Towards High-quality Clinical Trials And
Implementation Of Genomic Medicine

ATLAS Training Program

Course : CRC training course

Lecture : Review of cancer clinical trial protocols from a CRC perspective

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Review of cancer clinical trial protocols from a CRC perspective

Content

- From the International Conference on Harmonization (ICH)-Good Clinical Practice (GCP) guidelines: Role and definition of the protocol
- Perspective of CRC reading of the protocol
- Uncomfortable situations when conducting clinical trials
- Summary

Role And Definition Of The Protocol

From ICH-GCP: Protocol Definition

GLOSSARY 1.44 Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol typically also gives the background and rationale for the trial, but this information can be provided in other protocol referenced documents. Throughout the ICH-GCP Guidance, the term ‘protocol’ refers to the protocol and its amendments.

Role of the Protocol

GLOSSARY 1.17 Contract

A written, dated, and signed agreement between two or more involved parties that defines any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

Clinical Trial Protocol And Protocol Amendments

6. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)

The contents of a trial protocol should generally include the topics listed in the following slides. However, site-specific information may be provided on separate protocol page(s) or addressed in a separate agreement, and some of the information listed on the next slides may be contained in other protocol referenced documents, such as the Investigator's Brochure.

- 6.1 General Information
- 6.2 Background Information
- 6.3 Trial Objectives and Purpose
- 6.4 Trial Design
- 6.5 Selection and Withdrawal of Subjects
- 6.6 Treatment of Subjects
- 6.7 Assessment of Efficacy
- 6.8 Assessment of Safety

- 6.9 Statistics
- 6.10 Direct Access to Source Data/Documents
- 6.11 Quality Control and Quality Assurance
- 6.12 Ethics
- 6.13 Data Handling and Record Keeping
- 6.14 Financing and Insurance
- 6.15 Publication Policy
- 6.16 Supplements

Protocol Review Points

- Consistency
  - ✓ Is the same meaning expressed using different terms?
    Example) Investigational drug, ABC-123 (clinical trial code), International Nonproprietary Name (INN)

  - ✓ Are different items expressed using the same terms?
    Example) Discontinue･･･**stop** and do not restart
    End halfway through･･････**terminate**
    Stop and restart once the conditions are satisfied: Pause･･･**hold or suspend**

Partially amended from: Haruhiko Fukuda: Protocol preparation - Establishing a research plan. Introduction to Clinical Research Intermediate (Ed.), ICRweb
http://www.icrweb.jp/

- Ambiguous expressions
  - ✓ Do expressions such as “in principle” and “desirable” mean “not required”?

Preferred example) Perform a chest **CT** within **28** days before registration (with or without contrast)

~~Tumour assessment~~ ~~During screening~~

- Are there mistranslations or nuances in the translated version and English original version?
  - ✓ Example) or more, more than, and less than, etc.

Partially amended from: Haruhiko Fukuda: Protocol preparation - Establishing a research plan. Introduction to Clinical Research Intermediate (Ed.), ICRweb
http://www.icrweb.jp/

- Difficult to understand expressions

✓ **A** or **B** and **C** → ×

Example: Lung cancer or stomach cancer with lymph node metastasis

① (Lung cancer **or stomach cancer**) **and** lymph node metastasis

② Lung cancer **or** (stomach cancer **and** lymph node metastasis)

✓ Permitted actions = An action that is not a deviation

Example: “Permitted concomitant treatment, supportive care”

✓ Prohibited actions = An action that is a deviation or violation

Example: “At least 4 weeks have passed since the previous treatment (until the initiation of the investigational product)”

Partially amended from Haruhiko Fukuda: Protocol preparation - Establishing a research plan. Introduction to Clinical Research Intermediate (Ed.), ICRweb
http://www.icrweb.jp/

Reading The Protocol From A CRC Perspective

Principles of ICH-GCP

2. PRINCIPLES OF ICH-GCP

2.5. Clinical trials should be scientifically sound and described in a clear and detailed protocol.

In General Terms, What Is A Protocol?

