towards high-quality clinical trials and
implementation of genomic medicine

ATLAS Training Program

Course : CRC Training Course
Lecture Title : Supporting Safety Evaluation in Cancer Clinical Trials
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Education

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2011 Worked in a hospital (nurse)

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Supporting safety evaluation in cancer clinical trials

[Content of today's lecture]

- Purpose of safety evaluation
- What are adverse events?
- What is CTCAE?
- Causal relationship
- Actual support for safety evaluation
- SAE reporting

Purpose of Safety Evaluation

Why is safety evaluation important?

- DECLARATION OF HELSINKI　Risks, Burdens, and Benefits (16−18)
  - 16. In medical practice and medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

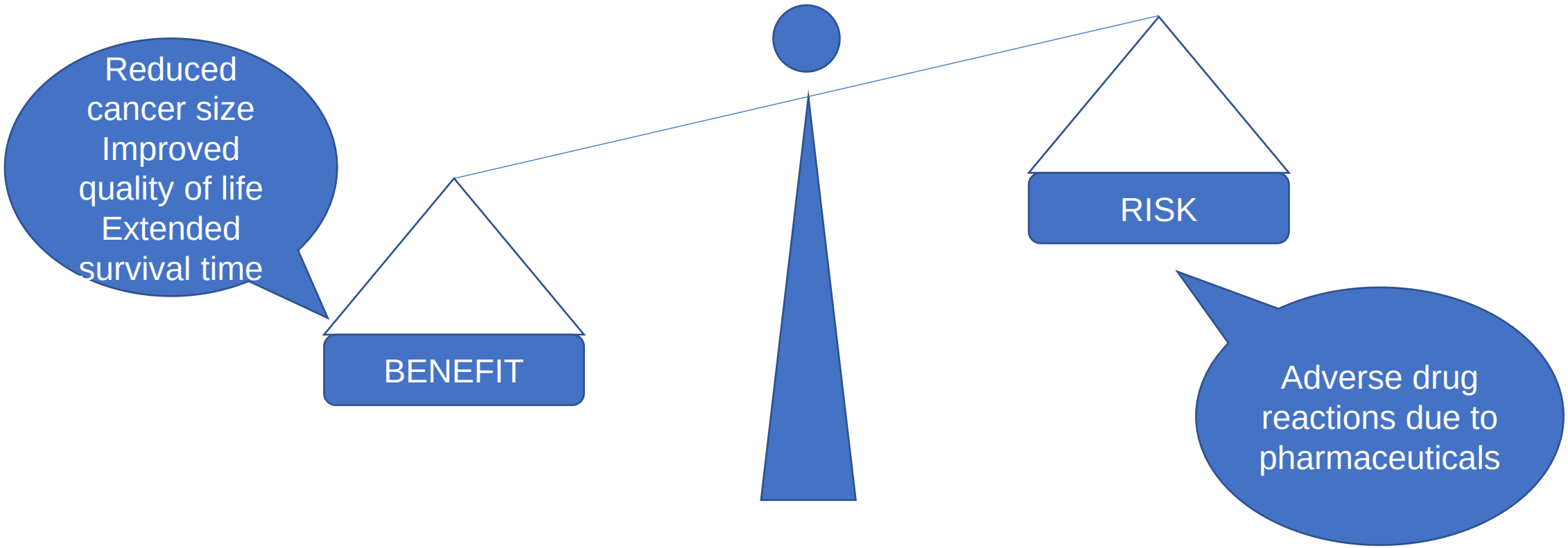
  - 17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to these individuals and groups in the research and to other individuals or groups affected by the condition under investigation.

    Measures to minimize risks must be implemented. The risks must be continuously monitored, assessed, and documented by the researcher.

