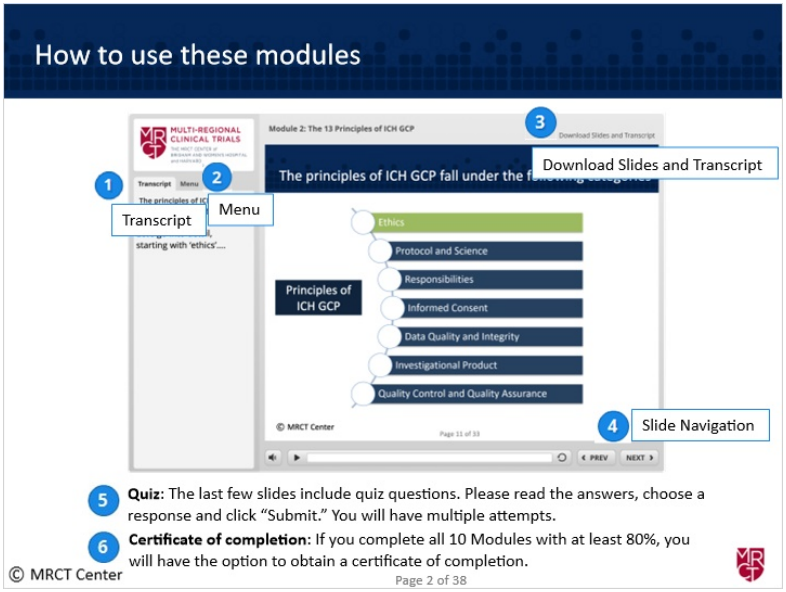
Module 10: GCP in Practice for Inspectors

1.1 Interpretation and application of ICH E6(R2)

Notes:

Welcome to Module 10 of this training on the interpretation and application of ICH E6(R2)

1.2 How to use these modules



Notes:

We want to familiarize you with how to use these modules. First, you can click on Transcript on the left side to read along with the audio. Second, if you click on Menu, next to Transcript, you can see where you are in this module. You can also go back to slides that you have previously viewed and listened to.

Third, you can click on the upper right on "Download Slides and Transcript" to view a printable PDF of the slides and transcript of the module. You can also click a link to the Guidelines for Good Clinical Practice.

Fourth, to move to the next slide, click "Next" after you listen to the audio. Click "Prev" to go to the previous slide.

Fifth, the last few slides include quiz questions. Please read the answers, choose a response and click "Submit." You will have multiple chances to answer correctly.

Sixth, if you complete all 10 Modules with at least 80%, you will have the option to obtain a certificate of completion.

1.3 Attribution and Disclaimer

Notes:

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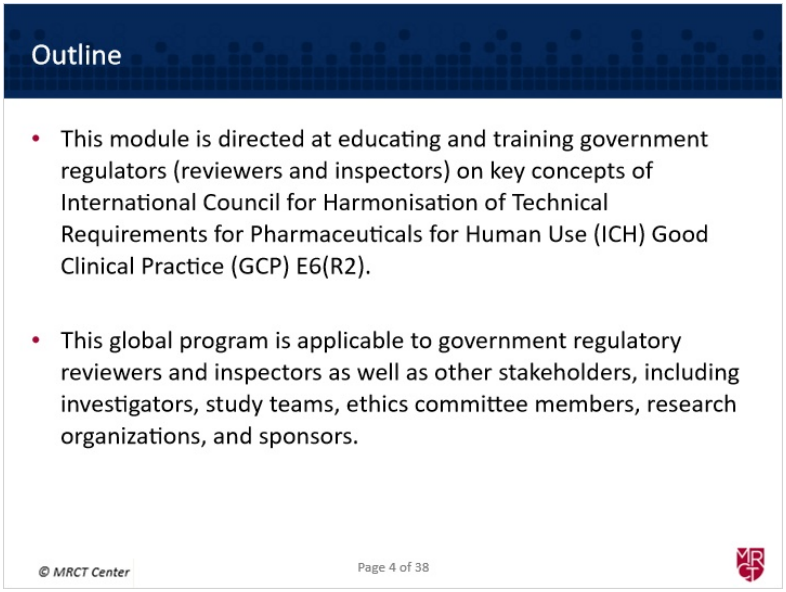
This training programme is recognised by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

This presentation includes the author's views on "Interpretation and application of ICH E6(R2)" theory and practice. The presentation does not represent official guidance or policy of authorities or industry.