- The word protocol appears around 100 times in ICH-GCP and forms the foundation of clinical research.
- All matters required in the clinical trial plan must be clearly stated in the protocol.
- It may be preferred to consider that protocols are never complete. Protocols require constant revision of obvious errors and ambiguous expressions.

Reading The Protocol From A CRC Perspective

- Is the protocol valid from an ethical perspective?
- Why is development of this Investigational product/device needed at the present time? (rationale)
- Are the prescribed tests and procedures necessary?
- Can the prescribed tests and procedures be performed at your institution?

CRC Perspective: Ethical Matters

Have ethical matters been considered?

- Does the protocol stipulate a code of ethics that requires compliance?
- Does the protocol stipulate that the trial is reviewed by a third party?
- Are the methods for obtaining consent appropriate?
- Is there a deadline for compensation? Is the description suitable?
- Has an inquiry/consultation point of contact been established for the subjects?
- Has the protection of privacy been considered? (anonymization, etc.)

CRC Perspective: Clinical Trial Design

- The following elements must be clear and mutually consistent in the clinical trial design
  - Target (characteristic of patient group)
  - Study Treatment (type of study treatment conducted)
  - Evaluation (how is evaluation performed)

    Example) Double-blind, placebo-controlled, randomized controlled trial

- Is the target “standard treatment” really the standard treatment?

Partially amended from: Noriko Yamashita: Review of cancer clinical trial protocols from a CRC perspective, Cancer Clinical Trial Textbook, First Edition, 2013

CRC Perspective: Clinical Trial Design

- Master protocol trial: Evaluates a combination of target treatments for multiple biomarkers or genetic alterations in one or more cancer types in multiple sub-studies
- Basket trial: Evaluates the therapeutic effect on the target genetic alteration regardless of the cancer type
- Umbrella trial: Confirms the genetic alteration in a single cancer type and changes the drug to be used depending on the genetic alteration

CRC Perspective: Selection/Exclusion Criteria

Have appropriate inclusion/exclusion criteria been established? (internal/external validity)

More trials are being conducted to “confirm the therapeutic effect depending on the biomarker and genetic alteration, regardless of the cancer type” as opposed to the conventional trials that aim “to confirm therapeutic effect for each cancer type”.

- Are there inconsistencies and/or ambiguous expressions in the protocol?
  - Consistency

    Example) Inclusion criteria for adjuvant therapy for patients without metastasis
    “AST/ALT may be up to ○ times the upper limit of the reference value
    if there is liver metastasis.”

Ineligible at the point where there is liver metastasis

CRC Perspective: Selection/Exclusion Criteria

- Are there ambiguous expressions?
  Example) Poorly controlled complications
  Example) Method of counting pre-treatment regimens
  Preoperative/postoperative therapies, endocrine therapy, molecular targeted drugs

- Are there ethical problems with the starting point of the wash out period?
- Is it acceptable to perform a medical interview, etc., or are tests required to determine the exclusion criteria?
  Example) Active infection

Partially amended from: Noriko Yamashita: Review of cancer clinical trial protocols from a CRC perspective, Cancer Clinical Trial Textbook, First Edition, 2013

Cancer Clinical Trials: Confusing Protocols

Study sponsor	Inclusion criteria	Exclusion criteria	Number of pages
A	14 + additional 6	16 + additional 11	5.5
B	12	21	6.5
C	21	19	6

- **Is cytology accepted or histological diagnosis required ?**
- **Is pathological diagnosis in your institution essential or pathological report from other institutions acceptable?**

There are also points to note in each item

Example) 1. ●● cancer confirmed by pathological diagnosis, with no confirmed distant metastases

* Stage●
* Tumor specimen of the primary lesion has been diagnosed as ●● in accordance with ●● guidelines
* Genetic alteration has/has not been confirmed

Gene amplification? Deletion? Fusion?

