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Guiding the Optimal Translation of New Cancer Treatments From Canine to Human Cancer Patients

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Abstract

On June 20, 2008 a meeting entitled “Translation of new cancer treatments from canine to human cancer patients”, sponsored by the National Cancer Institute in Bethesda Maryland was convened to discuss the potential value, opportunity, risks and rewards of an integrated and comparative drug development path for new cancer therapeutics that includes naturally occurring cancers in pet animals. A summary of this meeting and subsequent discussion are provided here to afford clarity on the conduct of these studies so as to optimize the opportunities provided by this novel drug development and modeling strategy.

Translation of new cancer treatments from canine to human cancer patients

The integration of studies that include pet dogs with cancer into the development path of new cancer drugs is becoming more common and is expected to increase as part of innovative drug development(1). The guidelines for the conduct and oversight of such non-clinical studies, intended to support the development of human cancer drugs or treatment delivery devices are not standardized and require input and discussion from several interested communities. Towards this goal, on June 20, 2008 a meeting entitled the “Translation of new cancer treatments from canine to human cancer patients” was held and sponsored by the National Cancer Institute in Bethesda, Maryland. Members of the pharmaceutical and biotechnology community, academia, and regulatory and federal agencies were invited to attend this open forum. While topics of device and biomarker development were also included in the agenda of this meeting, additional discussion on inclusion of dogs with cancer into these areas of study is needed to clearly guide optimal data integration. Such discussion summaries will be the topic of future reports from our groups. The following is a summary of the key points of the

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Statement of Translational Relevance

Naturally occurring tumors in dogs share many clinical and molecular similarities to human cancers that are difficult to replicate in other model systems. These spontaneously arising cancers provide an opportunity to answer critical questions in the development of new cancer drugs that are not currently answered in conventional preclinical models or in human clinical trials. The opportunity to build a comparative and integrated drug development path for new cancer drugs that includes pet dogs is now reasonable based on the release of the canine genome, the increasing availability of biological tools and reagents for the study of the dog, and the development of multi-center consortia capable to conduct clinical studies in advance or in parallel with human clinical trials. The discussion reported herein provides a guide on the optimal conduct of such canine comparative oncology studies to maximally benefit the development of human cancer drugs.

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discussion generated during and since this meeting on the topic of drug development. Based on this summary we propose a guide to promote implementation of an integrated and comparative approach to cancer drug development.

The Opportunity

The value of including pet dogs with cancer into studies intended to support the development of human cancer treatment strategies has been recognized for over 30 years. Recent reviews have summarized milestones and progress made in the field (1–8). These studies in dogs have aided the translational process in many ways. For example, the study of cancer drugs in dogs provides a unique opportunity to evaluate both the safety and activity of a novel drug in the same species (i.e. same species assessment of therapeutic index) before first in-human studies. Other examples include opportunities to understand pharmacokinetic and tumor pharmacodynamic relationships following drug exposure, and evaluation of the activity of new agents in the context of a naturally occurring cancer model(9). These data are currently difficult to obtain from conventional preclinical models or from human clinical trials alone. Table 1 summarizes recent studies in comparative oncology that have directly contributed to the development of new cancer drugs.

The opportunity now exists to extend the translational value of studies that include dogs with cancer. The value is enhanced by the completion of the canine genome sequence and the commercial availability of reagents and assay platforms useful to answer questions of tumor and drug biology (1,4,10–13). This translational opportunity is also now extended by a national infrastructure able to conduct multi-institutional studies[1] so as to provide data in a timely manner and more directly engage the veterinary oncology communities. This infrastructure may now also respond to the need of the pharmaceutical community for cancer models that can better inform the drug development path of new cancer drugs. Specific examples of studies conducted with this intent, both before and after an investigational new drug (IND) filing, were highlighted at the meeting (Table I). Collectively, these studies demonstrate the progress in the field of comparative oncology(2,3,14). Indeed, studies of pet animals with cancer are now increasingly "*integrated*" into the development path of new cancer treatments. ***Integration*** refers to the prospective design and development of trials where study endpoints are specifically aligned with the design and development of studies in other preclinical species and in human studies. The most successful comparative and integrated development efforts have several features in common:

- Prospective articulation of simple and specific questions that cannot be fully answered in conventional preclinical models or in early human clinical trials.
- Rigorous review process involving several individuals (scientists, veterinarians, and physicians) and disciplines, so as to ensure that study questions are prioritized and effectively answered.
- Commitment by the development team to review and use data from the non-human clinical studies within the totality of information available for the new treatment approach.

