADL	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL			
Definition: A disorder characterized by dysfunction of the trigeminal nerve (5th cranial nerve).						
Trochlear nerve disorder	Mild signs or symptoms; not interfering with ADL	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL			
Definition: A disorder characterized by dysfunction of the trigeminal nerve (4th cranial nerve).						
Vagus nerve disorder	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Moderate clinical signs, causing some difficulty with performing ADL; intervention indicated	Severe clinical signs, severely restricted in ADL	Life-threatening consequences; urgent intervention indicated	Death	
Definition: A disorder characterized by dysfunction of the vagus nerve (10th cranial nerve); does not include dysfunction of laryngeal nerves.						
Vestibular nerve disorder	Mild signs or symptoms; not interfering with ADL	Moderate clinical signs, causing some difficulty with performing ADL	Severe clinical signs, severely restricted in ADL	Life-threatening consequences; urgent intervention indicated		
Definition: A disorder characterized by dysfunction of the vestibular component of the vestibulocochlear nerve (8th cranial nerve); clinical manifestations may include head tilt, vestibular ataxia, pathological nystagmus or nausea.						
Other (specify, _____)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate: minimal, local or non-invasive intervention indicated; limiting age appropriate 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	
OCULAR/VISUAL						
Adverse Event	Grade	1	2	3	4	5
Cataract	Asymptomatic, detected on exam only	Symptomatic with moderate decrease in visual acuity	Symptomatic with marked decrease in visual acuity; operative intervention indicated			

(Continues)

OCULAR/VISUAL		Grade				
Adverse Event	1	2	3	4	5	
	Definition: A disorder characterized by partial or complete opacity of the crystalline lens of one or both eyes. This results in a decrease in visual acuity and eventual blindness if untreated.					
Conjunctivitis/ocular surface disease	Asymptomatic or minimally symptomatic but not interfering with function	Symptomatic, significant discharge; interfering with function but not ADL; topical antibiotics or other topical intervention indicated	Symptomatic and interfering with ADL; operative intervention indicated	Blindness; enucleation indicated	—	
	Definition: A disorder characterized by inflammation, swelling and redness to the conjunctiva of the eye.					
Dry eye syndrome	Mild, intervention not indicated	Symptomatic, interfering with function but not ADL; medical intervention indicated	Symptomatic or decrease in visual acuity interfering with ADL	Blindness; enucleation indicated	—	
	Definition: A disorder characterized by dryness of the cornea and conjunctiva with normal facial nerve function.					
Epiphora	Symptomatic, intervention not indicated	Symptomatic, interfering with function but not ADL	Symptomatic, interfering with ADL	—	—	
	Definition: A disorder characterized by excessive watering of the eye.					
Glaucoma	Elevated intraocular pressure (EIOP) with single topical agent for intervention; no visual deficit	EIOP causing early visual field deficit; multiple topical or oral agents indicated	EIOP causing marked visual deficits; operative intervention indicated	EIOP resulting in blindness; enucleation indicated	—	
	Definition: A disorder characterized by an increase in pressure in the eyeball due to obstruction of the aqueous humour outflow.					
Keratitis (corneal inflammation/corneal ulceration)	Abnormal ophthalmologic changes only; intervention not indicated	Symptomatic and interfering with function, but not ADL	Symptomatic and interfering with ADL; operative intervention indicated	Perforation or blindness, enucleation indicated.	—	
	Definition: A disorder characterized by inflammation to the cornea of the eye.					
Optic disc oedema (papilledema)	Mild; does not require treatment	Moderate; outpatient treatment required	Severe; inpatient treatment required	Bilateral blindness	—	
	Definition: A disorder characterized by oedema and swelling of the optic disc.					
Retinal detachment	Exudative; no central vision loss; intervention not indicated	Exudative and some visual acuity loss but intervention not indicated	Rhegmatogenous or exudative detachment; operative intervention indicated	Blindness	—	
	Definition: A disorder characterized by the separation of the inner retina layers from the underlying pigment epithelium.					
Retinopathy	Asymptomatic	Symptomatic with moderate decrease in visual acuity	Symptomatic with marked decrease in visual acuity; interfering with ADL	Blindness	—	
	Definition: A disorder involving the retina.					
Scleral necrosis/melt	Asymptomatic but not interfering with function	Symptomatic, interfering with function but not ADL; moderate decrease in visual acuity; medical intervention indicated	Symptomatic, interfering with ADL; operative intervention indicated	Blindness; painful eye with enucleation indicated	—	

