受託研究機構專案查訪(核)計畫介紹及實施現況

112.9.26

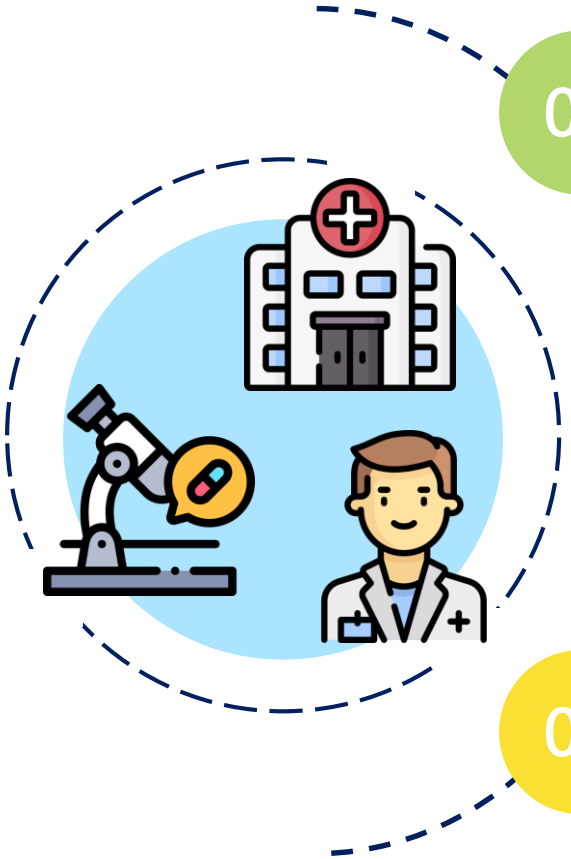
張婷雅 科長

藥品組臨床試驗科
衛生福利部食品藥物管理署

衛生福利部
食品藥物管理署
Taiwan Food and Drug Administration

http://www.fda.gov.tw/

大綱



01 計畫背景介紹

02 提升CRO及CRA品（素）質專案

03 近期及未來規劃

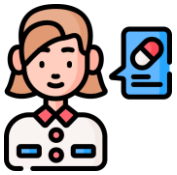
計畫背景

試驗機構(教學醫院)

研究倫理委員會IRB

試驗主持人(PI)

研究護理師(CRN)
/研究協調員(SC)



PI授權之其他人員
(試驗藥師...)

試驗委託者(藥商) Sponsor

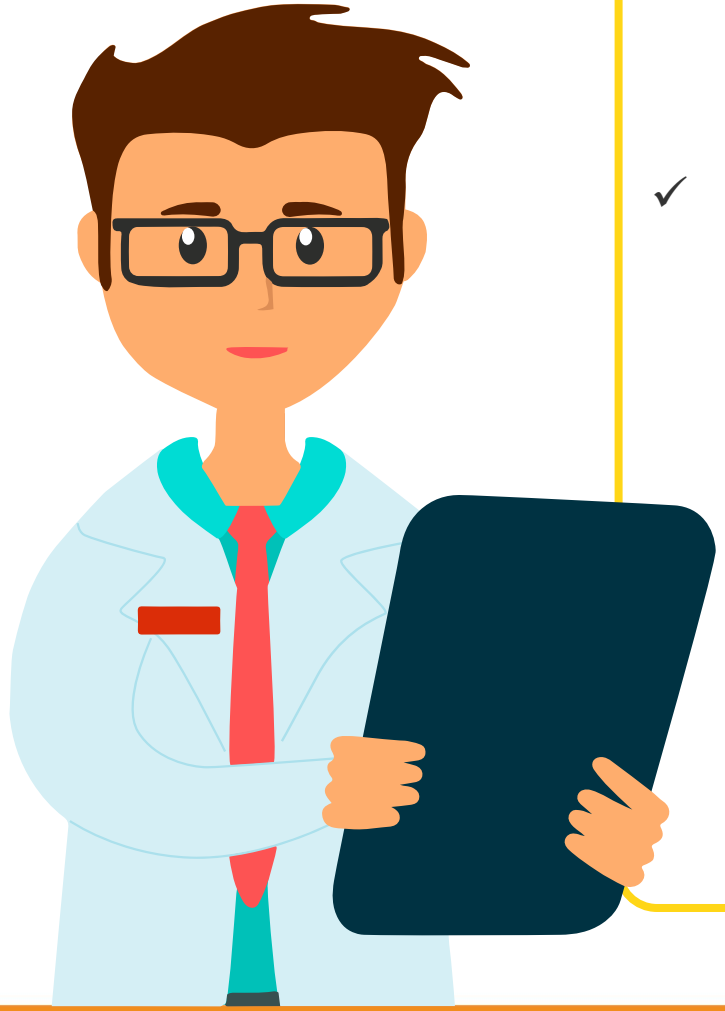
受託研究機構(CRO)