Trial Implementation

Protocol Development and Review

A non-human clinical study that includes pet dogs with cancer must be designed and implemented with the humane care of the pet animal cancer patient as a primary consideration,

[1]http://ccr.cancer.gov/resources/cop/COTC.asp

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with the informed permission of the pet owner, under the guidance of an accredited and appropriate institutional animal care. The scientific and translational motivation of the study must be balanced against the over-riding mandate for animal care.

For the most part, study designs implemented for pet dogs will be similar to the spectrum of designs used in human clinical trials. However, studies should not be constrained by the historic conventions of phase I, II and III studies, but should focus on answering specific questions that are necessary for progress of the product development strategy. As indicated above, the studies should have objectives that are clearly defined and prioritized that take advantage of the unique opportunities of the comparative oncology approach. For example the assessment of several endpoints in a single individual following a given drug exposure can include clinical endpoints supportive of anti-tumor activity, biological endpoints addressing mechanisms of action, identification and validation of biomarkers, and correlation of these endpoints with imaging and pharmacokinetics(9,15,16). It is likely that a single study will not and cannot answer all types of questions. Furthermore, it is likely that most early studies in pet dogs will not prioritize clinical activity of an agent, but will confirm questions of drug dose/schedule and biological activity and in so doing focus on validating or supporting an understanding of the mechanisms of action or therapeutic index. Later studies may prioritize anti-tumor activity against measurable tumors or against minimal residual disease, or to model personalized medicine approaches in oncology, opportunities uniquely possible in this model system. To optimally inform the development path of new human cancer therapy, comparative oncology studies should be flexible in design so as to efficiently respond to new data and interpretations that may be generated both within and outside the study.

The active pharmaceutical ingredient (API) considerations for these non-human clinical studies should not require that drug be prepared under good manufacturing process (GMP) product. API determinants should however consider the scientific and translational intent for the study, the need to provide informative (i.e. “clean”) data on a specific agent and to reduce risks of harm to the pet animal patient. With these in mind, agents prepared for non-human clinical studies in pet dogs should be:

- Sterile
- Endotoxin free
- High quality (active ingredient greater than 98% measured by sensitive detection)
- High purity (any impurity greater than 1% should be identified)

It is anticipated that the use of a GMP quality agent will become more important to the study sponsors as an agent progresses to and beyond the point of investigational new drug (IND) filing.

As discussed earlier, studies should be reviewed and approved by an Institutional Animal Care and Use Committee (IACUC) or similar bodies. These review boards will be responsible for the safety of pet animals, pet owners and animal health professionals who are involved with these non-clinical studies. The constitution, description, responsibilities and authority of an Institutional Animal Care And Use Committee are described in detail in Public Health Service Policy on the Humane Care and Use of Laboratory Animals and may be generalized to include studies supported by federal and non-federal funds (17). Given the unique features of these human product development studies, representation on the IACUC should include individuals with direct and specific experience in the conduct of clinical studies that include pet animals, and more specifically, pet animals with cancer. To ensure that the care of pet animals is prioritized during the conduct of these studies, a data safety management function should be provided by a group that is either distinct or overlapping with the IACUC or by the IACUC itself. The data safety management function should be provided by individuals with direct and

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specific experience in the conduct of clinical trials that include pet animals and have specific experience with current standards of care for pet animals with cancer, but who are not directly involved as investigators in a given study. This data safety management group may function in ways similar to a data safety management board (DSMB) responsible for the oversight of a human clinical trial (18). Briefly, the a DSMB function in the oversight of a comparative oncology study should:

- Review the research protocol and plans for data and safety monitoring.
- Evaluate the progress of interventional trial(s), including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, participant risk versus benefit, performance of trial sites, and other factors that can affect study outcome.
- Make recommendations to the IACUC and investigators concerning continuation or conclusion of the trial(s).
- Protect the confidentiality of the trial data and the results of monitoring a study.