OCULAR/VISUAL						
Adverse Event	Grade	1	2	3	4	5
Definition: A disorder characterized by necrosis of the sclera.						
Uveitis	Asymptomatic	Anterior uveitis; medical intervention indicated	Posterior or pan-uveitis; operative intervention indicated	Blindness		–
Definition: A disorder characterized by inflammation of the uvea of the eye.						
Vitreous haemorrhage	Asymptomatic, clinical findings only	Symptomatic, interfering with function but not ADL; intervention not indicated	Symptomatic, interfering with ADL; intervention indicated	–	–	–
Definition: A disorder characterized by blood extravasation into the vitreous humour.						
Other (specify, -----)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate 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	

PAIN						
Adverse Event	Grade	1	2	3	4	5
Pain	Mild pain not interfering with function	Moderate pain; moderately interfering with function or ADL; analgesic therapy indicated	Severe pain; significantly interfering with ADL; multimodal analgesia indicated	Disabling or uncontrollable pain		–
Definition: A disorder characterized by marked discomfort.						
Other (specify, -----)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate 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	

PULMONARY/RESPIRATORY						
Adverse Event	Grade	1	2	3	4	5
Apnea	–	–	Present; medical intervention indicated	Life-threatening respiratory or haemodynamic compromise; intubation or urgent intervention indicated	Death	
Definition: A disorder characterized by cessation of breathing.						
Aspiration pneumonia	Asymptomatic; radiographic findings	Symptomatic; medical intervention indicated	Clinical or radiographic signs of pneumonia or pneumonitis, hospitalization indicated	Life-threatening respiratory or haemodynamic compromise; intubation or urgent intervention indicated	Death	

(Continues)

PULMONARY/RESPIRATORY		Grade			
Adverse Event	1	2	3	4	5
Definition: A disorder characterized by inhalation of solids or liquids into the lungs.					
Bronchospasm, wheezing	Asymptomatic	Symptomatic, not interfering with function	Symptomatic, interfering with function	Life-threatening	Death
Definition: A disorder characterized by a sudden contraction of the smooth muscles of the bronchial wall.					
Cough	Symptomatic, non-narcotic medication only indicated	Symptomatic and narcotic indicated	Symptomatic and interfering with sleep or 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.					
Dyspnoea	Dyspnoea on exertion, but can walk without tiring	Dyspnoea on exertion and tires upon ambulating	Dyspnoea with ADL	Dyspnoea at rest; intubation/ventilator indicated	Death
Definition: A disorder characterized by discomfort due to difficulty breathing.					
Oedema, larynx	Asymptomatic oedema by exam only	Symptomatic oedema, no respiratory distress	Stridor; respiratory distress; interfering with ADL	Life-threatening; tracheotomy, intubation, indicated	Death
Definition: A disorder characterized by swelling due to an excessive accumulation of fluid in the larynx.					
Hypoxia	—	<O ₂ saturation with exercise	<O ₂ saturation at rest; continuous O ₂ supplementation required	Life-threatening; intubation or ventilation required	Death
Definition: A disorder characterized by a decrease in the level of oxygen in the body.					
Laryngeal collapse	Everted laryngeal sacculles or oedematous mucosa narrowing the laryngeal lumen	Medial collapse of cuneiform processes; impaired cuneiform abduction	Medial or ventral collapse of cuneiform and corniculate processes; paradoxical laryngeal motion	Life-threatening airway obstruction; urgent intervention indicated	Death
Definition: Pathologic distortion of laryngeal anatomy and function secondary to chronic inspiratory pressure.					
Pneumonitis/pulmonary infiltrates	Asymptomatic, radiographic findings only	Symptomatic, not interfering with ADL	Symptomatic, interfering with ADL; O ₂ indicated	Life-threatening; ventilatory support indicated	Death
Definition: A disorder characterized by inflammation focally or diffusely affecting the lung parenchyma.					
Pulmonary oedema	Radiologic findings only; minimal dyspnoea on exertion	Moderate dyspnoea on exertion; medical intervention indicated	Severe dyspnoea or dyspnoea at rest; oxygen indicated; limiting ADL	Life-threatening respiratory compromise; urgent intervention or intubation with ventilatory support indicated	Death
Definition: A disorder characterized by accumulation of fluid in the lung tissues that causes a disturbance of the gas exchange that may lead to respiratory failure.					
Pulmonary fibrosis	Minimal, estimated lung volume involved <25%	Patchy or bilateral changes with estimated lung volume 25- <50%	Dense or widespread infiltrates/consolidation with estimated involved lung volume ≥50%-75%	Estimated involved lung volume >75%	Death
Definition: A disorder characterized by the replacement of the lung tissue by connective tissue, leading to progressive dyspnoea, respiratory failure, pulmonary hypertension and right heart failure.					
Respiratory distress syndrome (ARDS)	—	—	Present, intubation not indicated	Present, intubation indicated	Death

