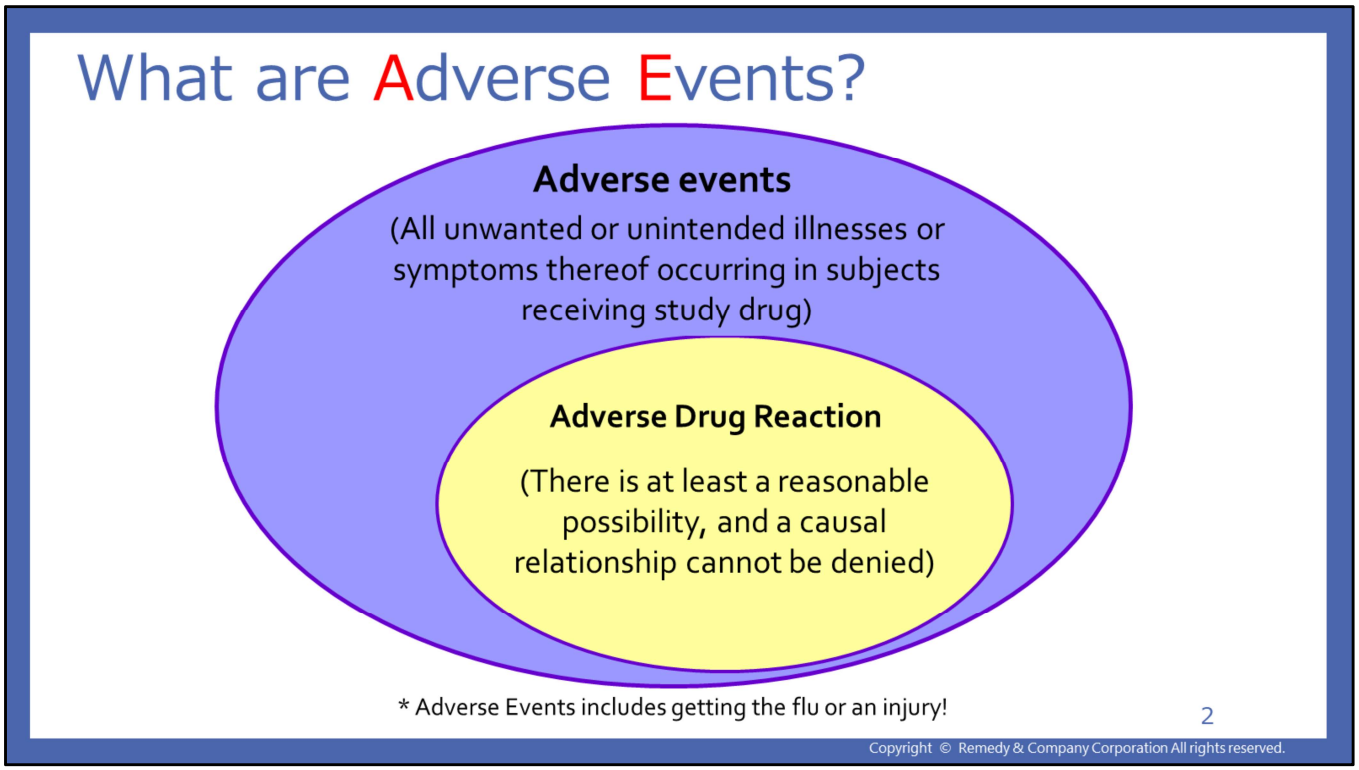
This portion of training will explain some of the basics you should know with regards to adverse events, severe adverse events and what to do when you need to report them.

We will cover what AEs, ADRs and SAEs are and how to define them.

We will cover what you should do as a monitor, including the information that you should collect and the timing in which you should abide by.

We will also cover a little bit about what MedDRA is and other pertinent points on what factors and information is important to take note of when looking at the causal relationship between an adverse event and an investigational drug.



First of all, let us understand the definition of an adverse event.

An adverse event is defined as any disease or symptom occurring in subjects after having received an investigational drug.

It does not necessarily indicate only cases that have a clear casual relationship with the administration of the investigational drug.

In other words, an adverse event is **any** unfavourable or unintended manifestation occurring in a subject who has received an investigational drug.

This even includes any abnormal laboratory findings.

Within this larger definition, “adverse drug reaction” is another term which is commonly used in clinical trials.

An adverse drug reaction is any adverse unintended reaction (including laboratory findings), to any dose of the investigational drug administered.

It refers to a reaction for which there is at least a reasonable possibility of a causal relationship between the investigational drug and the adverse event.

As long as the event that has occurred whereby a causal relationship cannot be denied in relation to the investigational drug, this can be considered an adverse drug reaction.

In clinical trials, the term "adverse drug reaction" is more commonly used rather than the more common English term "side effect," to mean an adverse reaction to the main pharmacological action.

In addition to understanding what an adverse event and adverse drug reaction is, it is important to know that there is a far more important set of adverse events which must be critically reported.

There are called **serious** adverse events.

These are adverse events that occur when an investigational drug is administered regardless of dose and fall under these 7 types of events:

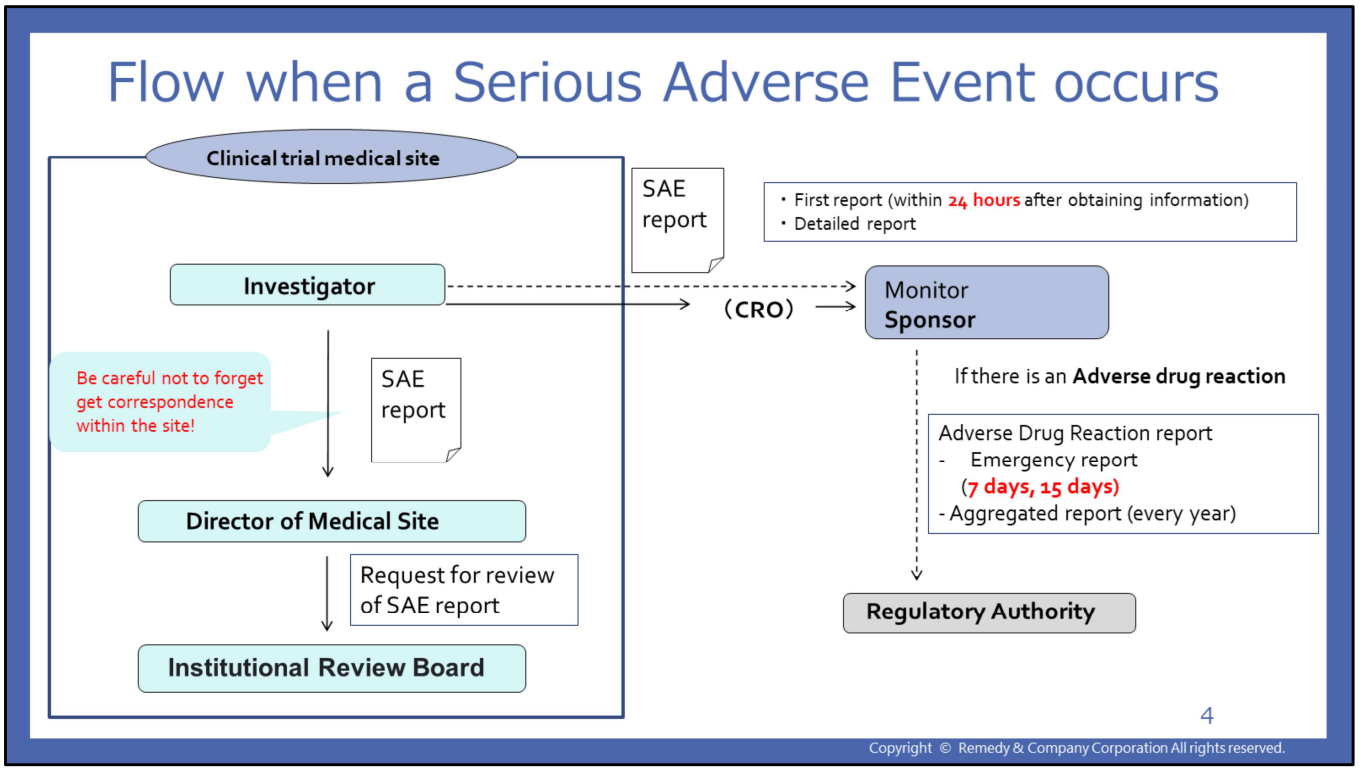
- The death of the subject.
- An event that may lead to death, or can lead to life-threatening complications.
- Events requiring immediate hospitalization for treatment or has led to the extension of duration of hospitalization.
- Any events that cause permanent or temporary disability. This also includes incapacity.
- Any events that can lead to permanent or temporary disability.
- Any cases that are considered serious according to the above conditions.
- And, any events that could cause or lead to any type of congenital disease or abnormalities, including birth defects resulting from the clinical trial.