臨床研究專員(CRA)

其他人員
(CTA, PM, SSUS)

試驗機構委託之管理機構
Site Management Organization (SMO)

計畫背景



✓ **臨床試驗服務產業興起**

- 生技醫藥產業生態改變，藥廠將臨床試驗服務外包
- 受託研究機構 (Contract Research Organization)興起

✓ **國內藥品臨床試驗人才問題**

- 臨床試驗案件數增加
- 往昔臨床試驗服務人才專業能力未受重視
- 試驗主持人反映**臨床研究專員(CRA)**素質良莠不齊，對於試驗計畫書內容、試驗設計、受試者納/排除條件等事項**專業不足/不熟悉**，造成試驗執行之困擾

目前臨床試驗服務人力培訓問題

- 訓練成效不明、無法反映於實務執行作業，課程未認證
- 訓練資源零散無完整性，欠缺系統性規劃

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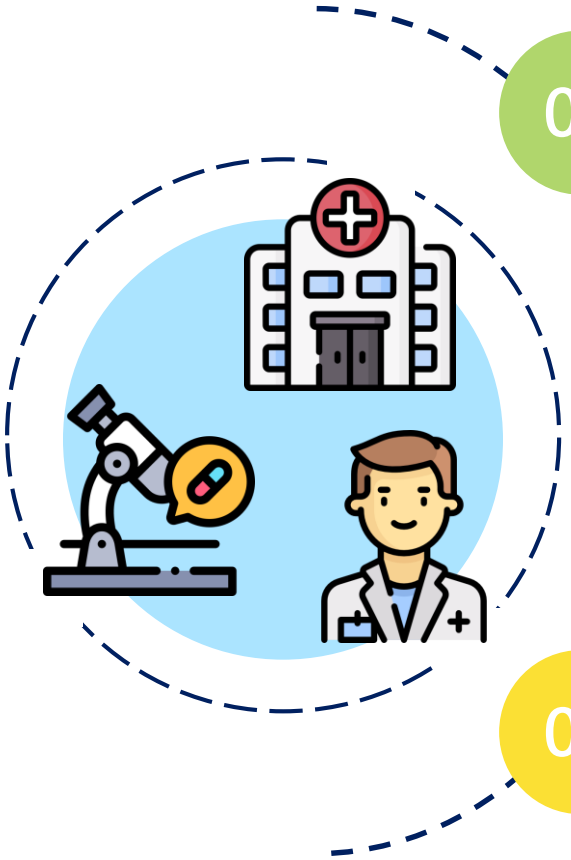