  - 18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

Citation:　https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/

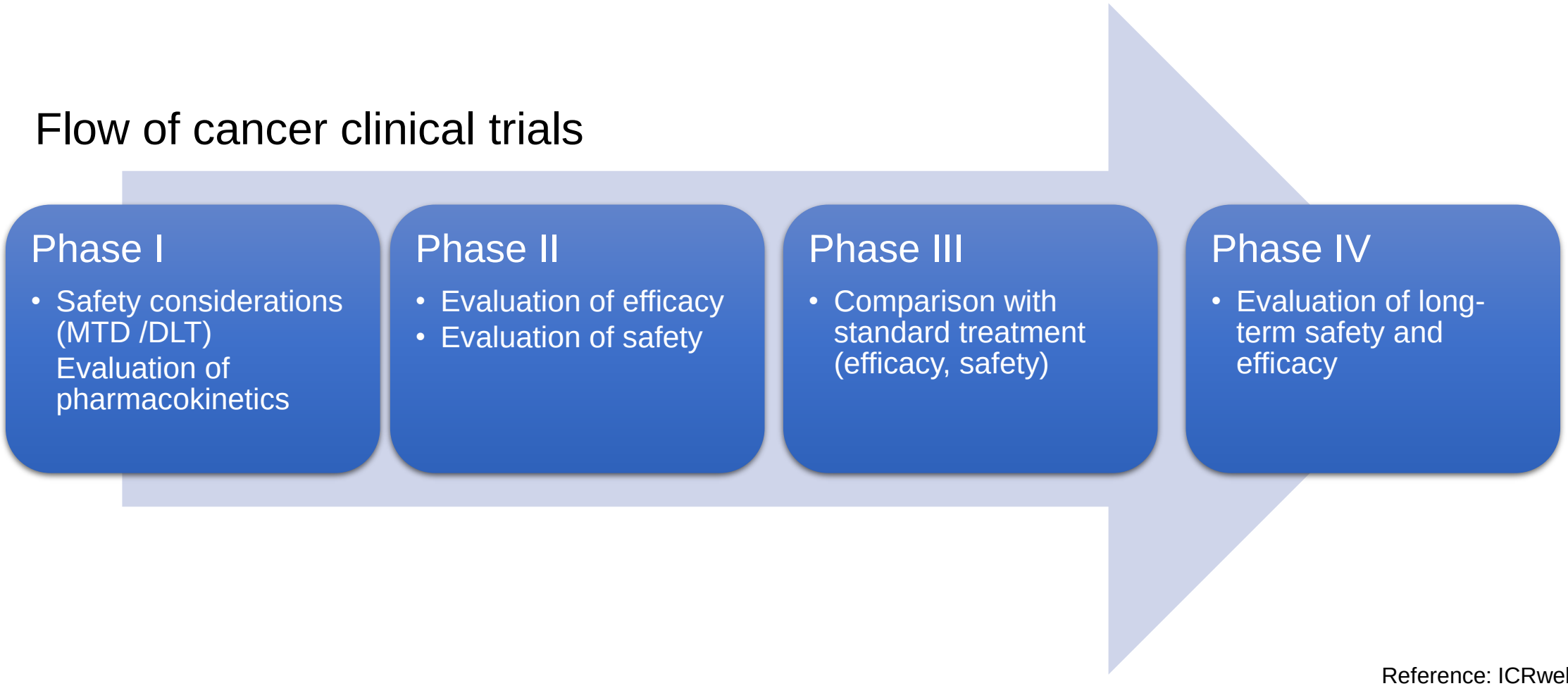
Why is safety evaluation important?



ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

Why is safety evaluation important?

Flow of cancer clinical trials



Reference: ICRweb

ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

Purpose of safety evaluation

- Ensure the safety of the participant

- Implement appropriate clinical trial treatment
  - Study drug dose reduction and discontinuation criteria
  - Appropriate management of adverse drug reactions

Reference: がん臨床試験テキストブック　Chapter 16.　有害事象の評価と報告（CTCAE）Hiroe Nozawa

What are adverse events?

What are adverse events?

- Adverse event (AE)
  - All undesirable medical events that occur in participants administered the drug (study drug)
  - **Regardless of the causal relationship** with the treatment

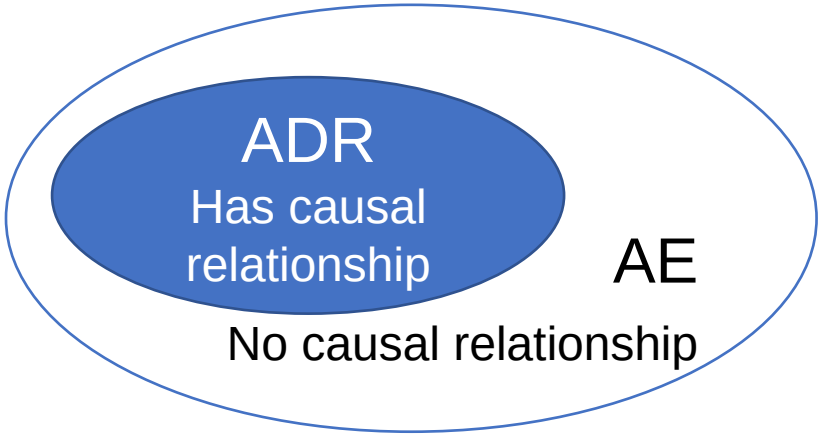
POINT!