It is important to note that the word "**serious**" is not synonymous with **"severe"**.

The term "severe" expresses the intensity of a specific event. It does not necessarily mean that there the event is medically significant.

For example, the intensity of a headache can be seen as mild, moderate, or severe, but would not be seen as a serious debilitating event.

The term "serious" relates to patient or event outcomes that endanger the patient's life or ability to function.



So, what are the processes which occur when there is a serious adverse event?

When an SAE occurs, the investigator is responsible for filling in an SAE report, which ultimately needs to be reported to the site, the sponsor and the regulatory authority.

At the clinical trial site, the investigator is obligated to report this to the director of the medical site, which then would also send this information for review to the institutional review board.

As a clinical monitor, you will be responsible for gathering this pertinent information to deliver the preliminary report to your sponsor.
Most commonly, this preliminary report must be submitted within **24 hours. This is commonly specified in the most of SOPs provided by your sponsor so please check it.**

Following that, a more detailed report written by the investigator on the transpired events and background should be provided.

At the same time, the investigator should send this SAE report to the director of the medical site, which in turn will be deliberated by the site IRB.

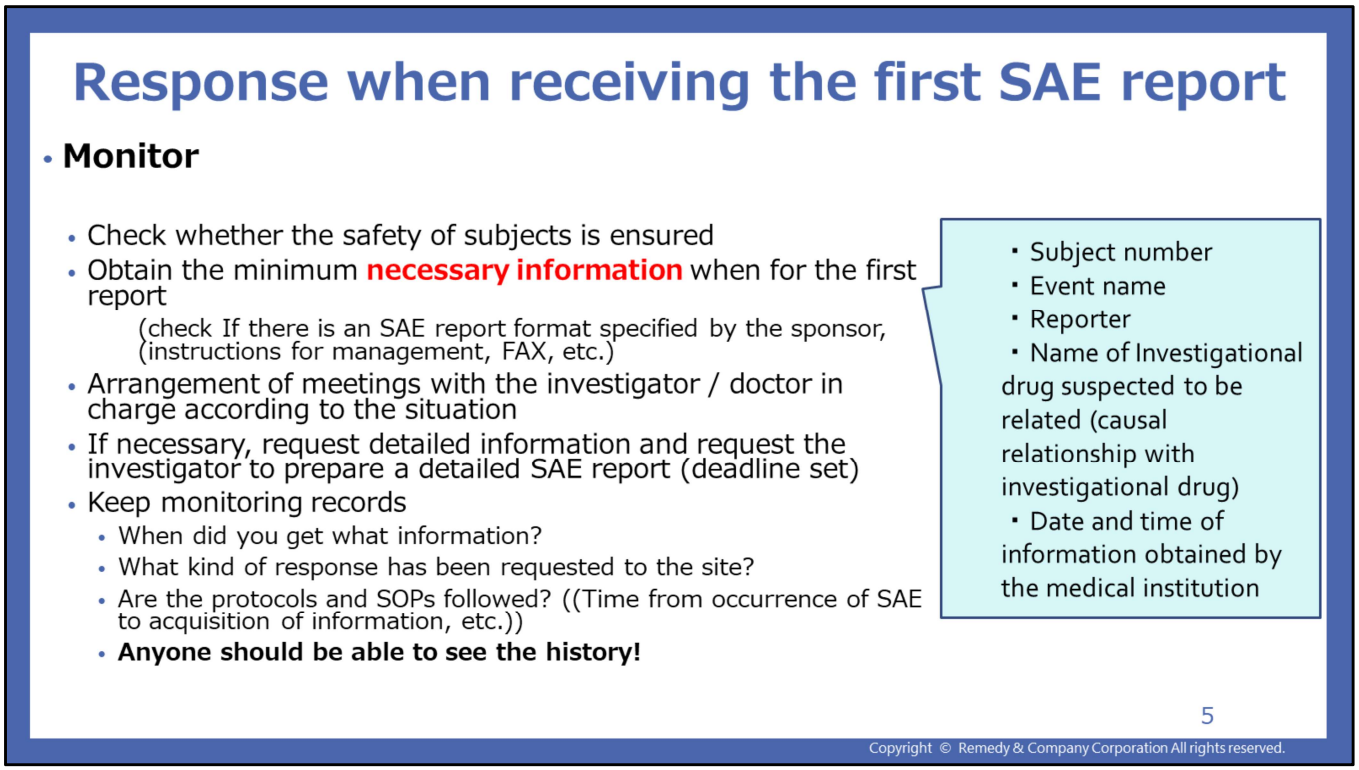
On the sponsor's side, the sponsor may wish to hear opinions from their medical advisors on the management and determination of the SAE.

After that, the Sponsor PV department will prepare a report for the purpose of regulatory authority reporting, if the adverse events for which causality cannot be denied.

If the event is determined to be an emergency, that is, the event has led to the death or the possibility of death due to an unknown SAE, it should be reported to the regulatory authority within **7 days**.

If the event is considered a known or unknown serious adverse drug reaction that has not led to death or the possibility of death, it should be reported to the regulatory authority within **15 days.**

An aggregated report of all serious adverse drug reactions should be regularly reported annually by the sponsor's PV department.



As a clinical monitor, you will be responsible for gathering this pertinent information to deliver the preliminary report to your Sponsor**.**

As this is an important procedure, it is important **read and check the SOPs provided by your sponsor.**

Often, the SOPs would include the SAE Report format, instructions, contact details and timing in which you should perform this reporting.