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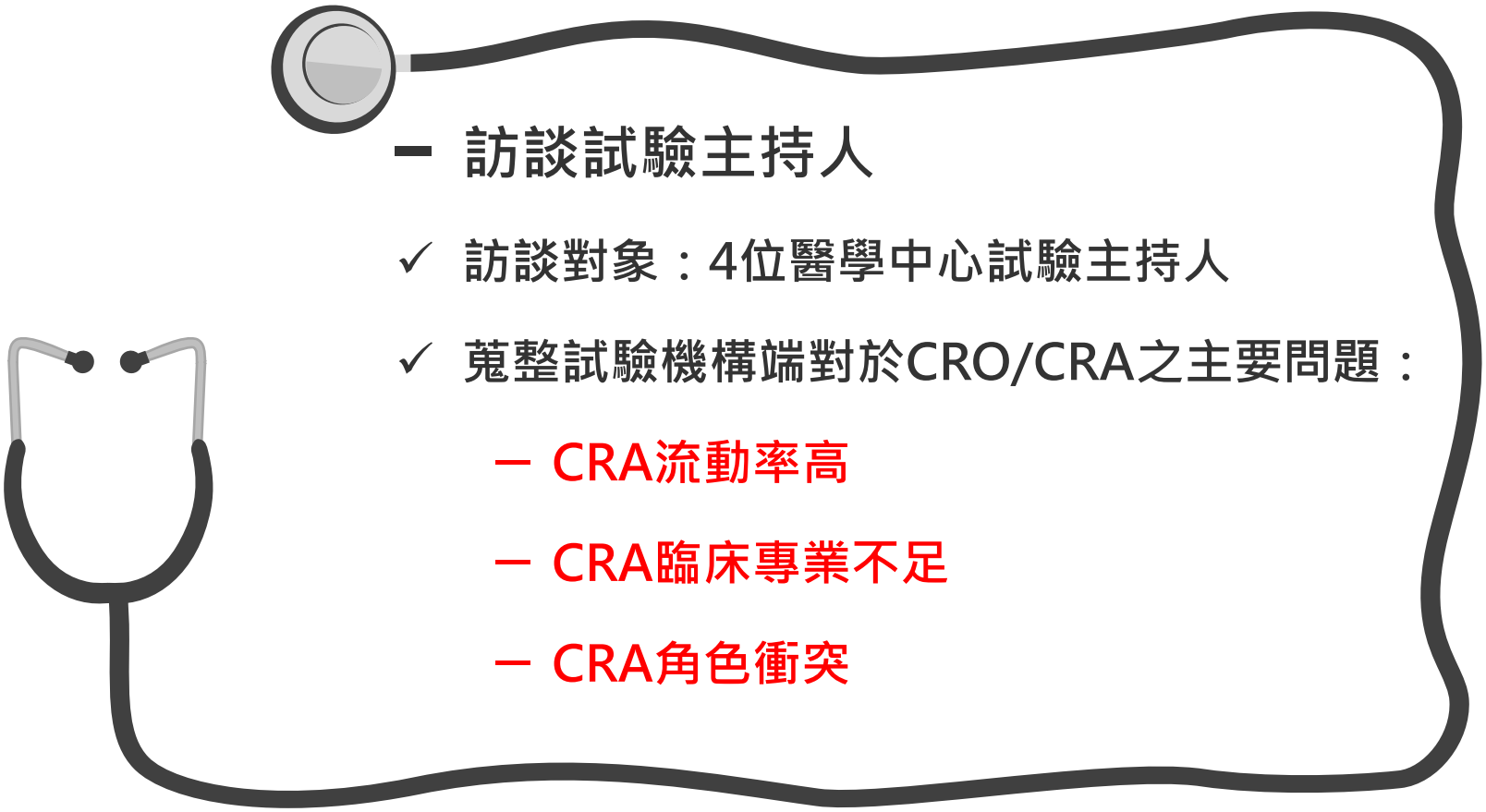
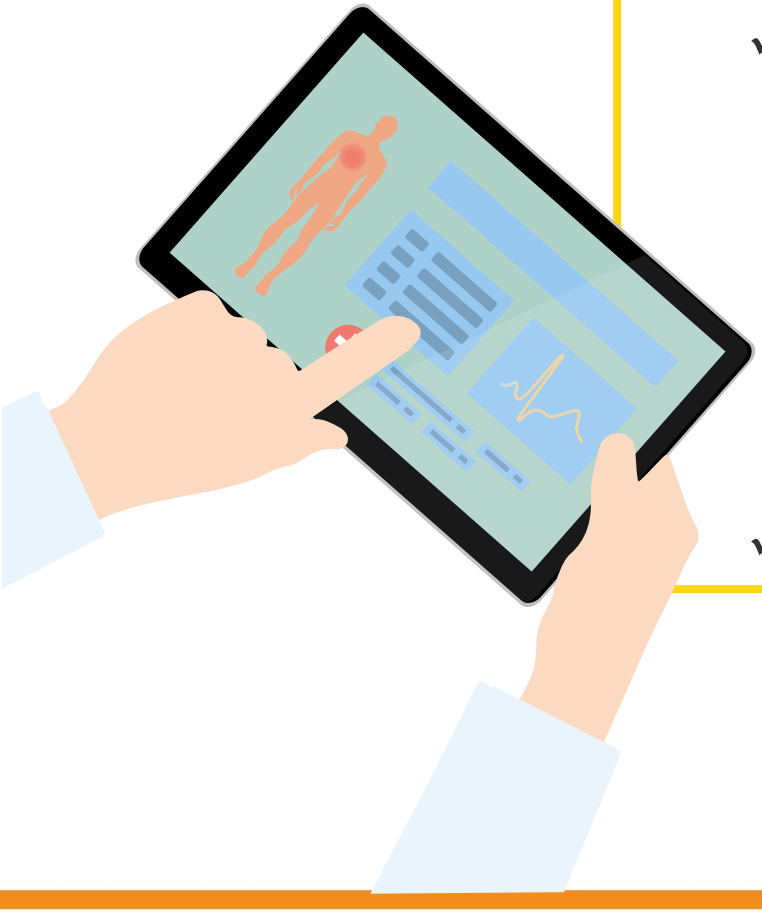
階段1：研析規劃提升CRO/CRA品（素）質方法



