



109 年度「新興醫療器材臨床試驗設計與管理研究」計畫

## 醫療器材臨床試驗教育訓練課程（三）

【承辦單位】



【地點】

中山醫學大學附設醫院

中 華 民 國 109 年 9 月 18 日

## 醫療器材臨床試驗教育訓練課程（三）

為培育並強化國內醫療器材臨床試驗相關人員之能量，特辦理臨床試驗法規與實務訓練課程，以提升國內執行臨床試驗之品質和效率，增進我國新興及高階醫材產業之國際競爭力。本課程以醫療器材臨床試驗法規與實務為主軸規劃相關議題，包含講述新版 ISO 14155 法規要求與改版重點，以及歐盟 MDR 之醫療器材臨床評估法規要求；另外透過臨床試驗設計、實務分享、以及統計方法應用等議題，使相關研究人員能更全面學習和理解醫療器材臨床試驗法規與實務上之執行要求。（免費課程）

- 主辦單位：** 衛生福利部食品藥物管理署
- 承辦單位：** 財團法人醫藥工業技術發展中心
- 協辦單位：** 中山醫學大學附設醫院人體研究倫理審查委員會
- 日 期：** 中華民國 109 年 9 月 18 日（星期五）
- 教育積分：** 提供衛福部醫事人員教育訓練「西醫師」、「護理師」繼續教育積分
- 認 證：** 提供 6 小時學習時數證明（電子檔）
- 上課地點：** 中山醫學大學附設醫院大慶院區行政大樓 12 樓慶壽國際會議廳（本課程提供同步線上直播）

時間	主題	講師
09:00~09:30	報到與課程開場致詞	食藥署代表/藥技中心代表
09:30~10:40	醫療器材臨床研究 ISO 14155:2020 新版法規說明	台北醫學大學附設醫院骨科部 吳孟晃 主任
10:40~10:50	休息	
10:50~12:00	伴隨式體外診斷試劑之臨床試驗設計	元鼎診所 曾嶽元 院長
12:00~13:00	中午休息	
13:00~14:10	歐盟醫療器材臨床評估法規要求	台灣德國萊因技術監護顧問股份有限公司 徐文達 驗證師
14:10~15:20	臨床試驗實務分享 – 以 AI 判讀肝臟腫瘤	雙和醫院影像醫學部 呂岳勳 主任
15:20~15:40	休息	
15:40~16:50	人工智能醫療器材之臨床試驗統計方法 – 以 AI 判斷糖尿病嚴重度與骨頭年齡為例	國家衛生研究院群體健康科學研究所 蕭金福 研究員
16:50~17:00	綜合討論與學習評量	



## 醫療器材臨床試驗教育訓練課程（三）

### 醫療器材臨床研究 ISO 14155:2020 新版法規說明

#### 醫療器材人體臨床試驗-優良臨床試驗規範

臺北醫學大學附設醫院骨科部脊椎骨科  
吳孟晃醫師

衛生福利部食品藥物管理署  
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• 現職：

- 臺北醫學大學附設醫院骨科部脊椎骨科主任
- 臺北醫學大學醫學系骨科學科專任助理教授
- 臺灣脊椎微創內視鏡醫學會理事
- 臺灣醫學設計學會理事
- 衛生福利部醫材臨床試驗培訓人員
- 美國史丹佛大學Biodesign醫材創新國際培訓講師
- AO骨科學會AOPEER醫學研究講師