For the first preliminary report, the absolute minimum information that you should acquire is listed on the blue box on the right:
✓ Subject number
✓ Event name
✓ Reporter
✓ Name of investigational drug suspected to be related
✓ Date and time of information obtained by the medical institution

While it is the responsibility of the investigator to ensure the safety of the subjects and prepare the report, as the Monitor, if necessary, request the investigator to prepare this and set a deadline.

Since the sponsor and other authorities who will receive the report will likely not have seen the actual event or patient, your correspondence, records and background information on the event and details should be promptly and properly recorded so that anyone who reads the report is able to discern what exactly has happened to the patient.

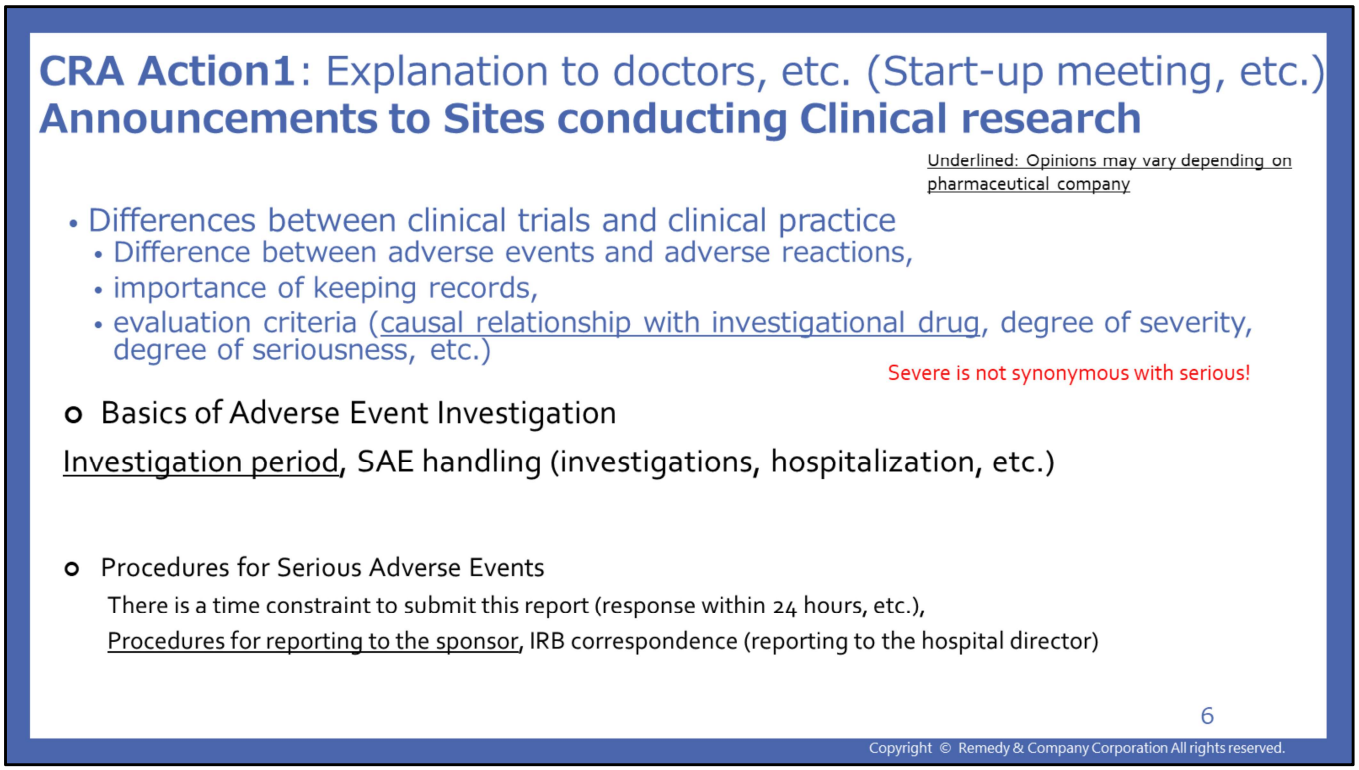
Anyone should be able to see the history of the event!

As a monitor, make sure that:

The detailed information on the SAE as well as its outcomes are properly documented and a detailed report from the principal investigator has been provided.

Check whether the IRB review request and deliberation is done.

With all these items properly documented, be sure to also directly check the source material.



As a CRA, you have several responsibilities to prepare the sites and its investigators on AE reporting.

In line with the sponsor's SOPs you should properly explain to the healthcare staff who are responsible for the clinical trial such as doctors and clinical research coordinators in advance.

For instance, during a start-up meeting, you should explain:
✓ The differences between clinical trials and clinical practice,
✓ The difference between adverse events and adverse reactions,
✓ The importance of keeping records,
✓ As well as the evaluation criteria as per the protocol attributed to the study.

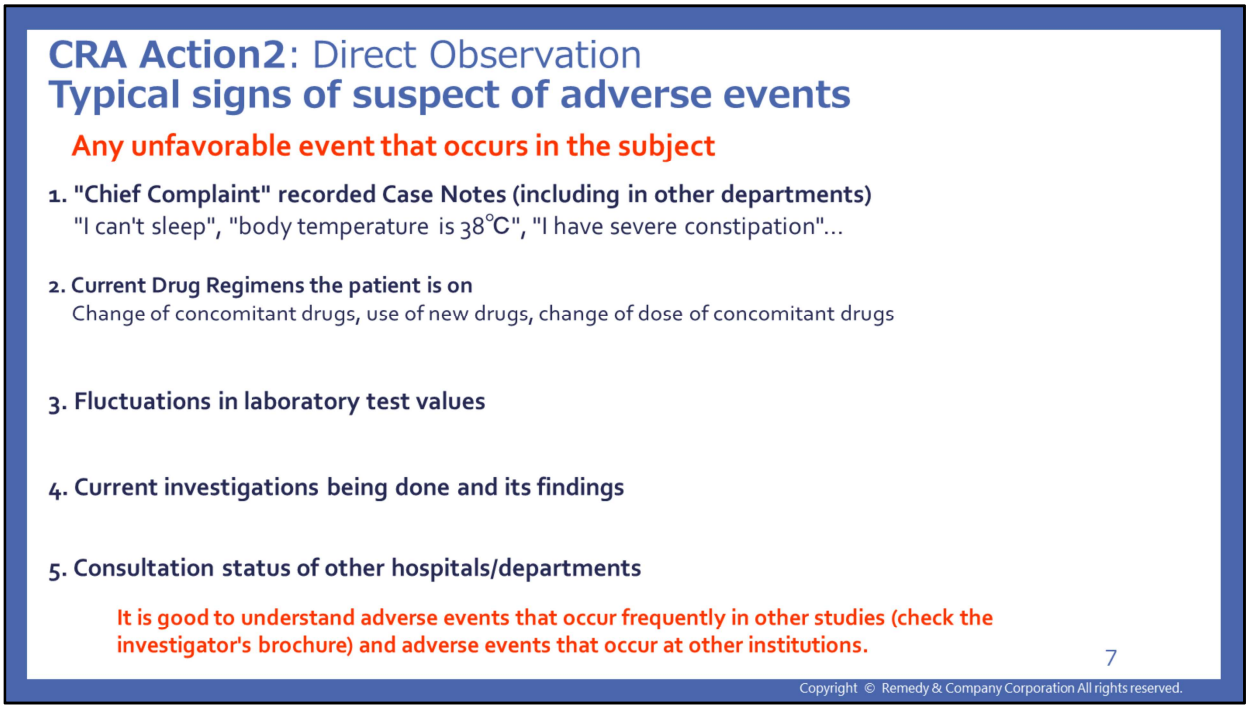
The procedure for adverse event investigation and reporting, the period within this should be performed and how to report and handle SAEs should be well briefed to the members in the site as well.