- 訪談試驗主持人
  - ✓ 訪談對象：4位醫學中心試驗主持人
  - ✓ 蒐整試驗機構端對於CRO/CRA之主要問題：
    - CRA流動率高
    - CRA臨床專業不足
    - CRA角色衝突

階段1：研析規劃提升CRO/CRA品（素）質方法



- 與臨床試驗相關協(學)會開會研商
  - ✓ 參與對象：
    - 台灣藥物臨床研究協會(TCRA)
    - 中華民國開發性製藥研究協會(IRPMA)
    - 台灣臨床研究倫理審查學會(TAIRB)
    - 臺灣護理師臨床研究學會(TACRN)
  - ✓ 共同研擬「CRA職能規劃草案」

階段1：研析規劃提升CRO/CRA品（素）質方法

「CRA職能規劃草案」重點如下：

1. CRA基本職能：

- ✓ 入職後實際進行試驗監測工作前，須完成**40小時**課程。
- ✓ 每年應接受最少**8小時**繼續教育課程。

2. 臨床試驗相關課程：

- ✓ICH E6: Good Clinical Practice (GCP)、GxP Training
- ✓臨床試驗相關法規、研究倫理相關課程
- ✓試驗監測相關課程 (Site Monitoring)
- ✓Informed Consent Review、Source Document Review、Monitoring Visit Report writing
- ✓Study and Site Management: Budget Management, Subject Recruitment & Retention, etc.
- ✓Documentation Management
- ✓Issue Escalation and Management/ CAPA Management、Safety Reporting Management
- ✓臨床試驗品質相關課程 (QC/ QA: Audit & Inspection)
- ✓臨床試驗專業課程或研討會
- ✓所負責之臨床試驗案之訓練，例如：Disease/ Therapy Area Training; Protocol Training, Relevant Manual Training等。

提升CRO及CRA品（素）質專案

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階段2：CRO專案查訪(核)計畫

實施期間：112年1月1日至12月31日

第一階段：查訪		第二階段：查核
查訪對象 ✓ 承接臨床試驗計畫案數較多 ✓ 執行臨床試驗曾發生重大試驗偏差或有發生缺失之風險者		**查核對象** ✓ 查訪時發現具體重大缺失 ✓ CRO規避、拒絕或妨礙查訪之進行 ✓ 發生試驗偏差之高度風險者
參與人員 ✓ 本署業務主管及查訪員 ✓ 外部專家委員		**參與人員** ✓ 本署查核員 ✓ 外部專家委員(必要時)
查訪重點 ✓ CRO內部人員管理 ✓ CRO人員之專業教育、訓練考核 ✓ 執行藥品臨床試驗監測、稽核等作業項目之情形		**查核重點** ✓ 依個案情形決定