- Before administration of the study drug, confirm whether adverse events are subject to reporting
- Even events unrelated to the study drug (example: falls, common cold) must be reported as AEs

Citation: CRCテキストブック第4版　有害事象報告：Chieko Suzuki

What are adverse events?

- Adverse drug reaction (ADR)
  - A harmful and unintended reaction to the drug, regardless of the administered dose
  - ADRs are adverse events in which a **causal relationship** with the drug **cannot be ruled out**



Citation: ICHガイドラインポケット資料集

What is CTCAE?

ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

What is CTCAE

- Common Terminology Criteria for Adverse Events (CTCAE)
  - International evaluation criteria for AEs in cancer clinical trials
  - Presents the terminology and definitions of severity for AEs
  - Can be used for all modalities (including pharmacotherapy, surgery, radiation therapy, and other combination therapies)
  - Revised to ver5.0 in November 2017

→ Revision to ver6.0 scheduled in the fall of 2022

ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

CTCAE configuration

- MedDRA System Organ Class (SOC)
  - 26 items (defined by organ/system, etiology, and purpose)
- CTCAE Terms
  - Correspond to MedDRA terms
- Grade
  - Defined as grades 1–5
- Definition
  - Clarification of each AE term
- Navigational Note
  - Other AE to refer to when grading the AE

CTCAE configuration

MedDRA SOC

Immune system disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Allergic reaction	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm, hospitalization indicated for clinical sequelae; intravenous intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Navigational Note: If related to infusion, use Injury, poisoning and procedural complications: Infusion related reaction. Do not report both.					

AE Term

Grade

Definition

Navigation Note

MedDRA ： Medical Dictionary for Regulatory Activities

An international medical glossary developed in collaboration with the ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use)

Citation:https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

CTCAE Grades

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

Cardiac disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Sinus tachycardia	Asymptomatic, intervention not indicated	Symptomatic; non-urgent medical intervention indicated	Urgent medical intervention indicated	-	-
Definition: A disorder characterized by a dysrhythmia with a heart rate greater than 100 beats per minute that originates in the sinus node.					
Navigational Note: -					

Grade 0 : No adverse event or within normal limits

Grade 1 : Mild; asymptomatic or mild symptoms; clinical or diagnostic observation only; intervention not indicated.

Grade 2 : Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).

Grade 3 : Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL.

Grade 4 : Life-threatening consequences; urgent intervention indicated.

Grade 5 : Death related to AE.

Citation:https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

Points to note when using CTCAE

- Principle of nearest match
  - Classify as the closest grade

Citation:https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

Points to note when using CTCAE

Example) Drip infusion administered to patient complaining of loss of appetite

→ Anorexia grade 3?

→ Should be determined based on actions to be taken

Anorexia	Loss of appetite without alteration in eating habits	Oral intake altered without significant weight loss or malnutrition; oral nutritional supplements indicated	Associated with significant weight loss or malnutrition (e.g., inadequate oral caloric and/or fluid intake); tube feeding or TPN indicated	Life-threatening consequences; urgent intervention indicated	Death

Definition: A disorder characterized by a loss of appetite.
Navigational Note: -

POINT!

- May be classified as grade 3 if infusion is medically necessary and as grade 2 when administered at the request of the patient. Thus, it is important to thoroughly interview and assess the participant's condition

Citation:https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

Points to note when using CTCAE

- Principle of no modification at baseline
  - The grade is not modified based on the condition at baseline before treatment

    Example) If a patient had nausea grade 1 before starting treatment

Gastrointestinal disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition	Inadequate oral caloric or fluid intake; tube feeding, TPN, or hospitalization indicated	-	-
Definition: A disorder characterized by a queasy sensation and/or the urge to vomit.					
Navigational Note: -					

POINT!

・Even if grade 2 nausea develops after starting treatment, it is not increased to grade 3

・Judgement is based on the definition

Citation:https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

Points to note when using CTCAE

- Grades for some AE are defined based on the change from baseline
  - → Diarrhea, weight loss, weight gain, etc.
  - → It is important to thoroughly record the baseline data

Investigations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Weight loss	5 to <10% from baseline; intervention not indicated	10 - <20% from baseline; nutritional support indicated	>=20% from baseline; tube feeding or TPN indicated	-	-
Definition: A finding characterized by a decrease in overall body weight; for pediatrics, less than the baseline growth curve.					
Navigational Note: -					

POINT!