Emphasis on the time constraints of submitting an SAE report within 24 hours and the respective steps should be clarified and pointed out so that no one misunderstands what to do.

For instance, what is the reporting method expected based on the SOPs? Is it via telephone or fax or email?

How should they respond during holidays? Whose contact information should be put in?

In case there is a need to ask further questions, be sure that the appropriate members are contactable.



Sometimes, as a CRA, it is possible to catch signs of suspected adverse events as they progress through the case notes.

When you have the opportunity to perform a site visit, it is possible to observe certain unfavourable events that may have occurred in the subject.

The 'Chief Complaint' or 'Presenting Complaint' written in the case notes, even if written from a different department, could give indicate that there are certain adverse events occurring after having received the investigational product.

It is also possible and important to see whether the current drug regimen the subject is on has changed, thus potentially indicating a change in clinical management of symptoms.

Fluctuating blood laboratory results could alert those responsible on the potential rise of an AE.

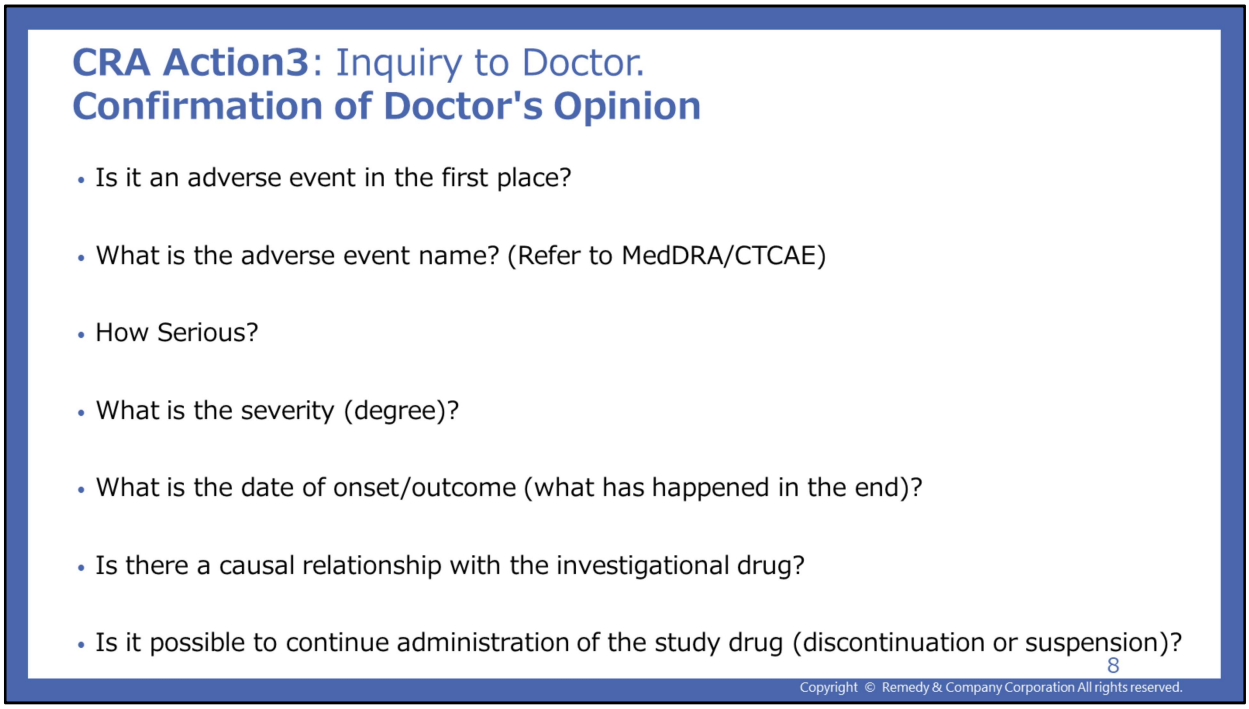
Other investigations such as CTs, X-rays or ECGs could also provide further insight.

The patient may have gone to another hospital or department for further consult on an issue.

All these points could give a clearer and better picture on reporting an AE.

It is good to understand the adverse events which occur frequently in other clinical studies related to the investigational product.

Check the investigator's brochure and communicate with other fellow CRAs or members involved in the study so that you are aware of other common AEs which are occurring at other institutions.



If there is such an adverse event, it is pertinent to confirm with the investigator handling the patient.

✓ Is it an adverse event in the first place?

✓ What is the adverse event name?

✓ How Serious?

✓ What is its severity?

✓ What is the date of onset/outcome (what has happened in the end)?

✓ Is there a causal relationship with the investigational drug?

✓ Is it possible to continue administration of the investigational drug?

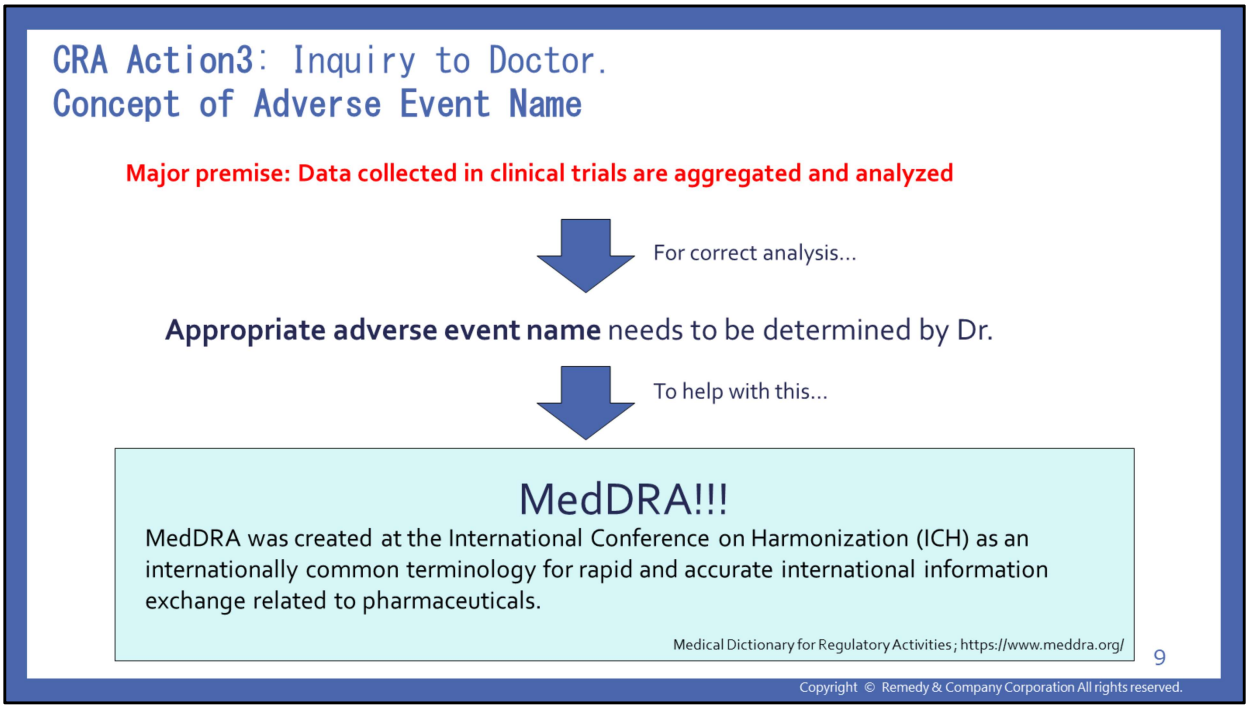
All these items should be determined by the investigator.