階段2：CRO專案查訪(核)計畫-查訪委員

林口長庚紀念醫院 - 賴瓊慧副院長

林口長庚紀念醫院 - 謝宜璋主任

台中榮民總醫院 - 李冠德主任

臺大醫院癌醫中心分院 - 楊志新院長

臺北醫學大學附設醫院 - 蕭世欣主任

高雄醫學大學附設中和紀念醫院 - 許超群醫師

高雄醫學大學 - 吳登強副校長

階段2：CRO專案查訪(核)計畫 - 查訪結果

發現問題		瞭解緣由
01 CRA流動率高		✓ 外商CRO：離職率高、平均年資短(約3年) ✓ 台商CRO：薪資考量，任滿2年即轉職外商 ✓ 平均每執行1件臨床試驗，會遭遇1人次CRA離職
02 CRA專業不足		✓ CRO因應人力需求，工作型態趨向專業分工模式 ✓ 訓練時間短(約3-6個月)，面對PI提問常出現**遲誤回答**、**文不對題**及**提供錯誤資訊**等情況 ✓ 部門間橫向溝通不足，無法及時回應試驗機構提問
03 CRA角色衝突		✓ 教學醫院常規**醫療業務繁重**，醫院臨床試驗人員(SC/CRN)離職率居高不下 ✓ CRA被期待以更積極的角色參與試驗，而非僅止於扮演GCP規範的「監測者」

階段2：CRO專案查訪(核)計畫 - 查訪結果

發現問題		建議事項
01 CRA流動率高		✓ 重視CRA實務訓練需求，鼓勵或扶植CRO建立「CRA實習制度」 ✓ 研擬完善且完整的培育制度，提升CRA專業職能 ✓ 加速臨床試驗數位化，減輕試驗執行人力負擔
02 CRA專業不足		
03 CRA角色衝突		✓ 明確化CRA與SC/CRN的角色職責分野，舉辦試驗人員職能精進工作坊，促進人員交流 ✓ 思考如何解決SC/CRN人力問題，及試驗過度集中於少數PI問題

階段2：CRO專案查訪(核)計畫 - 查訪結果

1 受託研究機構端

- ✓ SPONSOR成本考量委託CRO執行試驗
- ✓ 國際臨床試驗數增加CRO/CRA人力不足

→

- ✓ 為降低進入門檻，CRO業務分工細分
- ✓ CRA訓練3至6個月即獨立作業

→

- ✓ CRA臨床醫療觀念/醫學知識不足，無法即時解答問題或回答錯誤，增加試驗偏差風險
- ✓ 部分CRA未確實執行監測
- ✓ CRO各部門橫向聯繫不足

↓

2 試驗機構端

- ✓ 試驗遲滯
- ✓ 效率不好
- ✓ 試驗偏差增加

←

- ✓ 醫院端常規醫療業務繁重
- ✓ 病人傾向前往大型醫院看病
- ✓ 醫院量能不堪負荷
- ✓ 專業SC/CRN招募困難

←

- ✓ SC/CRN壓力增加
- ✓ 業界薪資普遍較高
- ✓ SC/CRN陸續轉職，導致試驗機構端人力更加不足

惡化

第二階段擴大查訪：SMO公司

查訪對象：4間SMO公司

查訪動機

醫療機構內部**執行人力不足**，量能不堪負荷，也導致專業**SC/CRN招募困難**，部分醫院轉而尋求委託**SMO公司**提供人力

查訪重點

- ✓ SMO公司運作及**內部人員管理**
- ✓ SMO人員之**專業教育**及**訓練考核**
- ✓ SMO公司提供服務項目之相關作業情形

發現問題

- ✓ SC/CRN角色定位模糊
- ✓ Freelancer執業登記於SMO下，惟缺乏管理制度及規範

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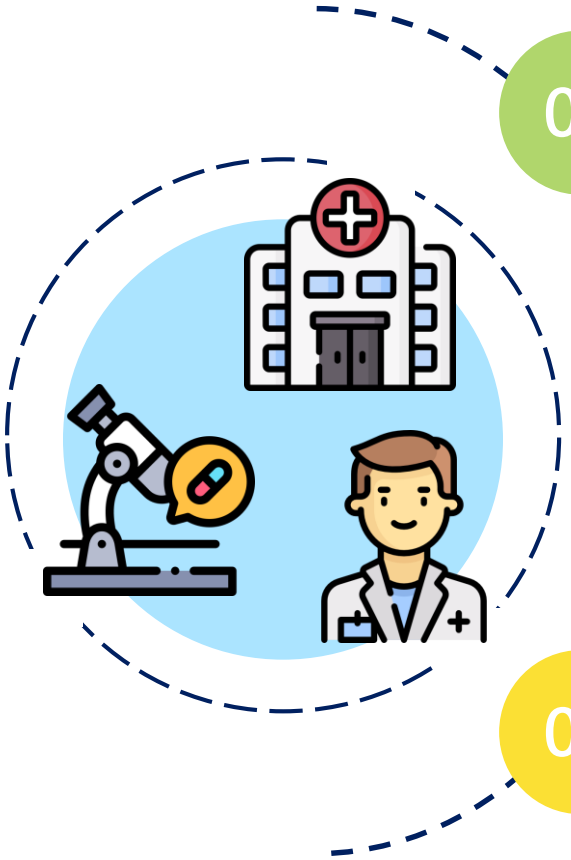