PULMONARY/RESPIRATORY						
Adverse Event	Grade	1	2	3	4	5
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.						
Tachypnea (not panting)		Respiratory rate up to 60 bpm	>60 bpm; increased abdominal effort	O ₂ indicated	Life-threatening; ventilatory support indicated	Death
Definition: A disorder characterized by abnormally rapid breathing.						
Other (specify, _____)		Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate 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
RENAL/GENITOURINARY						
Adverse Event	Grade	1	2	3	4	5
Acute kidney injury (Modified International Renal Interest Society [IRIS] grade)		Creatinine ≤ 1.6 mg/dL (140 $\mu\text{mol/L}$) with increase of ≥ 0.3 mg/dL from baseline	Creatinine 1.7-2.5 mg/dL (141-220 $\mu\text{mol/L}$); fluid responsive oliguria/anuria within 48 h.	Creatinine 2.6-5.0 mg/dL (221-439 $\mu\text{mol/L}$); fluid therapy (IV or SC) and/or renal diet indicated	>5.1 (440 $\mu\text{mol/L}$); renal replacement therapy (RRT) indicated	Death
Definition: A disorder characterized by the acute renal parenchymal injury loss of renal function and is traditionally classified as pre-renal (low blood flow into kidney), renal (kidney damage) and post-renal causes (ureteral or bladder outflow obstruction).						
Chronic kidney disease (International Renal Interest Society [IRIS] stage)		Asymptomatic; blood creatinine persistently increasing with in RR and/or SDMA as below OR SDMA persistently >14 $\mu\text{g/dL}$	Mild clinical signs, blood creatinine and/or SDMA as below:	Transitional clinical signs, SC or enteral fluid therapy indicated; blood creatinine and/or SDMA as below	Uremic; life-sustaining measures required; blood creatinine and/or SDMA as below	Death
Canine USG <1.030		<1.4 mg/dL (<125 $\mu\text{mol/L}$); SDMA <18 $\mu\text{g/dL}$	1.4-2.8 mg/dL (125-250 $\mu\text{mol/L}$); SDMA 18-35 $\mu\text{g/dL}$	2.9-5.0 mg/dL (251-440 $\mu\text{mol/L}$); SDMA 36-54 $\mu\text{g/dL}$	>5.0 mg/dL (>440 $\mu\text{mol/L}$); SDMA >54 $\mu\text{g/dL}$	—
Feline USG <1.035		<1.6 mg/dL (<140 $\mu\text{mol/L}$); SDMA <18 $\mu\text{g/dL}$	1.6-2.8 mg/dL (140-250 $\mu\text{mol/L}$); SDMA 18-25 $\mu\text{g/dL}$	2.9-5.0 mg/dL (251-440 $\mu\text{mol/L}$); SDMA 26-38 $\mu\text{g/dL}$	>5.0 mg/dL (>440 $\mu\text{mol/L}$); SDMA >38 $\mu\text{g/dL}$	—
Definition: A disorder characterized by gradual and usually permanent loss of kidney function resulting in renal failure.						
Cystitis (haematuria/pyuria included)		Asymptomatic; microscopic haematuria/pyuria, not requiring attributed drug discontinuation	Symptomatic; transient macroscopic haematuria; pain or antispasmodic medication indicated	Transfusion indicated; pain or antispasmodic medication; bladder irrigation indicated; requiring attributed drug discontinuation	Catastrophic bleeding; non-elective intervention indicated	Death
Definition: A disorder characterized by inflammation of the bladder which is not caused by an infection of the urinary tract.						
Glucosuria		Present but transient (<2 weeks)	Prolonged (>2 weeks)	—	—	—