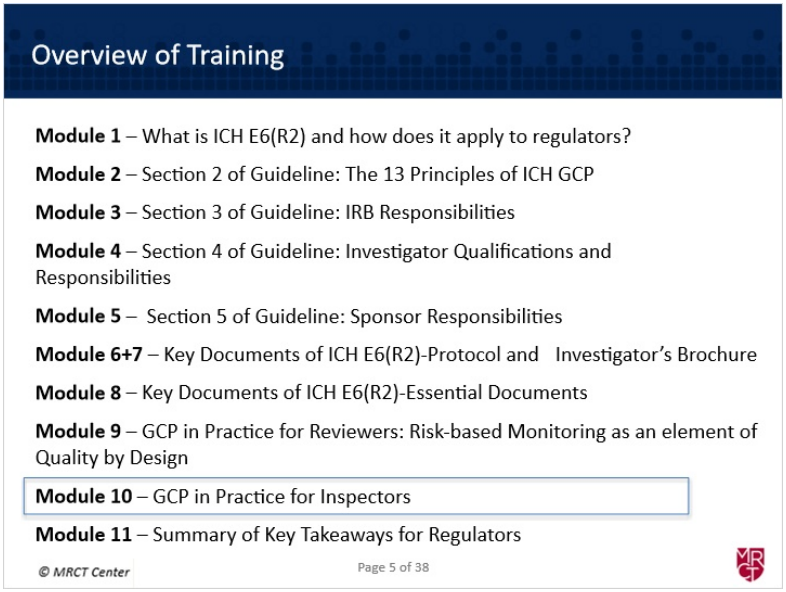
1.4 Outline



Notes:

Overall this training is directed at educating and training government regulatory reviewers and inspectors (as well as other stakeholders including investigators, study teams, ethics committee members, research organizations, and sponsors) on key concepts of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) E6(R2).

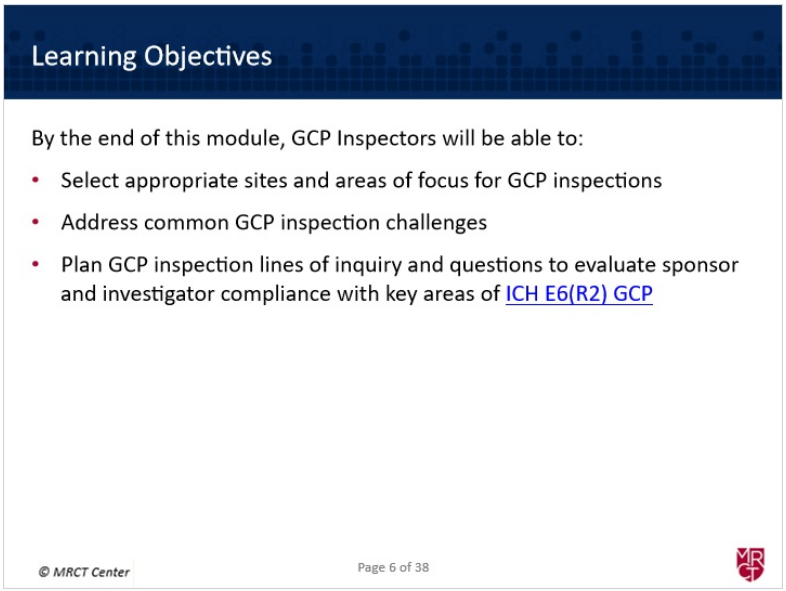
1.5 Overview of Training



Notes:

In Module 10 we will focus on GCP in Practice for Inspectors.

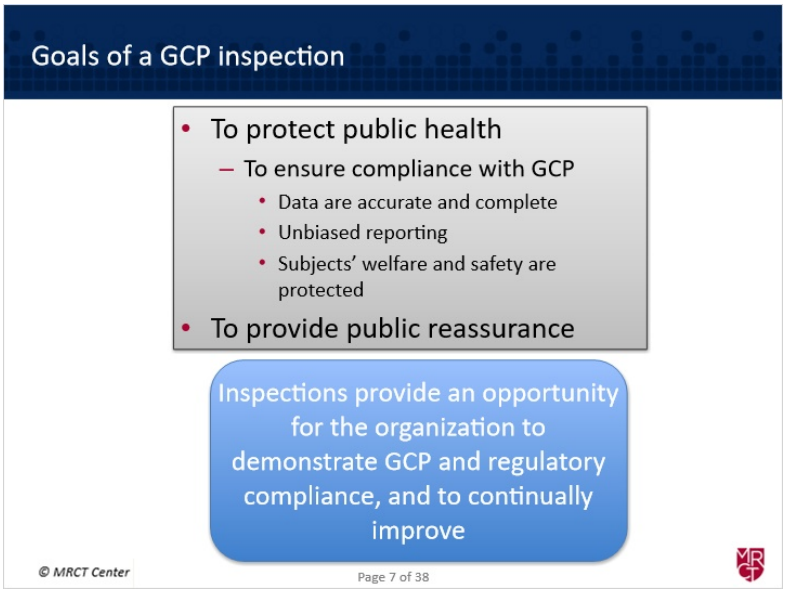
1.6 Learning Objectives



Notes:

By the end of this module, GCP Inspectors are expected to be able to:
Select appropriate sites and areas of focus for GCP inspections
Address common GCP inspection challenges
Plan GCP inspection lines of inquiry and questions to evaluate sponsor and investigator compliance with key areas of Revision 2 of ICH GCP

1.7 Goals of a GCP inspection



Notes:

The goals of a GCP inspection are to protect public health and to provide public reassurance. Ensuring compliance with GCP - that is, data are accurate and complete, unbiased reporting and that subjects' welfare and safety are protected, ensures in turn that public health is protected.

Inspections offer an opportunity to demonstrate just how well an organization works to GCP and regulations, and an opportunity to continually improve.