01 計畫背景介紹

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辦理藥品臨床試驗參與人員職能精進工作坊

時間：11月3日(五) - 11月4日(六)

地點：臺大國際會議中心

為提升藥品臨床試驗實務執行作業人員職能，協助各職能人員釐清角色定位及職責劃分並促進其交流

專題演講

- ✓ 受試者保護中心角色與職責
- ✓ 試驗委託者角色與任務
- ✓ 臨床研究專員角色與任務
- ✓ 試驗主持人之角色與職責
- ✓ 臨床試驗研究護理師角色與職業發展
- ✓ 藥品管理的角色與任務

經驗分享

- ✓ Site與 CRO團隊合作的經驗分享
- ✓ 腫瘤新藥臨床試驗的執行與溝通技巧分享

實務交流與各案情境推演

分組討論/報告

提升CRO及CRA品（素）質專案

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02 規劃實施CRO專案查訪（核）

03 檢修參與試驗人員相關法規

04 從長計議試驗參與人員培育制度

未來規劃

階段3：檢修參與試驗人員相關法規

檢視並研議國內臨床試驗應配合訂修之法規。如有涉及外部單位業管法規(如：參與試驗的醫事人員資格及權利義務等)，啟動跨機關(單位)法制溝通程序，以完善臨床試驗法規環境。

階段4：從長計議試驗參與人員培育制度

建立可長可久且符合實務需求之藥品臨床試驗參與人員「教(教育)」、「考(考試/考核)」、「訓(訓練)」、「用(任用)」制度，以根本解決試驗人力供需及人才培育問題。

試驗環境仰賴你我共同提升

Regulatory authority

PI/Site

Sponsor

CRO

謝謝聆聽

僅供查核說明會使用

Inspection Preparation & Management

Sharon Huang on behalf of Parexel

26 September 2023

parexel®

Table of Contents

Notification

Notification of Inspection

- Announcement of the inspection/visit plan
- Phone/email communication of the planned date
- Official letter notifying the date of the inspection/visit

Communication with Authority

- Confirm the following with TFDA:
  - Main contact window
  - Attendees & agenda
  - Inspection purpose/scope/items
  - Staff interview
  - Materials (e.g., self-evaluation form, questionnaires, presentation slide) to be provided to TFDA beforehand
- Logistics arrangement
- Equipment required (e.g., laptop with personal credentials for system access management)

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Preparation

With Heart™

Preparation – Kick Off

Determine the scope of the inspection

- Following receipt of the initial notification, hold a meeting to determine/identify departments involved based on scopes
- Based on the scope, identify inspection and coordination teams, consisting of leaders, team members and SMEs who are knowledgeable and experienced with the topics/processes/systems to be reviewed (as applicable)

Preparation – General

The following should be initiated as soon as possible following notification:

- Hold meeting to discuss preparation activities and areas of emerging risk and escalate issues as appropriate
- Ensure all relevant functions are included in inspection preparation
- Ensure team has access to relevant study documentation to allow adequate preparation
- According to contractual obligation, inform clients where applicable.

Preparation – Training

- Provide appropriate Inspection Awareness training to staff as needed and have the training properly documented
- Provide/recommend additional training, where appropriate, if gaps are identified during inspection preparation activities

Day of Inspection

Opening Meeting

A brief introductory meeting is held with the inspector(s) to:

- Review the inspector's credentials
- Determine the purpose and scope of the inspection. The discussion may also include other pertinent issues or concerns the inspector(s) or CRO may have.

Note Taking

- Assign a staff member (e.g., departmental representative familiar with processes) to be responsible for taking notes during the inspection
- All requests from the inspectors should be tracked in the Regulatory Inspection request tracker in order to manage follow up action items.