Definition: A disorder characterized by the excretion of glucose in the urine.					
Haemoglobinuria	Present	—	—	—	—
Incontinence, urinary	Occasional (eg, with coughing, sneezing, etc)	Spontaneous	Interfering with ADL; medical intervention indicated	Operative intervention indicated	Complications that result in euthanasia
Definition: A disorder characterized by insufficient voluntary control over urination					
Obstruction, urinary	Asymptomatic; radiographic or endoscopic finding	Symptomatic without hydronephrosis or renal dysfunction; urinary catheter placement indicated	Symptomatic; altered organ function; hydronephrosis; operative intervention indicated	Life-threatening; organ failure	Death
Definition: A disorder characterized by blockage of the normal flow of contents of the urinary tract.					
Ureteral obstruction	Clinical or diagnostic observation only; intervention not indicated	Partial obstruction; mild pyelectasia or ureteral dilation; medical management indicated	Symptomatic; moderate to severe pyelectasia or ureteral dilation; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: a mechanical or functional blockage of urine flow affecting one or both ureters or ureterovesicular junctions.					
Urethral obstruction	—	Partial or intermittent obstruction; medical management; indicated	Hospitalization, invasive intervention indicated (eg, indwelling catheterization, surgery, cystoscopy, voiding hydropropulsion, lithotripsy)	Life-threatening consequences; urgent intervention indicated	Death
Definition: A mechanical or functional blockage of urine flow at the level of the urethra.					
Proteinuria	Urine protein/creatinine ratio 0.2-0.5 for dogs or 0.2-0.4 for cats	Urine protein/creatinine ratio > 0.5 for dogs or > 0.4 for cats but transient (<14 days in duration)	Urine protein/creatinine ratio >0.5 for dogs or >0.4 for cats and prolonged ≥14 days duration)	—	—
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.					
Polyuria	—	Present; >50 mL/kg/day; not interfering with ADL	Present; >50 mL/kg/day; interfering with ADL	—	—
Definition: A disorder characterized by production of abnormally large volumes of dilute urine.					
Pollakiuria	Pet asks to be let out more frequently but <6 times/day; any change in frequency that lasts ≤2 days.	Pet asks to be let out 6-10 times/day; any change in frequency that lasts 2-5 days	Pet asks to be let out >10 times/day; any change in frequency that lasts >5 days; interfering with ADL	—	—
Definition: A disorder characterized by frequent daytime urination.					
Pyometra	—	Metritis or open pyometra without fever; medical management indicated	Open or closed pyometra with fever; IV antimicrobial, operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: purulent inflammation of the uterus caused by bacteria or other microbes.					
Stranguria	Minimal straining, attempts to urinate 1-3 times at a urination event, slightly reduced stream, signs persist up to 2 days	Moderate straining, attempts to urinate >3 times at a urination event, moderately reduced stream, signs persist 2-5 days; treatment indicated	Excessive straining, makes repeated attempts to urinate, severely reduced urine stream, signs persist >5 days; medical or surgical intervention required.	Life-threatening, urinary obstruction and post-renal failure result.	—