Trial conduct

In general, studies should be conducted in the spirit of Good Clinical Practice (GCP). GCP procedures and guidance for their use in veterinary species have been described and are available through VICH GCP (19). All VICH GCP procedures and regulations may not be relevant to the conduct of comparative studies. Attributes of the VICH GCP that should be prioritized in the conduct of these studies, include:

- Development and use of a complete study protocol with a complete consent form and consenting process
- Document management system that can manage protocol changes and modifications
- Training of qualified participating investigators on the conduct of the study
- Inspection of institutional facilities necessary for study conduct
- Contemporaneous entry of data using case report forms or a similar mechanism
- Training and use of relevant standard operating procedures (SOPs)
- Safety management approaches that includes monitoring and reporting of adverse events and serious adverse events to a DSMB and/or IACUC
- Mechanisms to verify the conduct and reporting of data within the study

Adverse events

The evaluation of toxicities related to a new human cancer drug has conventionally required controlled studies using inbred purpose-bred research animals (1). Non-human clinical studies that include pet dogs with cancer should not be considered as a means to replace these conventional and necessary toxicokinetic studies. However, the assessment of toxicity in tumor-bearing dogs may be a valuable complement to the safety assessment of a new drug. Furthermore, toxicokinetic data gathered in purpose-bred research animals may be used in the design of tumor-bearing dog studies when available. In rare instances, toxicokinetic data from purpose-bred dogs will not be available or may not be informative in the design of tumor-bearing dog studies(20). In such cases, as is the case in human phase I cancer studies, the first dog to receive a new cancer agent may be a tumor bearing dog. Such rare instances require careful consideration by the investigators, IACUC, and DSMB.

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Similar to early phase human clinical trials, adverse events are an expected outcome of studies of new anti-cancer agents in dogs with cancer. Expected adverse events are those events that are predicted before the conduct of a study. ***Expected adverse events*** may be drug-related (predicted by the mechanism of action of the drug or its evaluation in purpose-bred animals or other species), disease-related (predicted by the literature or experiential evidence in the veterinary oncology space), and/or study-related (i.e. associated with participation in the study; for example sedated procedures within the study). All **expected** adverse events must be clearly described in the protocol and in the informed consent process. It is understood that expected adverse events in cancer studies may be severe and may include death. All other adverse events that occur in the conduct of a study are referred to as ***unexpected adverse events***. It is important to note that expected adverse events may be defined as **unexpected** based on unexpected severity, frequency, pattern of response to supportive measures, or duration of the event. Unexpected adverse events that become evident in the conduct of the study, regardless of attribution (drug, disease, or study participation) should be reviewed, reported to the IACUC and/or DSMB and added to the informed consent if found to be repeatable. Additional suggested regulatory reporting of these unexpected adverse events is discussed below.

Reporting and Regulatory Review

A clear and open understanding of the standards for reporting data (to regulatory authorities and others) from comparative oncology studies is needed, and currently represents an impediment to progress in the field. In general, non-clinical trials that include pet dogs with cancer may be considered at two points in time in the life of a new human cancer treatment, either before an IND is filed (i.e. pre-IND) or after an IND is filed (i.e. post-IND). The implementation of a study, including protocol development and design, IACUC and data safety management, and trial conduct have been discussed above and are similar in both development settings (i.e. pre-IND and post-IND studies).