・Please note that weight loss and weight gain affect the dose of drip infusions.

Citation:https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

Points to note when using CTCAE

POINT!

- The CTCAE version is specified by the protocol, so the version must be checked. Share this information with the attending physician so that he or she can make correct judgements.

- Version differences
  - Version 5

Investigations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal	-
Definition: A finding based on laboratory test results that indicate an increase in the level of alanine aminotransferase (ALT or SGPT) in the blood specimen. **Navigational Note:** Also consider Hepatobiliary disorders: Hepatic failure					

  - Version 4

Investigations					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Alanine aminotransferase increased	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN	-

Citation:https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

Points to note when using CTCAE

- A semicolon (;) in the grade description means “or”

Ear and labyrinth disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Ear pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the ear.					
Navigational Note: -					

Citation:https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_50

Causal Relationship

Causal Relationship

- A causal relationship indicates the strength of the association between an AE and a treatment or procedure

Criteria for determining causal relationship

RELATIONSHIP	ATTRIBUTION	DESCRIPTION
Related to investigational agent/intervention	Definite	AE is clearly related to the intervention
	Probable	AE is likely related to the intervention
	Possible	AE may be related to the intervention
Unrelated to investigational agent/intervention	Unlikely	AE is likely unrelated to the intervention
	Unrelated	AE is clearly NOT related to the intervention

Citation: NCI GUIDELINES FOR INVESTIGATORS: ADVERSE EVENT REPORTING REQUIREMENTS FOR DCTD (CTEP AND CIP) AND DCP INDs AND IDEs

Causal Relationship

- All AEs are recorded and reported, regardless of whether there is a causal relationship
- Causal relationships are evaluated in accordance with the criteria specified in the protocol

POINT!

・ Ensure all information to be transcribed into the electronic data capture (EDC) is written in the source material without omission

→ Is the causal relationship evaluated using 2-stage or 5-stage evaluation? When there are two types of study drug, ensure descriptions of the causal relationships are included for each.

Example) Nausea Grade 2 2020.02.01- related to Study Drug A, Not related to Study Drug B

EDC: Electronic Data Capture

Reference: がん臨床試験テキストブック　有害事象の評価と報告（CTCAE） Hiroe Nozawa

Evaluation of Causal Relationship

FDA and European concepts

Reasonable possibility

Identify the study drug as the cause

Cannot be ruled out

Determine causal relationship based on accumulated group data

Identify causes other than the study drug

- Combination treatment
- Complication
- Medical history
- Natural progression of the target disease, etc.

Citation: JPMA News Letter No .151(2012¥09) 続編;くすりと有害事象の因果関係　Yasushi Komiya

Actual support for safety evaluation

Actual support for safety evaluation – Before starting treatment –

- At registration
  - Ascertain baseline
    - ➢ Weight, test values (AST, ALT, etc.), blood pressure, body temperature, heart rate, number of bowel movements, etc.

Reference: がん臨床試験テキストブック　有害事象の評価と報告（CTCAE） Hiroe Nozawa

Actual support for safety evaluation – During treatment –

- Before medical examination
  - Measure vitals
    - ➢ Check for abnormal values, measurement conditions, and items specified in the protocol
  - Confirm subjective and objective symptoms
    - ➢ Face-to-face observation, listening, and methods for dealing with AEs
    - ➢ Information may be recorded, but the doctor makes the determination

      Example) Diarrhea 6 times/day is OK; grade 2 diarrhea is not OK
  - Confirm test results
    - ➢ Check for abnormal values and changes from baseline

Reference: がん臨床試験テキストブック　有害事象の評価と報告（CTCAE） Hiroe Nozawa

Actual support for safety evaluation – During treatment –

- During medical examination
  - Support AE evaluation and description
    - Name of the event, grade, date of onset, causal relationship, intermittent/continuous…
    - Support communication between the participant and doctor
    - When needed, photographs may be taken of the symptoms
  - Confirm criteria for administration start, interruption, and discontinuation
    - Does the AE determined by the doctor correspond to interruption/discontinuation criteria?