Definition: A disorder characterized by straining to urinate.									
Urinary output—diminished	—	Mild oliguria: <1.0 mL/kg/h in a well hydrated and well perfused patient, responsive to medical diuresis	Oliguria: <0.5 mL/kg/h in a well hydrated and well perfused patient, resistant to medical diuresis	Anuria: absence of urine production	Death				
Definition: A disorder characterized by diminished production of urine.									
Urinary retention (including neurogenic bladder)	Hesitancy or dribbling, no significant residual volume	Bladder atony requiring transient indwelling catheter <72 h	Bladder atony requiring indwelling catheter ≥72 h; operative intervention indicated	Life-threatening consequences; organ failure	Death				
Definition: A disorder characterized by accumulation of urine within the bladder because of the inability to urinate.									
Urinary tract infection	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; oral antimicrobial intervention indicated	IV antimicrobial intervention indicated; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated	Death				
Definition: inflammation of the kidney, ureter, bladder or urethra caused by bacteria or other microbes.									
Urine colour change	Present	—	—	—	—				
Other (specify, _____)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate 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				
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (incl cysts and polyps)									
Grade									
Adverse Event	1	2	3	4	5				
Leukaemia secondary to oncology chemotherapy	—	—	—	Present	Death				
Definition: A disorder characterized by leukaemia arising as a result of the mutagenic effect of chemotherapy agents.									
Myelodysplastic syndrome	—	—	—	Life-threatening consequences; urgent intervention indicated	Death				
Definition: A disorder characterized by insufficiently healthy haematopoietic cell production by the bone marrow.									
Treatment related secondary malignancy (Specify, _____)	—	—	Non-life-threatening benign tumour or malignancy	Acute life-threatening secondary malignancy; blast crisis in leukaemia	Death				
Definition: A disorder characterized by development of a malignancy most probably as a result of treatment for a previously existing malignancy.									
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated;	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting ADL	Life-threatening consequences; urgent intervention indicated	Death				
Other (specify, _____)	Other (specify, _____)	Other (specify, _____)	Other (specify, _____)	Other (specify, _____)	Other (specify, _____)				

(Continues)

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (incl cysts and polyps)				
Grade				
Adverse Event	1	2	3	4 5
	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate 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
SEXUAL/REPRODUCTIVE FUNCTION				
Grade				
Adverse Event	1	2	3	4 5
Foetal death	—	—	—	—
				Foetal loss at any gestational age
Definition: A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation.				
Gynecomastia	Mammary gland enlargement without clinical effect on patient	Mammary gland enlargement with clinical effect on patient	—	—
Definition: A disorder characterized by excessive development of the mammary tissue in males.				
Infertility/sterility	—	Male: oligospermia/low sperm count Female: diminished fertility/oestrus	Male: sterile/azoospermia Female: infertile/anestrous	—
Definition: A disorder characterized by inability to reproduce.				
Mammary gland function/lactation	Mammary abnormality, not functionally significant	Mammary abnormality, functionally significant	—	—
Definition: A disorder characterized by disturbances in milk production or secretion.				
Vaginal discharge (non-infectious)	Mild	Moderate to heavy	—	—
Definition: A disorder characterized by excess vaginal secretions.				
Other (specify, -----)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate 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

SURGICAL: ANAESTHETIC COMPLICATIONS

		Grade			
Adverse Event	1	2	3	4	5
Iatrogenic injury due to anaesthetic procedures	No intervention required; without further consequences for the patient	Intervention required; without further consequences for the patient	Intervention required; further non-life-threatening consequences for the patient	Life-threatening consequences; urgent intervention indicated	Death

Definition: Injury to tissues or organs caused by placement or malfunction of anaesthetic equipment or devices, including endotracheal tubes, locoregional analgesic delivery systems and anaesthetic monitoring equipment, whether due to operator error or not.

Hypotension (anaesthetized patient)	Observation only; intervention not indicated	Non-urgent medical intervention indicated	Moderate, sustained; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
-------------------------------------	--	---	---	--	-------

Definition: A blood pressure that is below the normal expected level for an anaesthetized patient.

Hypertension (anaesthetized patient)	Observation only; intervention not indicated	Non-urgent medical intervention indicated	Moderate, sustained; medical intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
--------------------------------------	--	---	---	--	-------

Definition: A blood pressure that is above the normal expected level for an anaesthetized patient.