Remember that as a CRA, you are tasked to monitor the study but should in no situation influence the decision of the physician.

While it is important for you as a CRA to confirm and inquire a suspected adverse event if it has not been raised by the investigator.

The investigator should **NOT** confirm with the CRA whether it is an AE, because it is the investigator who decides that it is an adverse event.

If the investigator does not consider a suspected AE to be an adverse event, a reason must be given.

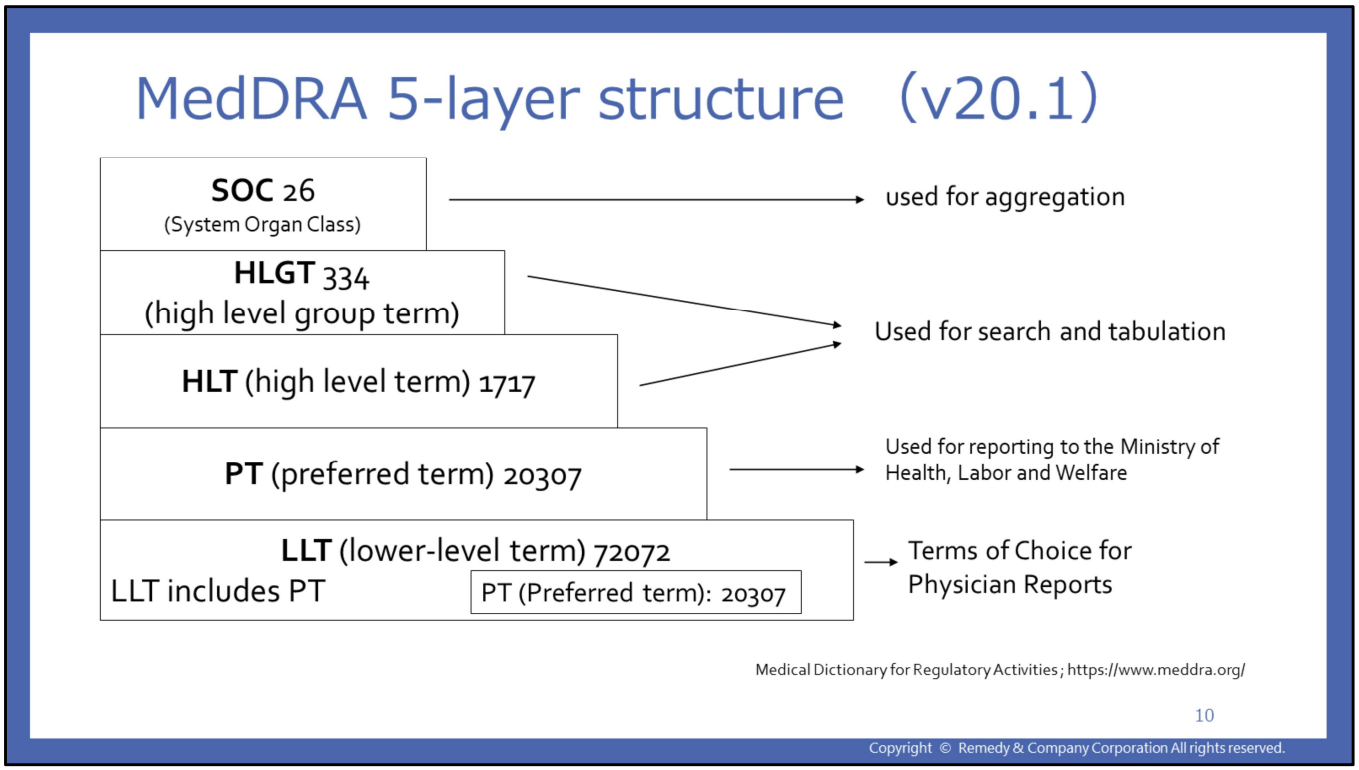


So, what if there has been an adverse event reported?

How do we collect this data so that it can be understood universally amongst all investigators and sites participating in the trial as well as the authorities who need to be aware of the adverse events?

To help with the purpose of standardized reporting and the use of standardized medical terminology, MedDRA was created.

MedDRA was created at the International Conference on Harmonization (ICH) as an internationally common terminology for rapid and accurate international information exchange related to pharmaceuticals.



MedDRA is organized in a 5-layered structure.

SOCs, which stands for System Organ Class. SOCs are commonly used for the purpose of data aggregation into large classifications by organs.

HLGT, high level group term and the following later level HLT, high level term are generally used for searching and tabulation.

PT, preferred term, includes the adverse events terms which are standardized so that it is more easily understood and categorized for the purpose of reporting.

In principle, this term is used for the purpose of reporting to the Ministry of Health of the country.

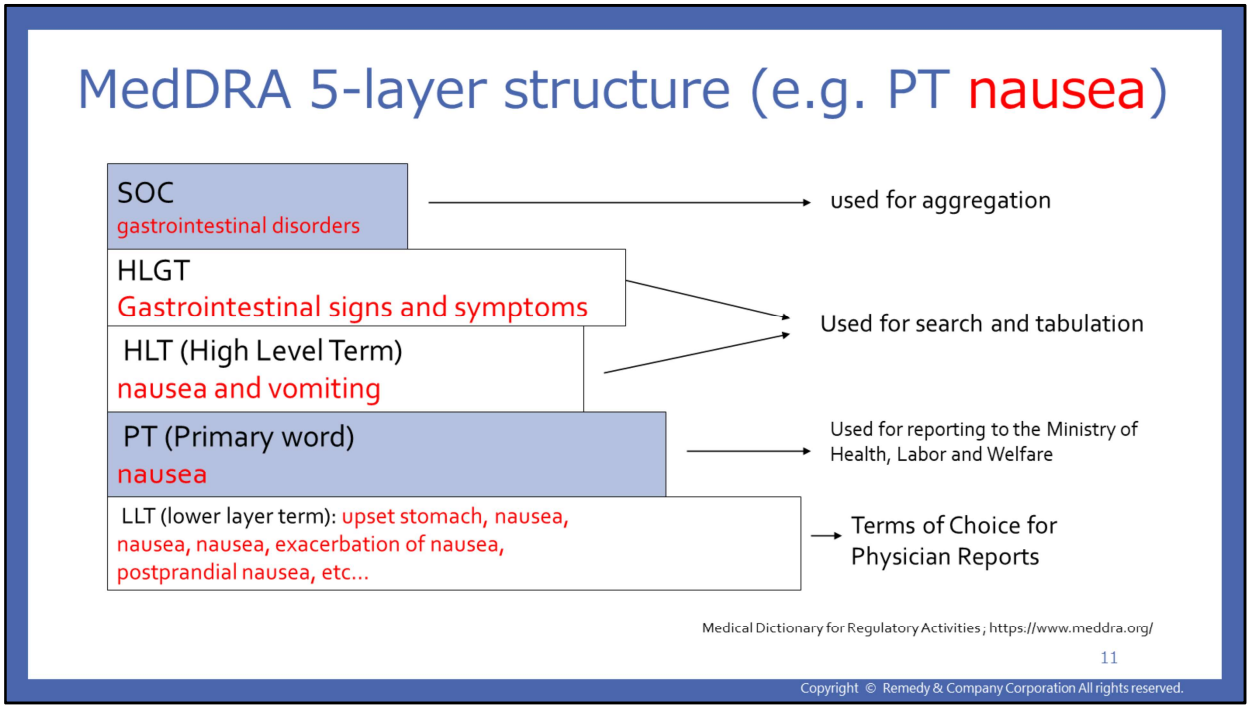
Last but not least is LLT, which means lower level term.