Pre-IND Studies

As discussed earlier, the evaluation of new cancer agents in pet dogs with cancer can be highly informative before first in human studies. Because these animal studies may have proof-of-concept or research motivations, it is possible that some of these agents will not necessarily proceed to human development and IND filing. Whether the human-intent research motivation of these studies should require the filing an Investigative New Animal Drug (INAD) through the FDA-Center for Veterinary Medicine (CVM) was a topic of detailed discussion both at and after our meeting. An INAD is a necessary component of the regulatory development of a new drug that is under development for use in the animal health market(21). The regulation that requires the establishment of an INAD is under the guidance of 21 CFR 511.1(b). This regulation addresses the “clinical investigation” of “new animal drugs” and does not address investigational agents intended for human use alone. The INAD provides notification to the FDA-CVM of the conduct of a study aimed at approval of a new animal drug, a description of the new drug, some assurance of the risk for the proposed studies and finally provides a reporting mechanism to monitor the distribution of a new animal drug undergoing clinical investigation before its approval, through the Notice of Claimed Investigational Exemption (NCIE) linked to the INAD process. The information and data required for an INAD filing will be generally met in the development of a study protocol that follows the trial implementation guidance provided above. Briefly, the data required for INAD filing includes:

- Proposed indication, dose and route of administration
- Established (generic) name, chemical structure and description of the drug
- Formulation including the concentration of the drug in a single dose

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- Information about components in the drug product in addition to the drug itself (e.g., salts, and excipients)
- Mechanism of action (if known)
- Summary of the results of any pilot studies already completed in dogs or other species

Based on the above it is reasonable that an INAD is not necessary for the conduct of these human-directed research studies. The suggested trial implementation guidance (proposed herein) including both IACUC and DSMB oversight more than adequately addresses the question of risk for the proposed studies to pet animals and includes details on API above those generally required by an INAD. Furthermore, based on the fact that human-intent research that involves purpose-bred research animals does not require an NCIE, (22), it is also reasonable that an NCIE should not be necessary for multi-institutional human-directed research studies that include pet dogs with cancer. Collectively, the additional value of an INAD for these comparative oncology studies appears to be small.

Whether or not an INAD is filed for tumor-bearing dog studies conducted in the pre-IND setting, a full report and associated primary data should be maintained as part of the legacy of the agent under development. Clear documentation of expected and unexpected adverse events should be a priority of all studies. Unexpected adverse events that occur should be reviewed during the study by the study sponsor, investigators and the DSMB. Actions to address unexpected adverse events within a ongoing canine study should include but are not limited to, dose and schedule attenuation, modification of protocol and informed consent, and notification of all investigators in multi-center studies.

A final study report and associated data should be included in an IND application package if the agent in question progresses through development (Table 2). The unexpected adverse events that occur in a study that includes pet dogs with cancer should be assessed carefully against all available and higher priority toxicokinetic data from purpose-bred research dogs and other species. We note that the identification of an unexpected adverse events occurring in tumor-bearing dogs that were not previously identified in purpose-bred research dogs is unprecedented. Based on experience with over 30 human cytotoxic chemotherapeutic agents commonly used off-label to treat pet dogs, no adverse events have been identified in tumor-bearing dogs that were not seen in purpose-bred research dogs[2]. In the rare and unprecedented circumstance that unexpected adverse events are defined in the conduct of a tumor-bearing dog study, it is reasonable that additional studies focused on that unexpected event should be conducted in either purpose-bred or tumor-bearing dogs before IND filing.

Post-IND Studies

Compared to the discussion of pre-IND studies, current regulations regarding adverse event reporting for the post-IND study of new human cancer agents in tumor bearing animals is provided by Investigational New Drug Application section 312.32 IND Safety Report(23)

- All serious and unexpected adverse events must be reported within fifteen days of their development.
- Events are unexpected if they are not defined as expected within a study protocol or investigator's brochure (irrespective of attribution).
- Events are further defined as unexpected based on frequency, severity and duration of recovery.

[2]http://ccr.cancer.gov/resources/cop/

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- Events are defined as serious if they are life threatening or if they result in hospitalization or prolongation of hospitalization, disability, birth defect or congenital anomaly, or death. Events that would have resulted in one of the listed outcomes but were averted by intervention are still considered to be serious.
- Serious should not be interchanged with severe. Events can be severe but not life threatening or lead to any of the outcomes characterized as serious.

Based on these criteria, any event that occurs in a study of a new human cancer agent conducted in tumor-bearing dogs that is either not serious or is expected, based on the protocol and informed consent, does not require expedited reporting (Table 2). Post hoc reporting of all adverse events with attribution and consideration should be provided with IND updates as a narrative at the completion of the study. This may include follow up studies to examine specific expected and unexpected adverse events.