Actual support for safety evaluation – During treatment –

- During onset of AE
  - Ensuring participant safety, dealing with AE
    - Depending on the protocol, there may be specifications on how to deal with AEs
    - Effectiveness of symptomatic treatment, whether prophylactic administration is needed after improvement
  - Confirm whether the AE corresponds to a severe AE (SAE) or AE of special interest (AESI)
    - If the AE corresponds to an SAE or AESI, prompt reporting is required
  - Be careful of prohibited concomitant drugs when the participant is seen at other clinical departments
    - Announce prohibited concomitant drugs in advance

SAE：Serious AE
AESI: AE of special interest

Actual support for safety evaluation – After the end of treatment –

- At the end of treatment
  - Confirm the AE/SAE collection period
    - Describe the event in the medical chart, ensuring that it is clearly stated that the person is subject to reporting

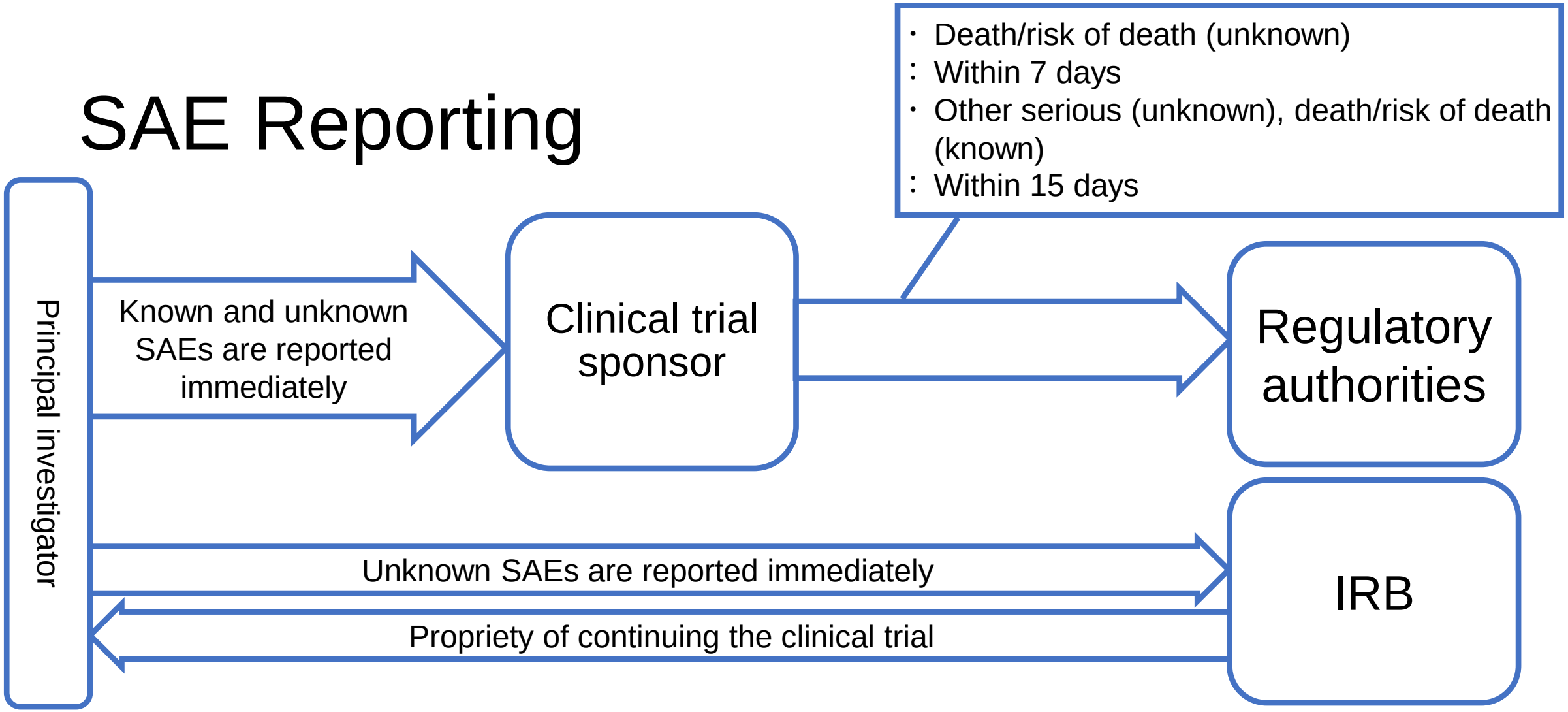
SAE Reporting

SAE：Serious AE

- Results in death
- Life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Congenital anomaly/birth defect
- Other serious events that require treatment to prevent the aforementioned outcomes