CRC Perspective: Registration/Allocation

Confirm the validity of the method for registering subjects and the registration procedure

- Registration method, how randomization results are obtained

  Fax, email, or EDC, etc.

- Registration procedures

  Whether slots are secured and if there is provisional registration or multi-stage registration

  Whether there is preliminary consultation with study sponsor and the number of required days

Partially amended from: Noriko Yamashita: Review of cancer clinical trial protocols from a CRC perspective, Cancer Clinical Trial Textbook, First Edition, 2013

CRC Perspective: Registration/Allocation

- Is the schedule from the time of consent and preliminary registration to the time of the main registration feasible?

  Example) Main registration must be completed within 7 days of preliminary registration, but sponsor confirmation requires 5 business days

Is this feasible?

- Can the registration procedures be completed within the permissible range for tests?

  Example) Registration must be completed within 28 days of testing, but diagnosis by central lab requires 3–4 weeks

Is this feasible?

Partially amended from: Noriko Yamashita: Review of cancer clinical trial protocols from a CRC perspective, Cancer Clinical Trial Textbook, First Edition, 2013

CRC perspective: Registration/allocation

- What information is required for registration?
  Sometimes, detailed background information is necessary

- Are the allocation factors easy to understand?
  Example) Recurrence, relapse

- Are the randomization results written in an easy-to-understand format?

Partially amended from: Noriko Yamashita: Review of cancer clinical trial protocols from a CRC perspective, Cancer Clinical Trial Textbook, First Edition, 2013

CRC Perspective: Administration Method/ Change Criteria

Are criteria set for minimizing risks, such as dose reduction or drug suspension?

- Are there clear criteria for initiating treatments and cycles, in addition to those for drug suspension?
- Administration change criteria: Applicable scope and possible period of drug suspension when multiple investigational drugs are used

  Example) Postpone administration if Grade 3 hematological toxicity occurs

① If the investigator determines that there is a casual relationship with investigational product A, but no causal relationship with investigational product B, should administration continue for investigational product B only? Should the administration of both IPs be postponed?
② If the investigator determines that there is no casual relationship with either investigational product A or B, can the administration of both IPs continue?

Partially amended from: Noriko Yamashita: Review of cancer clinical trial protocols from a CRC perspective, Cancer Clinical Trial Textbook, First Edition, 2013

CRC Perspective: Administration Method/ Change Criteria

- Formula for calculating dose (Example: Dubois formula, etc.), handling of fractions
- When was the baseline weight determined? When was the most recent weight determined?
- Is it possible to use commercial products, such as infusion sets, as administration materials?
- Should the empty IP bottles be returned? How remained IP should be managed? Should IPs be administered on the day of the study visit?
- Schedule visit allowance

Partially amended from: Noriko Yamashita: Review of cancer clinical trial protocols from a CRC perspective, Cancer Clinical Trial Textbook, First Edition, 2013

CRC Perspective: Administration Method/ Change Criteria

- Can the investigational product and control drug be provided by the sponsor, or can it be purchased in the institution?
- Does administration require any special dispensing methods or equipment?
- Designation of the order of administration when administering multiple drugs. Availability of pre-medication. Timing of vitals checking, blood collection, and electrocardiogram during administration
- Stability after dispensing

  Example: How long can the IPs be stored at room temperature before administration is completed?

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CRC Perspective: Evaluation/Schedule

What type of tests are used, and are they scientifically valid?
(balance between subject protection and safety monitoring)

- Is there consistency between the study calendar, main protocol text, and content of the informed consent form?
- Are there any tests that cannot be performed in your own institution?
- Is the test frequency appropriate? Are there detailed regulations on the test methods?
- Do the test items and timing set enable adverse event detection at an early stage?
- Are tests required at completion or discontinuation of the trial?
- Are the follow-up schedule and test/observation items appropriate?