Risk Reward for Post IND Studies

The value of conducting studies in tumor-bearing dogs after or during first in human studies is significant. These studies are positioned to uniquely inform the development and conduct of later stage studies in humans. Pet animal studies provide support of the mechanistic pathway and can establish proof of concept, often difficult to validate in conventional drug development strategies. Correlative studies that would be difficult to complete in humans including multiple biopsy and collection time points, are feasible in pet animal studies and can lead to modification or optimization of the human study design. In addition, pet dog studies can provide an assessment on treatment schedules, drug combination strategies, chronic drug exposures, and evaluation of correlative and surrogate endpoints. Finally, pet dogs with cancer provide a unique opportunity to evaluate activity of an agent in the setting of minimal residual disease in a timely manner, as well as to identify new disease subtypes or individuals (personalized medicine) that are responsive to a therapy. Despite the value of these additional data in the development path of new human cancer drugs, a concern raised, primarily from the pharmaceutical industry is how data, particularly unexpected adverse events, from such studies will impact ongoing human trials with the same or similar agents. These concerns and perception of risk is greatest for agents that are first in class or have less established histories in other species. The perception of risk is in part the result of a current lack of clarity as to the reaction of regulatory bodies to adverse events that may be reported in a dog study, and from within the industry that such data may “contaminate” the legacy of a new cancer drug. As indicated above, it is important to emphasize that expected adverse events, including those related to the disease (i.e. cancer and associated syndromes in often aged pet dogs), will be included in the comparative oncology study protocol for that drug. It is expected that tumor-bearing dogs will have a broad range of disease related complications including death. All such expected events will be clearly described in the protocol or investigator’s brochure as expected events, and as such will protect an agent from false attribution. As indicated earlier, the chance of uncovering a unique toxicity (i.e. unexpected) associated with a new cancer drug in tumor-bearing dogs is very small and has no current precedent.

Despite this small risk, the novelty of the comparative oncology drug development approach does not yet provide a sufficient basis of experience for how adverse event data from pet dog studies will be assessed by regulatory bodies. It is reasonable that a regulatory review of any events that occur in a pet dog cancer study will be considerate of the fact that an agent’s toxicity assessment is the mandate of controlled studies in non-diseased animals. Furthermore the tolerance to serious adverse events in the cancer therapeutic area is high and the need for new treatments equally high and pressing. The design of studies with tumor-bearing dogs should however include structures that may allow the evaluation of unexpected events if they occur. Such structures may include stopping rules that allow expansion of treatment cohorts (with

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either tumor-bearing or non-diseased animals) to determine if an unexpected event is reproducible. In so doing, an opportunity exists to answer and understand observed unexpected adverse events. This opportunity will allow appropriate actions to be taken in the design or conduct of human clinical studies with the same agent. If unexpected events are repeatable, it is possible that the human development path will be modified. This may include changes in eligibility and exclusion criteria for a study, additions to monitoring strategies, or changes to informed consent. The risks of these actions must be accepted as part of the value proposition provided by these pet dog studies.

In conclusion, the value and opportunity of an integrated drug development approach that includes non-clinical trials with pet animals with cancer has been increasingly demonstrated by the growth of this field. These studies provide a unique mechanism to answer questions that currently are left unanswered about novel cancer treatments. In doing so, the totality of data surrounding an agent is expanded and should result in optimized drug development paths. Through the input of key opinion leaders in the field of cancer drug development and comparative oncology, we propose a rigorous and efficient process for the implementation of an integrated and comparative approach to cancer drug development. We propose a process that prioritizes the care of pet animal patients who are included in these studies and balances this priority against the human-intent translational science interests of the study. We furthermore propose an approach to regulatory reporting of data from these trials both before and after a new cancer agent has entered human trial development. With a clarified trial implementation path in place, we expect an expansion of the opportunity for pet animals with cancer to uniquely inform the development of novel agents destined for the treatment of human cancer patients. We expect this outcome, in parallel, to improve the care and treatment options for pet animals with cancer.