Documentation Review and Tracking Requests

- Documentation requests/handling is managed by the coordination team and should be supported immediately
- Collect requested documentation and information and ensure feedback is provided in a timely manner.
- If specifically requested to provide paper copies, identify copies as such, stamp the front page as “confidential” and provide the QA representative with a duplicate set of documents given to the inspector. This allows the CRO to review what was given to inspectors in the event of questions or concerns.

Staff Interview

- When answering questions, think before you speak.
- Make sure you understand the question completely before responding. It is appropriate to ask clarifying questions, if needed.
- Be concise, truthful and factual. It is important to ensure consistent and honest feedback so that no conflicting information is provided.
- Be professional, polite and respectful.
- Appropriate back-ups/support/senior staff are available for guidance.

Closing and Follow Up

Closing

Closing is held at the conclusion of an inspection

- Prior to the closing meeting, inspection team has a private meeting for internal discussion
- CRO inspection management team should attend closing meeting.
- Take note of the findings highlighted by the inspectors and, where possible, address erroneous findings or provide additional clarification during the closing meeting
- Request erroneous findings be removed or modified
- Clarify how findings or meeting minutes will be formally provided to CRO (Inspection report, letter, timeline) and feasibility to review the draft findings/meeting minutes before finalization.
- Confirm timeline for responding to inspection observations

Takeaways

Key Takeaways

- Preparation
  - Timely and adequate preparation is essential for a successful inspection
- Parexel Standards
  - Standards are in line with ICH GCP and local regulations to ensure patient safety and data validity
- Requirements
  - Know and follow relevant industry, company, departmental and project requirements
- Documentation
  - Ensure the documentation is completed, up-to-date and accurately reflects activities
- Handle Issue Appropriately
  - Identify, document, escalate and address any issue with right actions

Wishing you good luck for your future inspections…

Thank you

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NTU Cancer Center
台大癌醫中心

CRO and SMO survey
Investigator's view

James Chih-Hsin Yang M.D., Ph.D.
楊志新教育部國家講座及台大講座教授
National Chair Professor,
Graduate Institute of Oncology, NTU
台灣大學醫學院腫瘤醫學研究所

Superintendent,
National Taiwan University Cancer Center
台大醫院癌醫中心分院院長

台灣大學醫學院附設醫院癌醫中心分院

CRO’s responsibility (1)

ensuring the successful execution of clinical trials.

- Regulatory Compliance

Ensuring adherence to regulatory guidelines and ethical standards.

Maintaining accurate and complete documentation.

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CRO's responsibility (1)

❖Informed Consent

Ensuring informed consent procedures are followed.

Protecting the rights and welfare of study participants

❖Study Protocol

Reviewing and understanding the study protocol thoroughly.

Ensuring all study activities align with the protocol.

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CRO's responsibility (3)

❖Site Selection

Identifying and selecting appropriate clinical trial sites.

Conducting site evaluations and assessments.

❖Investigator Relationship

Building and maintaining strong relationships with investigators.

Facilitating effective communication with site personnel

CRO’s responsibility (4)

- Monitoring

Regularly monitoring the progress of clinical trials.

Verifying data accuracy and patient safety.

- Data Collection

Collecting, reviewing, and documenting clinical trial data.

Resolving data discrepancies and ensuring data integrity.

CRO's responsibility (5)

❖Safety Reporting

Timely reporting of adverse events and safety concerns.

Coordinating with the Safety Monitoring Committee.

❖Drug Accountability

Tracking and managing the distribution of investigational drugs.

Ensuring drug accountability and compliance.

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CRO's responsibility (6)

❖Quality Assurance

Assisting with quality assurance audits and inspections.

Maintaining a high standard of data quality.

❖Documentation

Properly archiving essential study documents.

Maintaining a detailed and organized Trial Master File (TMF).

CRO's responsibility (7)

- Regulatory Submissions

Assisting in the preparation of regulatory submissions.

Providing necessary documentation to regulatory authorities.

CRO's responsibility (8)

❖Collaboration

Collaborating with cross-functional teams (e.g., clinical, regulatory, and medical affairs).

Facilitating effective teamwork and communication

❖Problem Solving

Identifying and addressing issues and challenges proactively.

Implementing corrective and preventive actions (CAPA)

❖Reporting and Communication

Regularly reporting trial progress to sponsors.

Communicating updates and issues promptly.