Hypoxemia (anaesthetized patient)	—	Transient, responsive to mechanical ventilation or inspired oxygen	Sustained, moderate to severe; intervention indicated (eg, PEEP, reintubation, thoracocentesis)	Life-threatening, urgent intervention indicated	Death
-----------------------------------	---	--	---	---	-------

Definition: Lower than normal partial pressure of oxygen (PaO₂ < 60 mm Hg) in the blood of an anaesthetized patient.

Hypercapnia (anaesthetized patient)	—	Transient, responsive to mechanical ventilation or changing carbon dioxide absorbent	Sustained, moderate to severe; intervention indicated (eg, PEEP, reintubation, thoracocentesis)	Life-threatening consequences; urgent intervention indicated	Death
-------------------------------------	---	--	---	--	-------

Definition: Higher than normal partial pressure of carbon dioxide (PaCO₂ > 45 mm Hg) in the blood of an anaesthetized patient.

Other (specify _____)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate 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
-----------------------	---	---	---	--	-------

SURGICAL: INTRA-OPERATIVE COMPLICATIONS

		Grade			
Adverse Event	1	2	3	4	5
Intra-operative		Incidents managed with change in operative tactics but without further consequences,			Death

(Continues)

SURGICAL: INTRA-OPERATIVE COMPLICATIONS				
		Grade		
Adverse Event	1	2	3	4
soft tissue injury	Incidents managed with minimal change in operative tactics and without further consequence	for example, primary repair of injured structure	Incidents with further non-life-threatening consequences, for example, resection or reconstruction of injured structure	Incidents with further life-threatening consequences; urgent intervention indicated
Definition: Injury to soft tissues adjacent or adherent to the intended operative site.				
Incorrect implant placement	Suboptimal placement or positioning that does not substantially impair implant function or result in revision	Suboptimal placement or positioning that results in intra-operative revision or reduced implant function	Incidents with further non-life-threatening consequences; requiring invasive action such as reoperation, endoscopy, etc	Incidents with life-threatening consequences or resulting in major functional impairment
Definition: Surgical introduction of implantable materials in a manner or position inconsistent with the ideal/intended operative plan.				
Intra-operative fracture or bone injury	Clinical or diagnostic observation only; intervention not indicated	Immobilization or other non-operative intervention indicated	Operative intervention indicated	Life-threatening consequences; urgent intervention indicated
Definition: Traumatic injury to the bone during surgery in which the continuity of the bone is broken; includes errors in drilling.				
Intra-operative technical or equipment failure	Incidents managed with minimal change in operative tactics and without further consequences for the patient	Incidents managed with changes in operative tactics but without further consequences for the patient	Incidents with further non-life-threatening consequences for the patient	Incidents with further life-threatening consequences for the patient; urgent intervention indicated
Definition: Malfunction of operative equipment, instruments or implantable materials, whether due to operator error or not.				
Tumour capsular disruption	Incidents resulting in minor disruption; minimal contamination of surrounding tissues	Incidents resulting in moderate to severe disruption; gross contamination of surrounding tissues	—	—
Definition: Loss of integrity of anatomic barrier structures containing tumour tissues, due to surgical manipulation.				
Other (specify, _____)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate 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
SURGICAL: POST-OPERATIVE COMPLICATIONS				
		Grade		
Adverse Event	1	2	3	4
Adhesions	Clinical or diagnostic observation only; intervention not indicated	Symptomatic; medical management indicated	Symptomatic; invasive intervention indicated	Life-threatening consequences; urgent intervention indicated
Death				