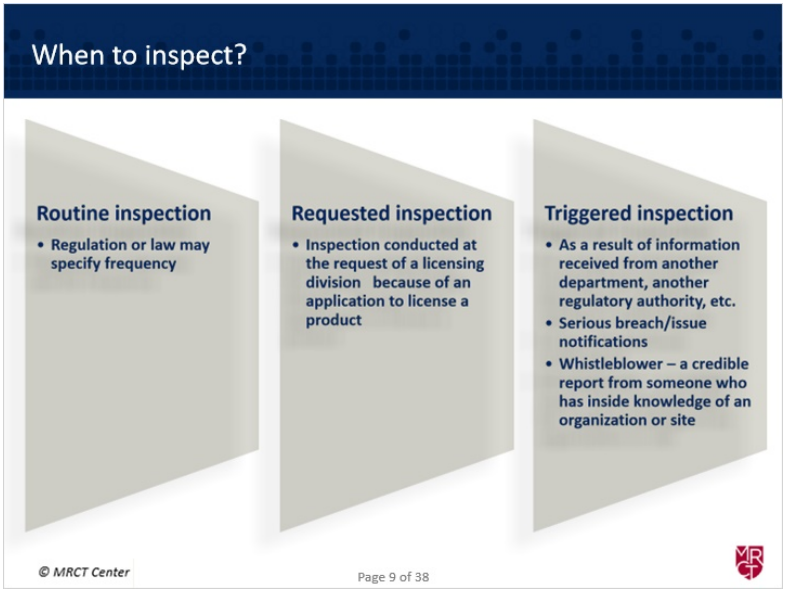
1.8 What standards do inspectors inspect to?

Notes:

So, what standards do inspectors inspect to?

- The first is to the relevant regulations and guidelines applicable to the inspector's area.
- Inspectors also inspect to ICH Good Clinical Practice standards.
- They will also check that the protocol has been followed
- and they will check that the organization is following it's own procedures.
- The situation is more complex with regard to guidance. As indicated in EMA document *Procedure for European Union Guidelines and Related Documents Within the Pharmaceutical Legislative Framework,* Guidance documents are not mandatory, although following guidance enables the inspector to be reassured that the correct standards have been met. However, an organization may choose not to follow a guidance document. Assuming that the organization has still met the required standards, there is no issue. From an inspector's perspective, not following guidance and doing things in a different way may require additional scrutiny, to be sure that the correct standards have indeed been met by the organization.

1.9 When to inspect?

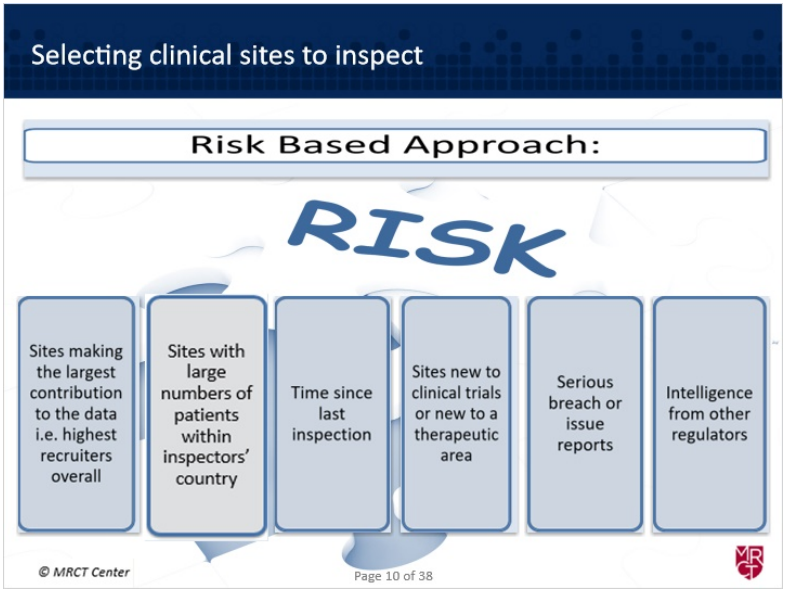


Notes:

So, when should inspections be scheduled?

- In some cases, a local regulation or law may specify routine inspections at a certain interval.
- It is very common for an inspection to be scheduled associated with an application to license a product.
- And some inspections are triggered, that is, there is a specific reason for them. Reasons include information received from another source, or as follow up to a serious breach or serious issue. Occasionally, credible information may be received from someone with inside knowledge that indicates that an inspection is needed, this is known as a "whistleblower".

1.10 Selecting clinical sites to inspect



Notes:

Generally a risk based approach is used when selecting clinical sites to inspect. Obvious targets for inspection are:

- Sites making the largest contribution to the data, and
- Sites with the largest number of patients. However, there are other factors to consider.
- It may for example be better to select the third highest recruiting site if recent inspections of other studies have shown no issues at the two highest recruiting sites, especially if that third site has not previously been inspected so is of unknown quality. Therefore, time since last inspection, whether a site is new to a therapeutic area, or has been cited for a serious breach or issue should be considered.
- And of course, intelligence from other sources can also help to ensure that inspections are targeted at the highest potential risks.