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Table 1

List of presenters from the "Translation of new cancer treatments from canine to human cancer patients" meeting on June 20, 2008.

Introduction		
Lee Helman, MD	National Cancer Institute	Obstacles in the cancer drug development path
Steven Hirschfeld, MD, PhD	National Institute of Child Health and Human Development	Framing the data to address expectations(24)
Session I: Human Pre-Investigational New Drug Studies		
Steve Libutti, MD	National Cancer Institute	Targeted delivery of TNF-α to tumor associated vasculature through the RGD motif concept and preclinical development in murine models(25)
Melissa Paoloni, DVM	National Cancer Institute	Validation of safety, targeting and activity in dogs with solid tumors(1,20)
Wendy Levin, MD	Pfizer	In what ways can dogs with cancer inform the development of agents that are first in class?
Cheryl London, DVM, PhD	The Ohio State University	Establishing pharmacokinetic, pharmacodynamic, efficacy correlations in dogs with cancer(9)
Session II: Human Post-Investigational New Studies		
Laurence Baker, DO	Southwest Oncology Group	Rapamycin and rapalogs in patients with sarcoma
Chand Khanna, DVM, PhD	National Cancer Institute	Translation and integration: Studies of rapamycin in dogs with osteosarcoma(26)
Daniel Tumas, DVM, PhD	Gilead Pharmaceuticals	Human development path
David Vail, DVM	University of Wisconsin	Correlation of PK, PD, efficacy and imaging in dogs with lymphoma(15,27,28)
Session III: Early Device Evaluation		
Lisa Forrest, DVM	University of Wisconsin	Tomotherapy treatment plan evaluation and validation in dogs with head and neck cancer(16,29)
Robert Jeraj, PhD	University of Wisconsin	Imaging as a biomarker: Importance of image quality in translational research(30)
Session IV: Preclinical Biomarker Evaluation		
Yuval Shaked, PhD	University of Toronto	The benefits and challenges in using circulating endothelial precursor cells as a cellular biomarker to determine the optimal biological dose of antiangiogenic drugs(31,32)
Anthony Mutsaers, DVM	University of Toronto	Studies of angiogenesis inhibitors in dogs with naturally occurring cancers(33,34)
Session V: Before and Beyond Phase I and Future Trial Designs		
Joseph Tomaszewski, PhD	National Cancer Institute	Phase 0 trials in cancer drug development(35,36)
Douglas Thamm, DVM	Colorado State University	Informing human clinical trials beyond Phase I(37)

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Table 2

Trial and Regulatory Reporting of Expected and Unexpected Adverse Events

Pre IND Studies

Adverse events	Trial Reporting/Actions	Regulatory Reporting
Expected[1]	• Record within Protocol CRFs • Notify DSMB or IACUC if serious	• Upon study completion, if agent moves to IND submission then all trial data should be provided with accompanying study narrative.
Unexpected[2]	• Record within Protocol CRFs • Notify DSMB and IACUC • Notify investigators, modify consent form if serious	• Upon study completion, if agent moves to IND submission then all trial data should be provided with accompanying study narrative

Post IND Studies

Adverse events	Trial Reporting/Actions	Regulatory Reporting
Expected	• Record within Protocol CRFs • Notify DSMB or IACUC if serious	• Upon study completion all trial data should be provided with accompanying study narrative
Unexpected	• Record within Protocol CRFs • Notify DSMB and IACUC • Notify investigators, modify consent form if serious	• If serious, 15-day report of events to the study sponsor, (IND file and IRB) • Upon study completion all trial data should be provided with accompanying study narrative

[1] ***Expected adverse events:*** may be drug-related (predicted by the mechanism of action of the drug or its evaluation in purpose-bred animals or other species), disease-related (predicted by the literature or experiential evidence in the veterinary oncology space), and/or study-related (i.e. associated with participation in the study; for example sedated procedures within the study).

[2] ***Unexpected adverse events***: all other adverse events that occur in the conduct of a study. It is important to note that expected adverse events may be defined as **unexpected** based on unexpected severity, pattern of response to supportive measures, or duration of the event.