SURGICAL: POST-OPERATIVE COMPLICATIONS					
Grade					
Adverse Event	1	2	3	4	5
Definition: An abnormal union of tissues or organs due to inflammation or injury.					
Dental malocclusion	Observation only; no intervention indicated	Local irritation requiring topical care/lifestyle change	Surgical (tooth extraction) or orthodontic intervention indicated	—	—
Definition: Abnormal alignment of the teeth.					
Implant complications	Clinical or diagnostic observation only; intervention not indicated	Cage-side or non-invasive management indicated, including antibiotics	Invasive intervention indicated to remove, revise or replace implant	Life-threatening consequences; urgent intervention indicated	Death
Definition: A functional or positional problem with an indwelling medical device or material, such as migration, dislodgement, functional impairment, infection or breakage.					
Mandibular drift	Observation only; no intervention indicated	Local irritation requiring topical care or lifestyle change	Surgical (tooth extraction) or orthodontic intervention indicated	—	—
Definition: Movement of the mandible relative to the maxilla over time, such that the mandible becomes misaligned with the maxilla.					
Oronasal fistula	Observation only; no intervention required	Medical/lifestyle changes indicated (change in diet consistency, outpatient antibiotics to treat bacterial rhinitis/aspiration pneumonia etc)	Surgical intervention indicated; aspiration pneumonia requiring in-hospital management that is, O ₂ , IV antibiotics	—	Death
Definition: Development of a communication between the oral and nasal cavities.					
Prehension difficulties	Occasional dropping of food noted but not interfering with ADL	Change in oral diet type or consistency required; transient weight loss	Transient tube feeding required; supplemental tube feeding required to maintain body weight	Oral intake largely impossible; complete tube feeding required to maintain body weight	Death
Definition: Difficulty in picking up food by mouth, or difficulty in holding food inside the oral cavity.					
Residual flow through an attenuated vessel	Negligible residual flow without clinical consequences; intervention not indicated	Mild residual flow with possible clinical consequences; serial monitoring or medical management indicated	Moderate residual flow with likely clinical consequences; reattenuation indicated if feasible	Complete or near-complete failure of attenuation; life-threatening consequences possible; reattenuation indicated if feasible	—
Definition: Ongoing post-procedural blood flow through a vascular structure deliberately targeted for therapeutic attenuation (such as by surgical placement of ligatures or other attenuating devices, or via intravascular introduction of occlusive materials).					
Surgical site stenosis or stricture	Clinical or diagnostic observation only; intervention not indicated	Symptomatic; medical management or change in lifestyle (eg, diet, exercise) indicated	Symptomatic; invasive intervention indicated (eg, stent, surgery, luminal dilation, tube feeding)	Life-threatening consequences including obstruction, airway compromise; urgent intervention indicated	Death
Definition: Narrowing of a surgically repaired mucosal structure, stoma or anastomosis.					
Visceral perforation	Clinical or diagnostic observation only; intervention not indicated	Symptomatic; medical management indicated	Symptomatic; invasive intervention indicated (eg, stent, surgical repair, diversion or excision)	Life-threatening consequences; urgent intervention indicated	Death

(Continues)

SURGICAL: POST-OPERATIVE COMPLICATIONS						
Adverse Event	Grade	1	2	3	4	5
Definition: Loss of integrity of the wall of hollow viscus (eg, trachea, oesophagus, stomach, intestine, rectum, uterus, ureter, urinary bladder, gall bladder) due to direct trauma or ischaemia and necrosis; at an anatomic site not directly involving a surgical repair or incision.						
Wound complication	Observation only; topical intervention indicated	Local care indicated	Operative intervention indicated	Life-threatening consequences	Death	
Definition: Development of a new problem at the site of an existing wound; complications that do not meet criteria for wound infection or wound dehiscence.						
Wound dehiscence or anastomotic leakage; biliary	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Symptomatic; invasive intervention indicated (eg, surgical repair, cholecystostomy)	Life-threatening consequences; urgent operative intervention indicated	Death	
Definition: Bile leakage at the site of previous surgical intervention involving the liver, bile ducts or gall bladder.						
Wound dehiscence or anastomotic leakage; enteric	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated	Symptomatic; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death	
Definition: Enteric leakage at the site of previous surgical intervention involving oesophagus, stomach, intestine or rectum.						
Wound dehiscence or anastomotic leakage; urinary tract	Asymptomatic diagnostic finding; intervention not indicated	Symptomatic; medical intervention indicated, including retrograde placement of indwelling urinary catheter	Symptomatic; Invasive intervention indicated (eg, surgical repair, stent, cystostomy, nephrostomy or peritoneal drainage catheters)	Life-threatening consequences; urgent operative intervention indicated	Death	
Definition: Urine leakage at the site of previous surgical intervention involving the kidney, ureter, urinary bladder, prostate or urethra.						
Wound dehiscence; not otherwise specified	Incisional separation, intervention not indicated	Incisional separation managed with local care (Cage side suturing or bandaging) or medical intervention	Fascial disruption or dehiscence without evisceration; revision by operative intervention indicated	Life-threatening consequences; symptomatic hernia, evisceration, major reconstruction, resection or amputation indicated	Death	
Definition: Separation of the approximated margins of a surgical wound; excludes surgically created wounds specifically categorized as enteric, biliary or urinary tract dehiscence.						
Wound infection	Localized, local intervention indicated	Oral antimicrobial intervention indicated	IV antimicrobial intervention indicated; invasive intervention indicated (eg, debridement, drainage, repair)	Life-threatening consequences; urgent intervention indicated	Death	
Definition: An infectious process involving a traumatic or surgically created wound.						
Other (specify _____)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate 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	