1.11 Selecting sponsors and other organizations to inspect*

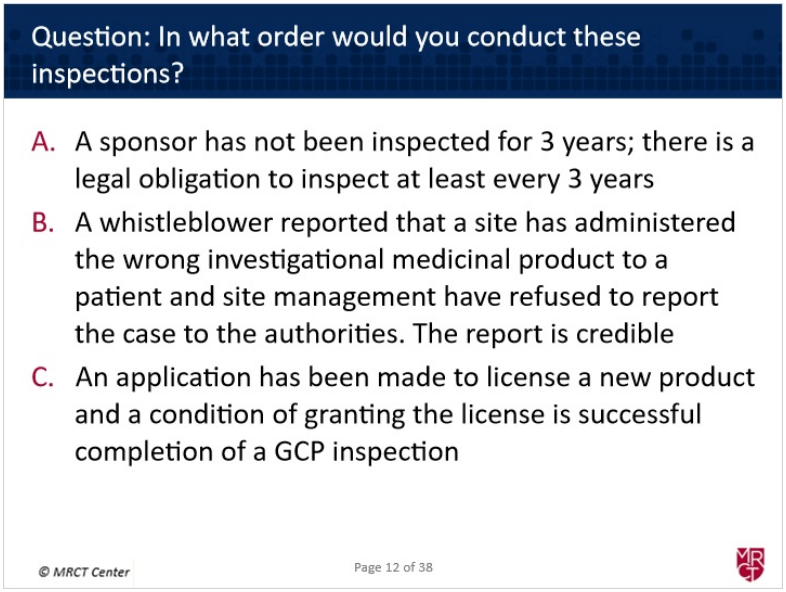
Notes:

A risk based approach should also be used in selecting sponsors and other organizations to inspect. Risk will depend on factors such as:

- The number and type of clinical trials being conducted overall or within the country or area,
- The nature of the trial, for example, is this a new molecular entity for the sponsor or organization?
- Time since the last inspection and its outcome or an organization that has not previously been inspected
- and any non-compliance, for example, known delays to receiving reports, or reports of serious breaches or issues.

A wide range of organizations involved in clinical trials can be selected for inspection including Independent Ethics Committees or Institutional Review Boards.

1.12 Question: In what order would you conduct these inspections?



Notes:

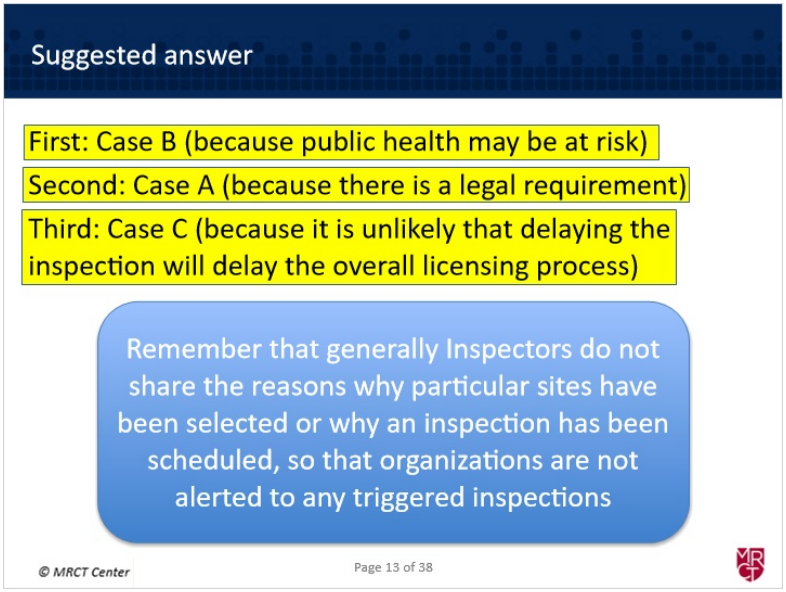
Imagine that you have three inspections to schedule. Which of these examples would you give highest priority to, and which the lowest priority?

A. A sponsor has not been inspected for 3 years; there is a legal obligation to inspect at least every 3 years

B. A whistleblower reported that a site has administered the wrong investigational medicinal product to a patient and site management have refused to report the case to the authorities. The report is credible

c. An application has been made to license a new product and a condition of granting the license is successful completion of a GCP inspection

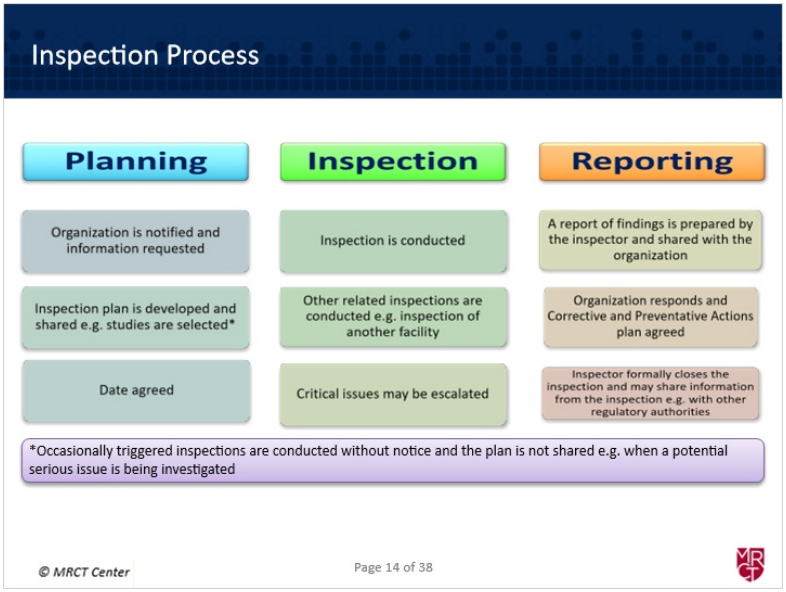
1.13 Suggested answer



Notes:

The suggested answer is highest priority given to example B, because there is a potential risk to public health. The lowest priority is given to example C, because it is unlikely that delaying the inspection slightly will affect the overall licensing process. This leaves example A in the middle, where there is a legal requirement to inspect by a certain time. It is important to remember that inspectors generally do not share the reasons why particular inspections have been scheduled, so that organizations cannot distinguish triggered inspections from routine inspections.

1.14 Inspection Process



Notes:

Here is an outline of the various steps involved in the inspection process, starting with planning, then the actual inspection, and then reporting of the inspection.

- In the planning stage the organization is notified, information is requested, an inspection plan is developed and scheduling occurs.

- During the inspection, all relevant areas are reviewed, including related facilities, and critical issues may be escalated

- Lastly a report of findings is prepared by the inspector and shared with the organization. The organization should respond with Corrective and Preventive Actions as applicable. Upon closing the inspection, the inspector may share information with other regulatory authorities.

It should be noted that occasionally, inspections may take place without any notice, for example to urgently investigate a serious issue, but generally

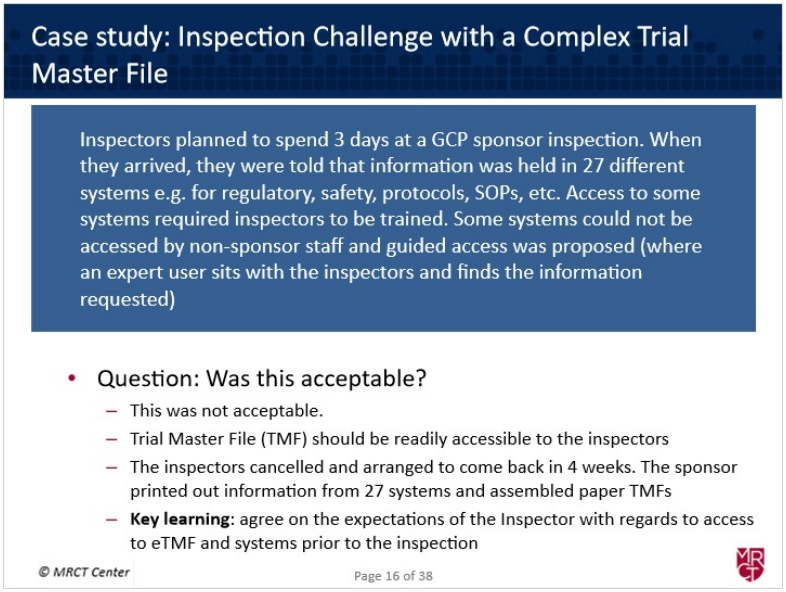
planning is key to a successful inspection, to make sure that everyone and everything is ready.

1.15 Inspection Focus

Notes:

The focus of an inspection will vary depending on circumstances. This slide gives some of the typical areas of focus for a sponsor inspection, many will also be applicable to a CRO or site inspection. Other areas may also be included depending on circumstances, for example medical advice/medical oversight, insurance arrangements, report writing, contracts, compliance with local regulations, etc. How many did you think of?

1.16 Case study: Inspection Challenge with a Complex Trial Master File



Notes:

Let us consider a case study:

Inspectors planned to spend 3 days at a GCP sponsor inspection. When they arrived, they were told that information was held in 27 different systems e.g. for regulatory, safety, protocols, SOPs, etc. Access to some systems required inspectors to be trained. Some systems could not be accessed by non-sponsor staff and guided access was proposed (where an expert user sits with the inspectors and finds the information requested)

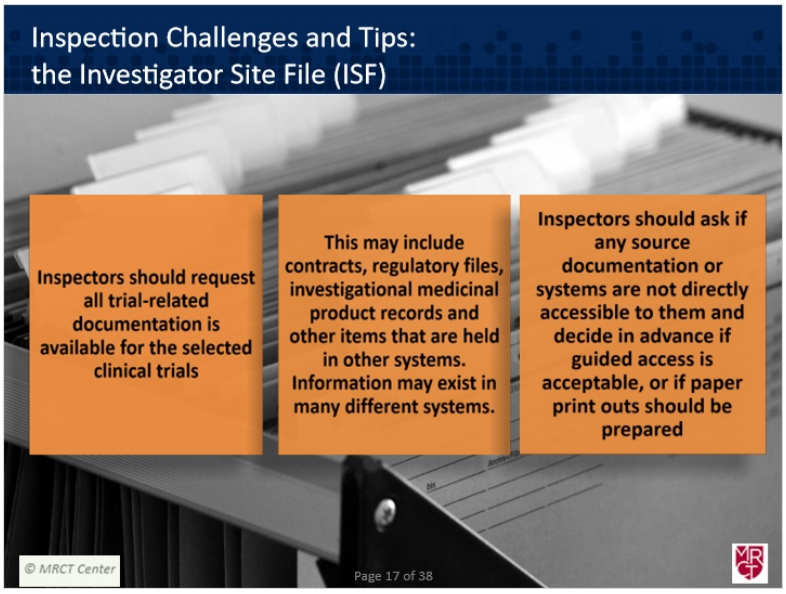
Was this acceptable?