Reference: ICH E2A Guideline

SAE Reporting



Reference: ICH-GCP

ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

Immediate reports

	Guideline Content
Events subject to immediate reporting	① Unknown serious ADR ② Other ・ Clinically significant increase in the frequency of known serious ADRs ・ When the patient is exposed to a high risk, such as no effective pharmaceuticals for a life-threatening disease ・ When new important findings on safety (carcinogenesis, etc.) are obtained from animal studies
Immediate reporting deadline	① Known death/risk of death: within 7 days (report submission within 15 days) ② Other unknown serious: within 15 days
Minimum required information	① Patient identification, ② Suspect drug, ③ Information source, ④ ADR
Reporting method	Format is not set
Other actions	Must be reported to the principal investigator and IRB in accordance with GCP

Reference: ICHガイドラインポケット資料集

ICRweb: https://www.icrweb.jp/icr_index.php?lang=en

Support in the event of an SAE

- Items to be confirmed before starting the clinical trial
  - SAE reporting method, submission forms
    - ➢ EDC? Fax? Email? What reporting method is used if an EDC is not supported?
    - ➢ Is prompt reporting required if the outcome or grade changes?
  - What is subject to SAE reporting?

    → Is hospitalization due to worsening of the primary disease or an SAE?
  - Emergency contact
  - SAE reporting period

Reference: CRCテキストブック第4版 臨床試験の実施から終了まで:Takahiro Haseyama

Support in the event of an SAE

- Obtaining information, contact
  - Information must be promptly reported after the principal investigator/sub-investigator learns of the event
    - ➢ Most clinical trials require the first report to be submitted within 24 hours
  - Inform the participant of the point of contact for holidays and evenings
    - ➢ Early detection and early response are important
  - If the participant is admitted to another hospital, ask for information using medical referral forms or similar documents
    - ➢ Provide support to obtain the required information, such as date of onset, administered medication, etc.

Reference: CRCテキストブック第4版　臨床試験の実施から終了まで:Takahiro Haseyama

Support in the event of an SAE

- Support for the participant
  - Ensuring the safety of the participant is the top priority
  - Be careful of prohibited concomitant drugs and therapies
    - ➢ Ensure that the safety of the participant is not compromised by restricting use of certain drugs
  - Unblinding
    - ➢ In double-blinded studies, it may be required to unblind the study in accordance with the treatment strategies after onset of an SAE

Reference: CRCテキストブック第4版　臨床試験の実施から終了まで:Takahiro Haseyama

Support in the event of an SAE

- Assisting with preparation of the report
  - Assisting with preparation using appropriate reports
    - ➢ Reporting to the sponsor
    - ➢ Reporting to the sponsor is stipulated by the protocol, and reporting to the director of the medical institution and IRB is stipulated by the medical institution and regulations of each country
  - Prompt reporting
    - ➢ Most clinical trials require the first report to be submitted within 24 hours
  - Assist with descriptions of the reporting items in the source material
    - ➢ The minimum required information is the name of the event, causal relationship, date of onset, grade, and reason the event was determined to be an SAE

Reference: CRCテキストブック第4版　臨床試験の実施から終了まで:Takahiro Haseyama

Support in the event of an SAE

- Reporting to the sponsor
  - Reporting is required regardless of whether there is a causal relationship
  - Construct a system for obtaining responses even on weekends and holidays
    - ➢ Create a file for each clinical trial, describing the reporting format, method, and emergency contact details

      This information is prepared to enable a response to SAEs even if the CRC in charge is not available

Reference: CRCテキストブック第4版　臨床試験の実施から終了まで:Takahiro Haseyama

Events other than SAE subject to reporting

- AESIs
  - Some events must be reported regardless of the severity
    - ➢ Note that some conditions such as grade 2 oral mucositis is very common, so the participant may continue taking the study drug
    - ➢ Call attention to these matters by writing them in a conspicuous location on the medical chart
- Other
  - Events such as drug-induced liver injury, drug-induced renal injury, overdose, and pregnancy are specified for each protocol

Reference: 薬剤疫学 Jpn J Pharmacoepidemiol, **19**（2） Dec 2014:123

References

- 公益財団法人パブリックヘルスリサーチセンター がん臨床研究試験事業教育研修小委員会, cancer clinical trialsテキストブック, 医学書院(2013)
- 日本臨床薬理学会, CRCテキストブック第4版, 医学書院(2021)
- ICH　GCP ポケット資料集
- PMDA ICH -E2　CLINICAL SAFETY DATA MANAGEMENT https://www.pmda.go.jp/int-activities/int-harmony/ich/0024.html
- NIH Cancer Therapy Evaluation Program https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40