LLTs are the general descriptive medical terms used by physicians when they create reports.

These can vary and differ depending on the physician and how they prefer to describe the medical condition they have reported.

It is because of how variable these terms are, that MedDRA helps standardize these by fitting them into the above layered categories so that everyone can understand what sort of adverse event has been reported.

To keep things simplified for data managers and medical monitors, the two most relevant layers that we need to know are SOC and PT.



Let us use an example.

As reported and written by the physician, the subject experienced postprandial nausea, that is, the subject has experienced nausea after eating his meal.

Another physician has reported that another subject experienced an 'upset stomach' after administration of the investigational product.

To categorise and standardize these adverse events, the PT 'Nausea' is used to categorise these two events as they are essentially the same type of adverse event being experienced during the study.

Within, MedDRA, this PT can be further grouped and categorized in the following upper layers, all the way up to SOC, which would lie in the larger organ classification of gastrointestinal disorders.

MedDRA Points to note when monitoring

When reporting adverse events, physicians should be asked to provide precise, detailed terms to describe the events.

Physician reporting terms	Choice of LLTs	Automatic determination of SOC
thrombocytopenia (disease)	Thrombocytopenia	Blood/lymphatic disorders
	platelets decreased	clinical examination
upper respiratory inflammation	Inflammation of the upper respiratory tract	respiratory
	Upper respiratory tract infection	Infection
pneumonia	pneumonia	Infection
	Interstitial pneumonia	respiratory
dizzy	Vertigo	ear and labyrinth disorders
	dizziness	nervous system disorders

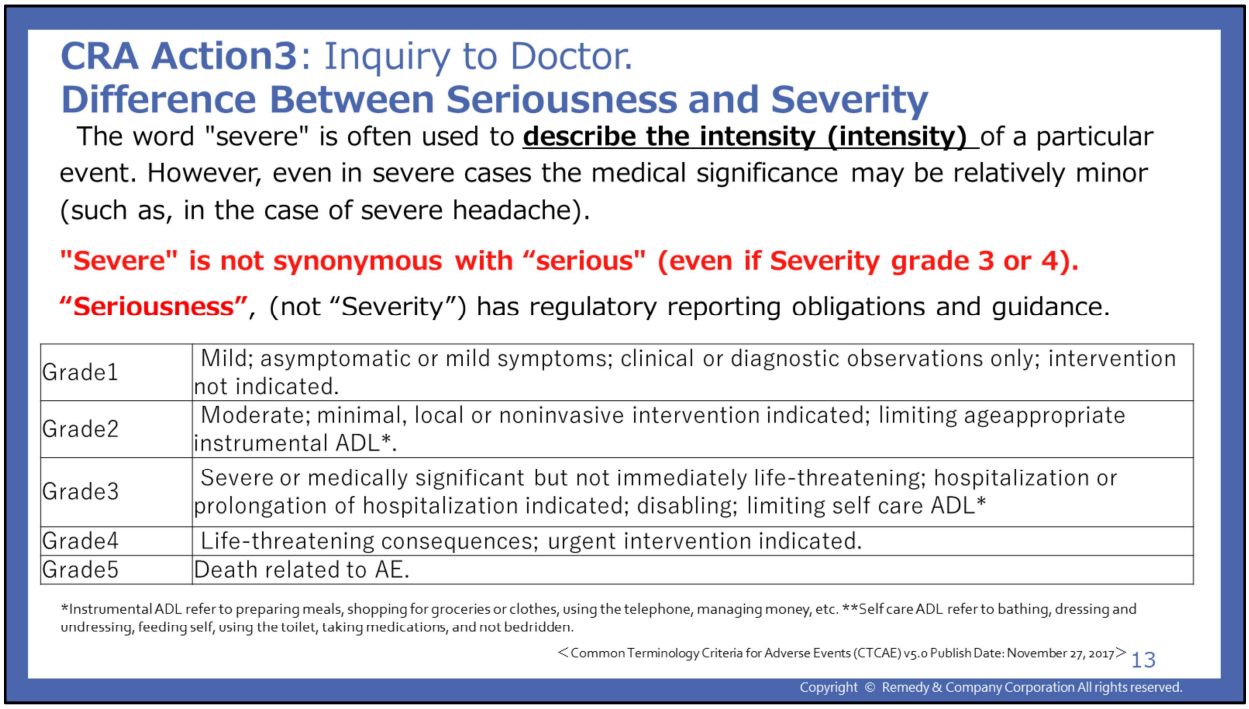
12

When reporting adverse events, physicians should be asked to provide precise, detailed terms to describe these events.

This helps the medical monitors and data managers understand how to properly define and categorize the adverse event according to MedDRA.

A vague term, can lead to different choices in LLTs and PTs, which results in a potentially different SOC category.

Sometimes it is important to confirm with the physician where possible on the appropriateness of the reporting terms they have used.



As mentioned previously,
It is important to understand the distinction between "**serious**" and **"severe"**.