This was not acceptable. TMF should be readily accessible to the inspectors

The inspectors cancelled and arranged to come back in 4 weeks. The sponsor printed out information from 27 systems and assembled paper TMFs, which took huge amounts of resource and time

Key learning: agree expectations around access to eTMF and systems prior to the inspection

1.17 Inspection Challenges and Tips:



Notes:

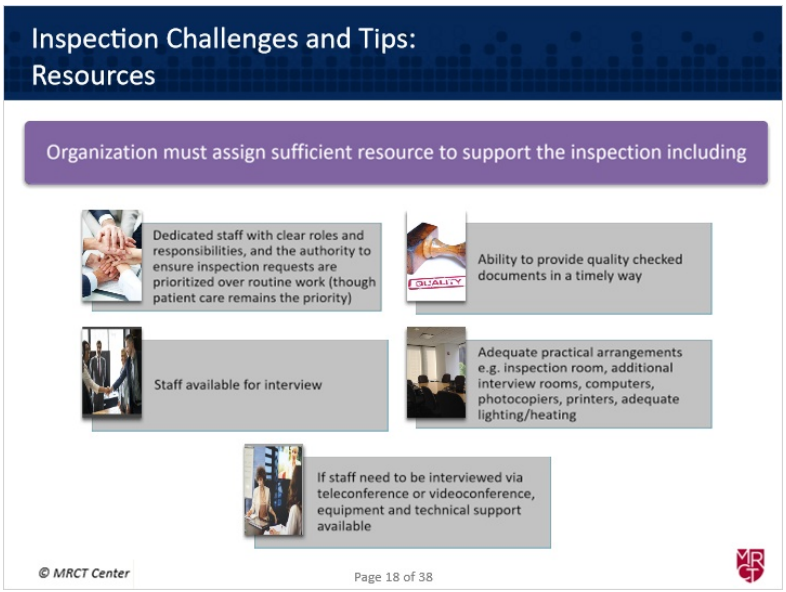
Inspectors will request that all trial-related documentation is made available for the clinical trials.

In addition to the main TMF, this may include contracts, regulatory files, investigational medicinal product records, pharmacovigilance, data management and statistics, that are held in other systems. Information may exist in many different systems.

Inspectors should ask if any systems are not directly accessible to them and decide in advance if guided access is acceptable, or if paper print outs should be prepared.

The Investigator Site File may also be complex and again, it is important to request that all trial related documentation is accessible for a successful inspection, or alternative arrangements agreed.

1.18 Inspection Challenges and Tips:

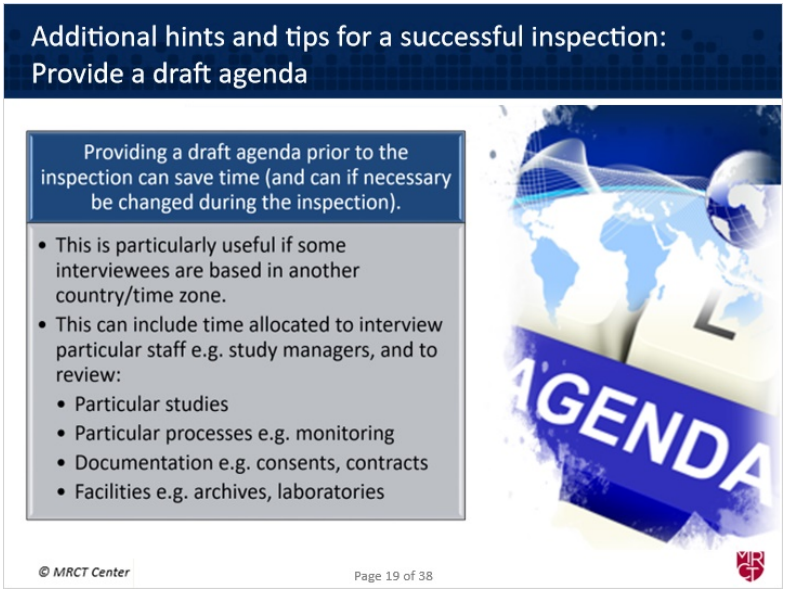


Notes:

Another challenge for a successful inspection is resources. Organizations being inspected must continue their normal clinical trial work, as well as provide sufficient resources to support inspection arrangements.