SMO's multifunctional roles

- Maintain a group of trained responsible research associates
- Robust quality assurance program
- Adherence to industry standards
- SOPs to follow
- Site adaptation

Inhouse drug developers vs CRO

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- Product vs. Performance
- Professionalism vs. Procedures
- Passion vs Passive
- Proud vs. Practicality
- Precious vs. Prudent

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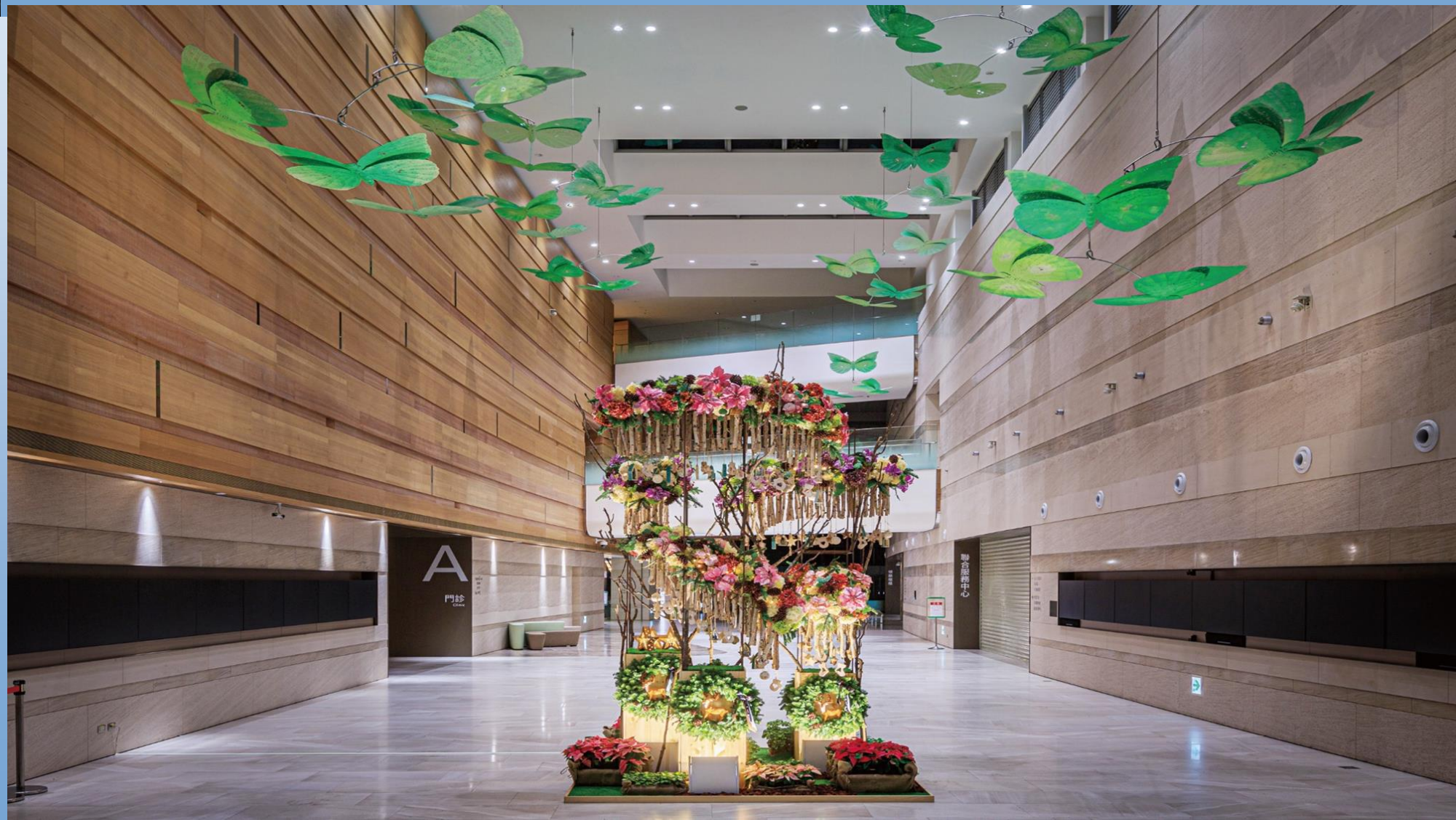
台 大 癌 醫 中 心

THANK YOU



Acknowledgement

ChatGPT 3.5

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