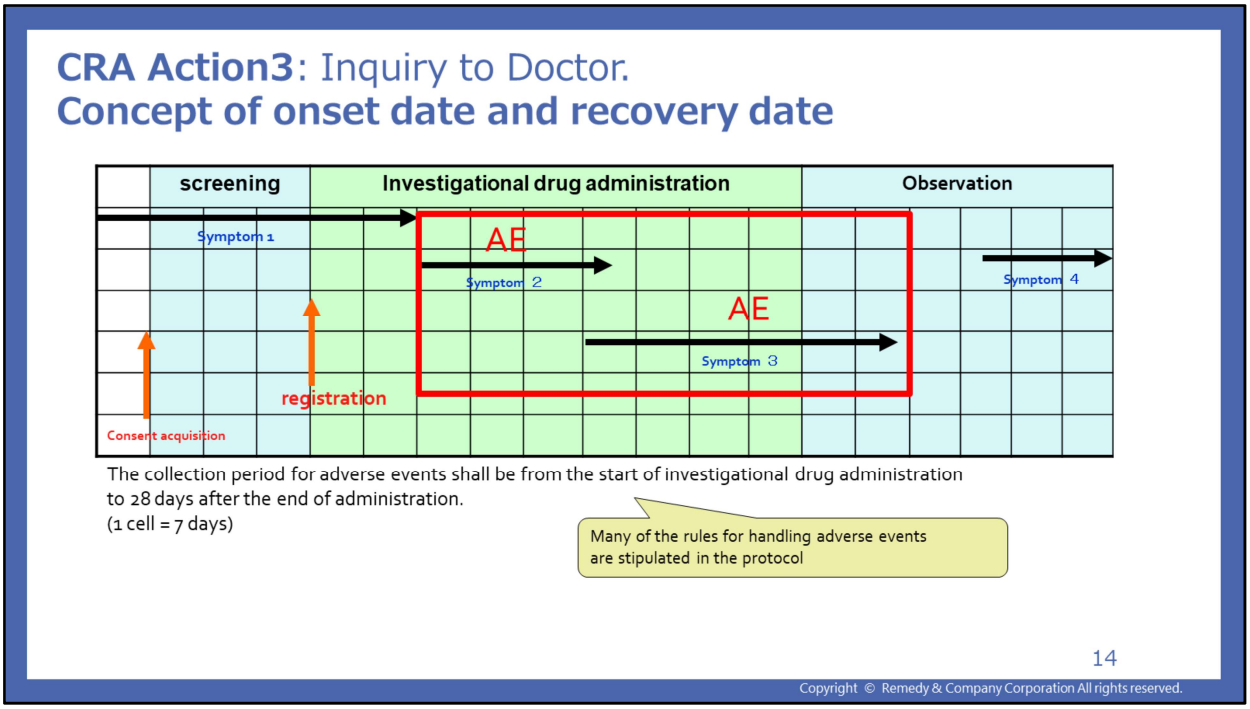
The word "severe" is often used to **describe the intensity** of a particular event.

Even in severe cases the medical significance may be relatively minor.

For instance, a "severe headache" may not necessarily be defined as a life-threatening event.

In other words, "**serious**" is not synonymous with **"severe",** even if a severity of grade 3 or 4 is seen.

"Seriousness" or a serious adverse event is subject to regulatory reporting obligations, with specific timelines and guidance for reporting.



In addition to understanding these definitions, the date and timing of when the symptom or adverse event has occurred is very important as it determines whether it should or should not be defined as an AE.

Many of the rules for handling and defining adverse events are stipulated in the protocol.

For instance, in this image example, the collection period for adverse events has been defined to be from the start of investigational drug administration up to 28 days after administration.

Symptom 1 was seen during screening of the patient due to a pre-existing complication.

While the subject still had this complication, he was still eligible to be enrolled into the study and was given the investigational drug.

Because symptom 1 had occurred **before** he was given the investigational drug, this not considered as an AE.

However, symptom 2 had occurred during the administration of the investigational drug.

In this case, symptom 2 had occurred **after the start of** administration of the investigational drug and therefore is determined as an adverse event.

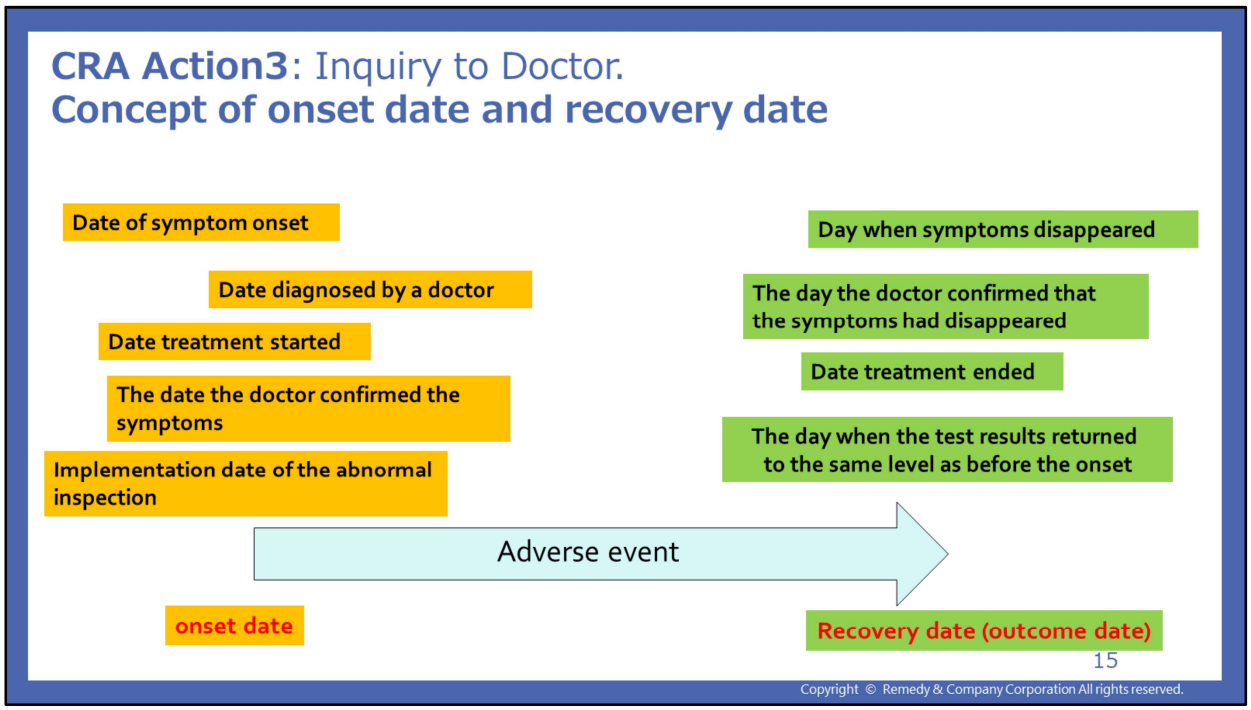
What about symptom 3?
Symptom 3 had occurred during the period of administration of the investigational drug but had persisted past 28 days.

Because the onset of symptom 3 had occurred **still within the period of** investigation drug administration, it is therefore still determined as an adverse event.

As for symptom 4, this symptom had occurred during the period of observation planned in this protocol.

As this symptom had not occurred during the period stipulated in the protocol as the collection period for AE, there is no need to consider this as an AE.

It is important to remember that many of the rules for handling adverse events are stipulated in the protocol so please read it carefully.



It is important to record the progression of the adverse event.

The dates and records in orange are all pertinent points which are needed to confirm the date of onset of the adverse event.