It is important that dedicated staff are identified to take on responsibility for organizing the inspection. Clear roles and responsibilities should be identified to ensure inspection requests are prioritized. A key role for one of the staff members is to ensure a quality check for all requested documents in a timely way. Staff should be available for interview and practical arrangements, including technical support and availability of equipment where necessary, should be made prior to the inspectors arriving onsite.

1.19 Additional hints and tips for a successful inspection:



Notes:

Providing a draft agenda before the inspection makes the inspection as efficient as possible, and the agenda can be updated as necessary during the actual inspection, for example if an issue is found which needs additional focus. Many organizations are global, with staff based in different countries and time zones, and a draft agenda will enable planning so that people and documents are ready when the inspector requires.

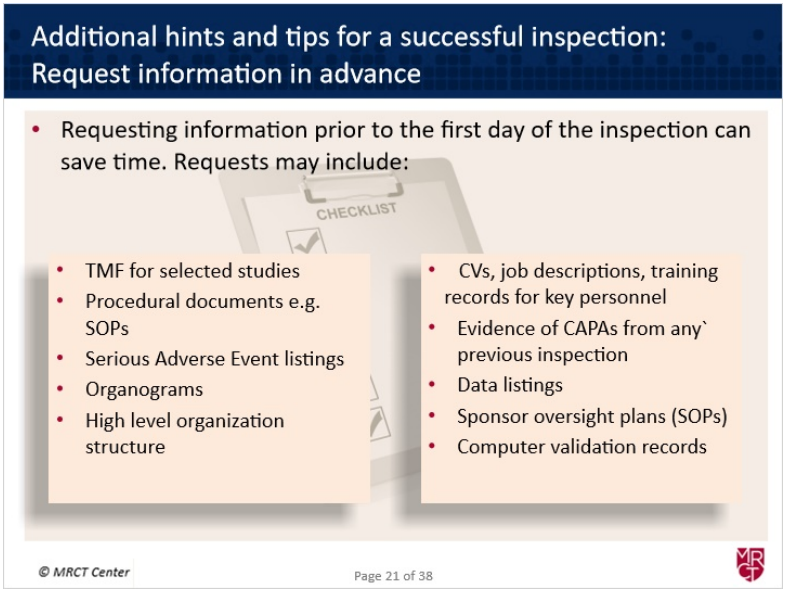
A draft agenda can also include time allocated to interview particular staff, such as study manager, to review particular studies, particular processes, such as monitoring, documentation, such as consent forms and contracts, and facilities such as archives and laboratories.

1.20 Additional hints and tips for a successful inspection:

Notes:

Providing a draft agenda also allows the inspection site and location to be confirmed, and any facilities based elsewhere to be identified and plans made to visit if required.

1.21 Additional hints and tips for a successful inspection:

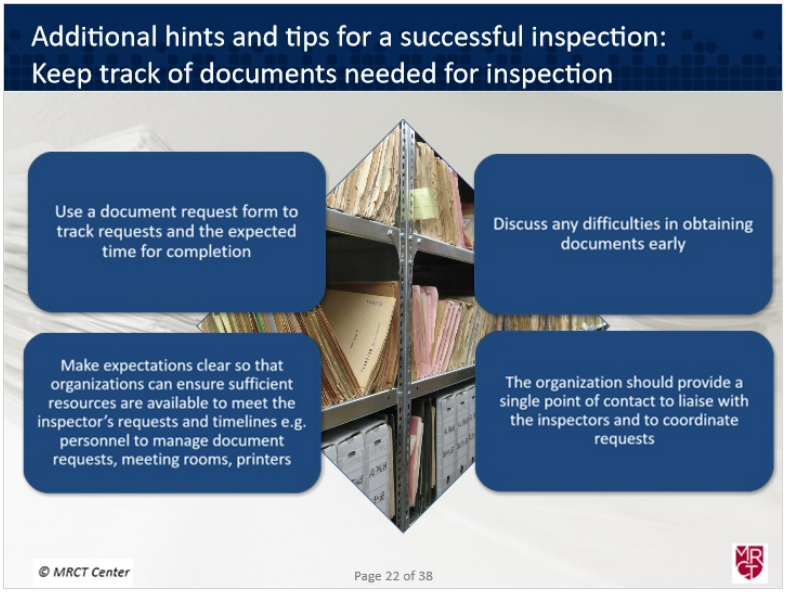


Notes:

Requesting information that should be available for the start of the inspection can make the whole process much more efficient. Examples of documents that may be requested include but are not limited to the trial master file (TMF), SOPs, serious adverse event listings, organograms and details of the high level structure of the organization.

Take a moment to review additional examples provided on the slide. Of course, other document requests will be generated during the inspection, for example as a result of interviews, but many documents can be identified prior to the inspection or on arrival, that need to be reviewed.