VASCULAR		Grade			
Adverse Event	1	2	3	4	5
Capillary leak syndrome	Asymptomatic	Symptomatic; medical intervention indicated	Respiratory compromise or pressor support	Life-threatening; ventilatory support 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, ischaemia-reperfusion injuries, toxemias, medications or poisoning. It can lead to generalized oedema and multiple organ failure.					
Lymph leakage/lymphedema	Asymptomatic	Symptomatic; medical intervention indicated	Severe symptoms; radiologic, endoscopic or elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by the loss of lymph fluid into the surrounding tissue or body cavity.					
Peripheral arterial ischaemia	—	Brief (<24 h) episode of ischaemia managed non-surgically and without permanent deficit	Recurring or prolonged (>24 h) and/or invasive intervention indicated	Life-threatening, disabling and/or associated with end-organ damage (eg, limb loss)	Death
Definition: A disorder characterized by impaired circulation to an extremity.					
Phlebitis	—	Present	—	—	—
Definition: A disorder characterized by inflammation of the wall of a vein.					
Thrombosis/thrombus/embolism	—	Deep vein thrombosis or cardiac thrombosis; intervention not indicated	Deep vein thrombosis or cardiac thrombosis; intervention indicated (eg, anticoagulation, lysis, invasive procedure)	Embolic event including pulmonary embolism or life-threatening thrombus	Death
Definition: A disorder characterized by occlusion of a vessel by a thrombus that has migrated from a distal site via the blood stream.					
Vasculitis (not including perivascular injection of drug)	Mild, intervention not indicated	Non-steroidal medical intervention indicated	Steroids indicated	Ischaemic changes; amputation or surgical debridement indicated	Death
Definition: A disorder characterized by inflammation involving the wall of a vessel.					
Ischaemia	—	Brief (<24 h) episode of ischaemia managed medically and without permanent deficit	Prolonged (>24 h) or recurring clinical signs and/or invasive intervention indicated	Life-threatening; disabling; evidence of end-organ damage	Death
A disorder characterized by impaired circulation to an extremity or body tissue/organ.					
Other (specify, -----)	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or non-invasive intervention indicated; limiting age appropriate 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

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Kimberly A. Selting  <https://orcid.org/0000-0002-7995-3618>

Kristen M. Weishaar  <https://orcid.org/0000-0003-2827-2246>

ORCID

Amy K. LeBlanc  <https://orcid.org/0000-0001-7656-9859>

Matthew Atherton  <https://orcid.org/0000-0002-9830-3151>

Jenna H. Burton  <https://orcid.org/0000-0002-1895-8298>

Nicola J. Mason  <https://orcid.org/0000-0002-6149-4927>

Michelle Oblak  <https://orcid.org/0000-0001-8489-4643>

Laura E. Selmic  <https://orcid.org/0000-0001-6695-6273>

How to cite this article: LeBlanc AK, Atherton M, Bentley RT, et al. Veterinary Cooperative Oncology Group—Common Terminology Criteria for Adverse Events (VCOG-CTCAE v2) following investigational therapy in dogs and cats. *Vet Comp Oncol.* 2021;19:311–352. <https://doi.org/10.1111/vco.12677>