CRC Perspective: Determining Effects

Are the methods used to evaluate the study treatment valid?

- Response rate

  Are there regulations regarding the slice width for CT/MRI?

  Have any areas been modified from RECIST?

  Is a confirmation period required to determine the CR/PR for the best overall response?

- Survival time

  Are there clear definitions for the response determination date and protocol treatment discontinuation date?

CRC Perspective: Adverse Events

- Definition of AEs
- Definition of AEs of special interest
- CTCAE Version
- AE collection period and reporting procedures
- Is it necessary to report events associated with progression/ worsening of cancer as AEs?

Partially amended from: Noriko Yamashita: Review of cancer clinical trial protocols from a CRC perspective, Cancer Clinical Trial Textbook, First Edition, 2013

CRC Perspective: Serious Adverse Events

Are there appropriate procedures for reporting SAEs? Is there a system in place that enables rapid determination?

- Definition of SAEs, reporting deadlines, reporting method
  Is there a reporting format specific to the sponsor?
  Many trials require reporting to the sponsor within 24 hours

- Create an environment where PI/SIs can report SAEs when no CRCs are present
  EDC report ⇒ Account acquisition/management request, create input method sample
  Fax and email reports ⇒ Sample for how to complete the sponsor regulation form and clarify the contact details

CRC Perspective: Events That Require Prompt Reporting

- Definition of adverse events of special interest, reporting deadlines, reporting method

  Example) Possible drug-induced liver injury
- Overdose
- Pregnancy

- Create a process whereby doctors can report when no CRCs are present (as is the case with serious adverse events)

Uncomfortable Situations Encountered When Conducting Clinical Trials

Uncomfortable Situations During Clinical Trials

- Required items are not described in the protocol, and are only described in the procedures

  → These items should be described in the protocol, but the procedures were prepared after deliberation on ethics and scientific matters by the institutional review board

- Requirements that are “not tolerated by the sponsor”, which are not described in the protocol

  Cannot be registered

  → These items should be clearly stated in the protocol

Summary

Summary

- The protocol forms the foundation for conducting clinical trials; therefore, it is important to prevent protocol deviations due to simple errors and/or protocol deviations that occur because of misunderstandings or misinterpretation of the protocol
- However, complete protocols do not exist, and thus there will be inconsistencies and typing errors
- It is important to separately check for ambiguous descriptions and areas of uncertainty, as well as to create a record of these items

The sponsor views the protocol from a corporate perspective, whereas investigators view the protocol from the perspective of scientific interest. Thus, CRCs should review the protocol from the subject's perspective.

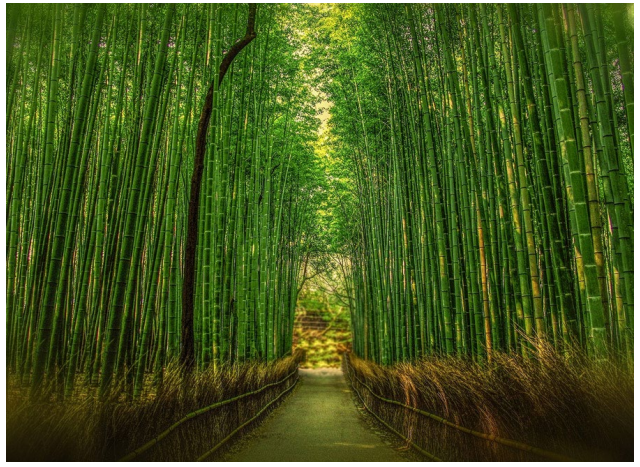
CRCs conducting a detailed protocol review can prevent unnecessary deviations from the protocol and protect the subjects.

If CRCs review the protocol during the preparation stage and consult on reasonable schedules and procedures in line with the standard medical care provided at the institution, the clinical trial can be seamlessly implemented and screening and recruitment would be performed efficiently.

- Thank you for your attention








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