1.22 Additional hints and tips for a successful inspection:

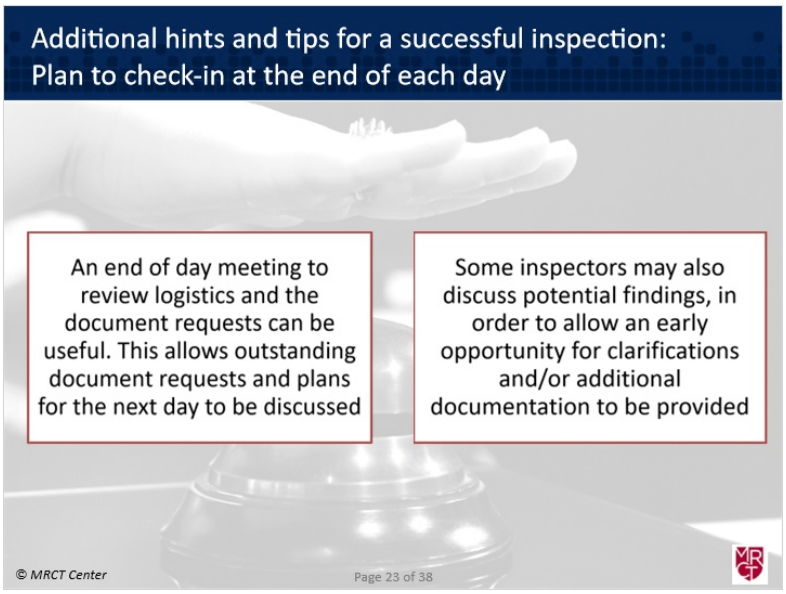


Notes:

Inspections have a fast pace as there is limited time that inspectors are on site. There are usually many interviews and document requests, and documents may have similar names. It is important to keep track of which documents have been requested, which have been provided and which have been reviewed.

- Use of a request form to track requests and the due day/time is useful.
- If there will be a delay in obtaining a document, this should be discussed at an early stage so other activities can be planned and the inspector can come back to the missing document at a later stage. This can happen for example where a document needs to be provided by staff working in another time zone.
- Do make expectations clear; more staff will of course be needed to support an inspection with a large number of inspectors, but there will also be additional requirements for example for separate meeting rooms so inspectors can conduct interviews in parallel.
- It is usually most efficient for the organization to appoint an inspection "Host" to act as a single point of contact with the inspectors, to coordinate requests.

1.23 Additional hints and tips for a successful inspection:

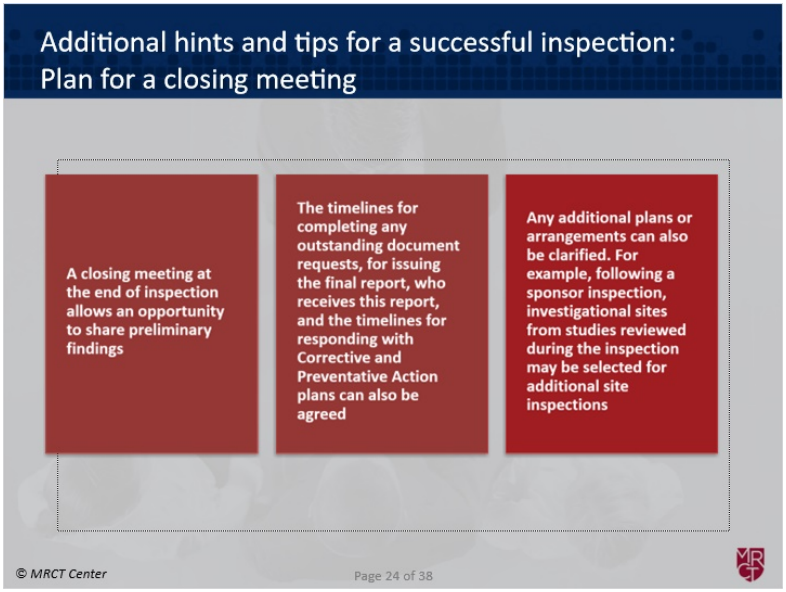


Notes:

Many inspectors request an end of day meeting. This can be used to review practicalities - the logistics, any changes to the draft agenda for the next day, a check on when any outstanding document requests will be available, etc.

Some inspectors will also outline potential findings, which may allow clarifications and additional documents to be provided during the actual inspection rather than afterwards.

1.24 Additional hints and tips for a successful inspection:



Notes:

Most inspections end with a closing meeting. This allows the inspectors to share preliminary findings.

The meeting also provides an opportunity for confirming timelines for documents, and when the final report will be issued and to whom. Expectations around provision of a Corrective and Preventative Action plans can also be made clear.

Sometimes, there will be additional plans to be made, for example following a sponsor inspection, investigator sites may be selected for inspection, and the full report only issued after these additional inspections.

1.25 Hints and tips for a successful inspection:

Notes:

The organization will need to provide responses to inspection findings, including Corrective and Preventative actions.

- It is crucial that the root cause of an issue is identified, otherwise any actions will not fully address the issue and it is likely to reoccur.
- The plan should contain an initial corrective action and also a longer term preventative action, to stop the issue arising again in the future. If the cause is given as human error and the action is retraining of staff, it is likely that the root cause has stopped too soon and the real cause has not yet been identified.
- It is also important to check that the actions are clear and really do address the root cause.
- Finally, the timelines need to be realistic; not too long, such as a year to add a sentence to a Standard Operating Procedure, and not too short, for example planning to totally review and redesign a global process in only 2 months. Inspectors may need to go back to the organization to ask for the CAPA to be updated with more detail or different timelines before it is agreed.