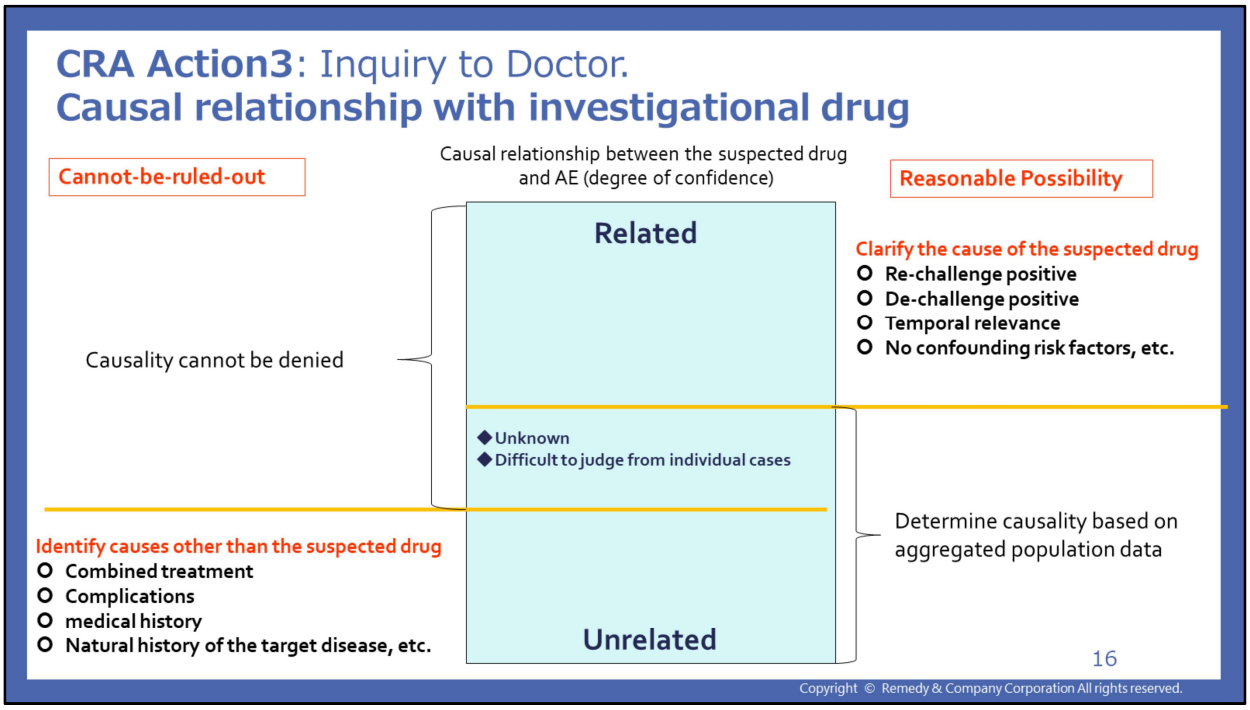
The dates and records in green are needed to confirm the date of recovery (or the outcome) of the adverse event.

For AEs related to laboratory abnormalities, values at onset and recovery are required.

This helps us determine the progression and the severity of fluctuation in its readings.

The same applies when the grade changes.

It is important to note that outcome dates for laboratory abnormalities are relatively less likely to remain in source documents.



The causal relationship between the AE and the investigational drug is often a challenge to define.

This image shows some of the conditions which would help doctors, monitors and other study members consider whether the transpired AE is related or unrelated to the investigational drug.

The degree of confidence in which an AE is related to the drug can be further reinforced by the temporal relevance, that is, the timing of the AE in relation to the administration of the drug.

If the AE occurs again when the investigational drug is re-administered to the patient, this is called a re-challenge positive.

If the AE disappears when the investigational drug is removed, this is called a de-challenge positive.

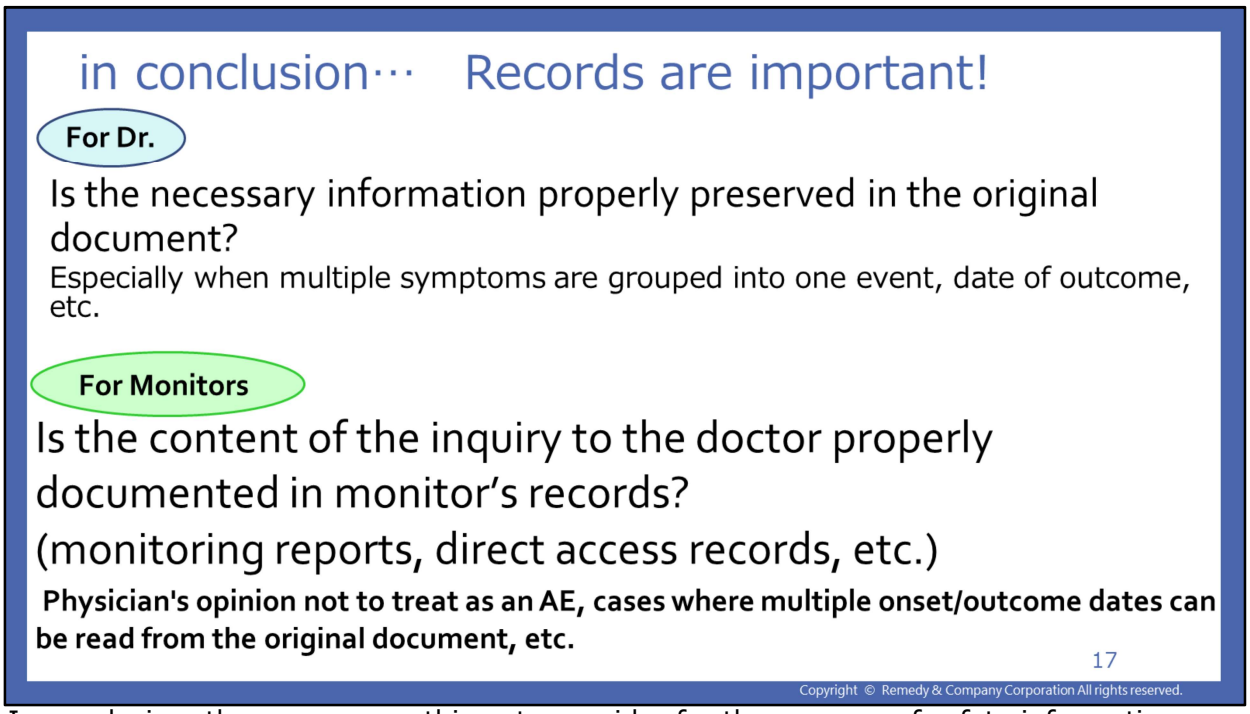
This direct temporal correlation can help further reinforce the causal relationship with the drug.

On the other hand, if the physician is capable of identifying and sufficiently explaining that there is another cause which has led to the reported sdverse event, this would help reinforce confidence in showing its non-causal relationship to the investigational drug.

Patient history for other pre-existing conditions, complications or concomitant treatment can help determine this further.

There are some situations in which there is not enough clarity to sufficiently explain that the AE is not caused by the drug.

In such cases, the causal relationship cannot be ruled out or out right denied.



In conclusion, there are many things to consider for the purpose of safety information monitoring and reporting.

We have covered what AEs, ADRs and SAEs are and how to define them.

We have covered the basic flow of handling an SAE, its timing of reporting and what you should do as a monitor, including the information that you should collect.

We have covered also a little bit about what MedDRA is and other pertinent points on what factors and information is important to take note of when looking at the causal relationship of an AE to the investigational drug.

It is suffice to say that detailed information and proper records of the event and the safety of the subject is crucial for the purpose of safety information monitoring.

As a physician, remember that the information recorded and reported should be properly preserved in the original source document.

It is also an important task for doctors to provide as much of the necessary information to help ensure the right decision has been made.

As a monitor, it would be your responsibility to ensure that the inquiry to the doctor is well documented and that items which should be reported as per sponsor SOP and protocol have been followed.

And…remember, adverse event evaluations and determinations are meant to be done by physicians!

As a CRA, you should not influence or try to determine the AE as opined by the investigator.

Thank you.

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