臺北醫學大學  
TAIPEI MEDICAL UNIVERSITY



臺北醫學大學附設醫院  
Taipei Medical University Hospital



R ROTHMAN  
ORTHOPAEDICS



STANFORD BYERS CENTER FOR  
BIODESIGN



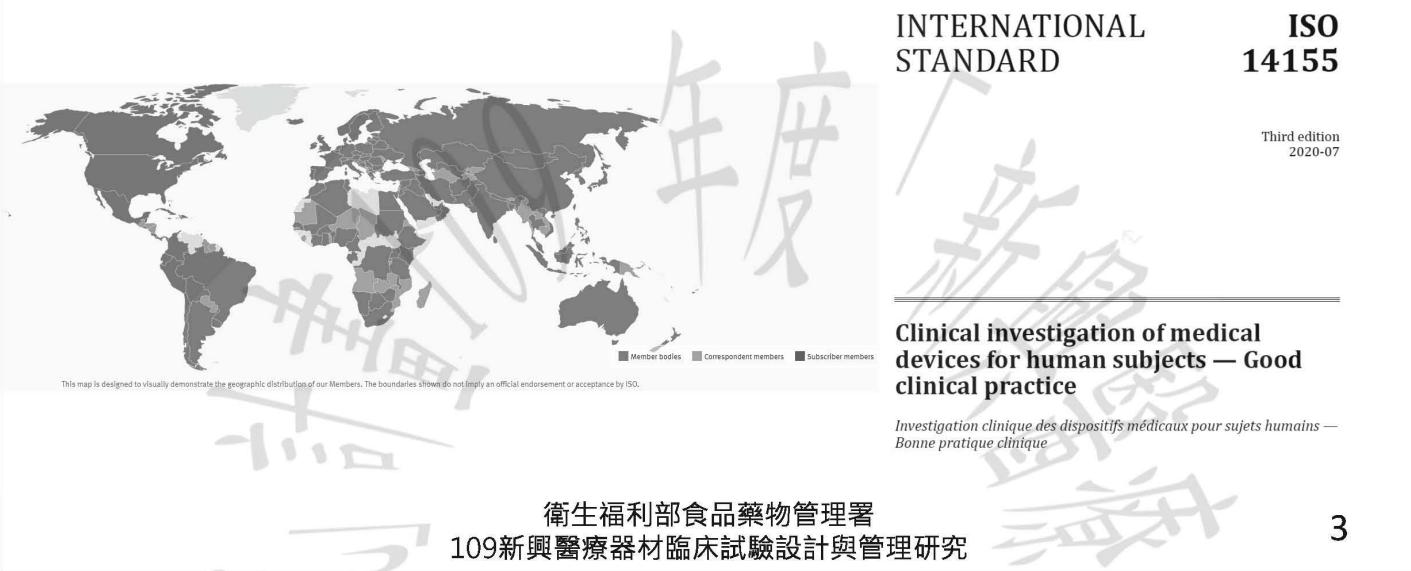
THE CATHOLIC UNIVERSITY OF KOREA  
SEOUL ST. MARY'S HOSPITAL



香港大學  
THE UNIVERSITY OF HONG KONG

## 課程目標

- 了解ISO14155法規之各項要求
- ISO14155法規與各國法規之間差異



## 課程大綱

1. Scope of ISO14155:2020
2. Ethical considerations
3. Clinical investigation planning
4. Clinical investigation conduct
5. Suspension, termination and close-out of the clinical investigation
6. Responsibilities of the sponsor
7. Responsibilities of the principal investigator

# ISO14155

Objective of ISO is to address GCP for medical devices

- design
- conduct
- recording
- reporting

... of clinical investigations with medical devices.

Applicable to:

- sponsors
- investigators
- ethics committees
- regulatory authorities
- other bodies involved in the conformity assessment of medical devices



ISO 14155 is not a stand-alone document when conducting clinical investigations in the EU.

- Medical Device Directive(MDD) and Active Implantable Medical Device (AIMD) contain important information:
  - Justification for clinical investigations
  - Essential requirements of the device
  - Regulatory notifications
  - Safety reporting
- National regulations
- MEDDEV documents such as:
  - MEDDEV 2.7/1 Clinical Evaluation
  - MEDDEV 2.12 Post Market Clinical Follow-Up
  - MEDDEV 2.7/2 Guide for Competent Authorities
  - MEDDEV 2.7/3 outlining requirements for Serious Adverse Event Reporting
  - MEDDEV 2.7/4 Guidelines on Clinical investigations



## ISO 14155 is recognized by the FDA with some exceptions

- Safety reporting
  - 21 CFR Part 812
  - More specific reporting formats, timelines and follow-ups
- Ethics committee requirements (IRB)
  - 21 CFR Part 56
  - More details - No contradictions
- Informed consent requirements
  - 21 CFR Part 50
  - More details - Minor differences

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## 醫療器材臨床試驗計畫案申請須知

- 醫材臨床試驗
- 計劃書, 主持人手冊, 受試者同意書, 個案報告表, 臨床前資料, 切結書, 期中報告, 結案報告, 試驗機構收案表, 貨品進口同意書
- 與 ISO14155互有補充

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## 醫療器材優良臨床試驗規範

- 遵循 ISO 14155 的精神，內容與藥品優良臨床試驗規範相似。
- 重點是要求醫療器材臨床研究應符合下列要項：
  - 確保試驗設計合乎科學和倫理的考量；
  - 應遵守赫爾辛基宣言，保障受試者或病患之健康福祉、隱私權與安全；
  - 臨床試驗前應取得病患的同意書，試驗尚未核准不可有受試者進入試驗；
  - 對於試驗計畫書的設計、執行的理由、計畫查核點、假說、盲性試驗、隨機取樣、清除期、基準量測、暴露量評估、取樣數目、試驗方式、時程控制、風險分析等，均應確實規劃並予以監測執行；
  - 確保臨床試驗每一步驟的程序都被完成，以取得足夠科學性有效的佐證資料與數據（Valid scientific data）；
  - 試驗資料應被妥善紀錄、保存，報告、解釋與修正；
  - 臨床試驗的不良事件和不良反應（AE/SAE）需確實通報，並進行必要之後續追蹤。

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## What's new?

This third edition cancels and replaces the second edition (see ISO 14155:2011), which has been technically revised.

The main changes compared to the previous edition are as follows:

- inclusion of a summary section of GCP principles (see [Clause 4](#));
- reference to registration of the clinical investigation in a publicly accessible data base (see [5.4](#));
- inclusion of guidance with regards to clinical quality management (see [9.1](#));
- inclusion of risk-based monitoring (see [6.7](#));
- inclusion of guidance statistical considerations (see [Annex A](#));
- inclusion of guidance for ethics committees (see [Annex G](#));
- reinforcement of risk management throughout the process of a clinical investigation (planning to consideration of results) including [Annex H](#);
- clarification of applicability of the requirements of this standard to the different clinical development stages (see [Annex I](#));
- inclusion of guidance on clinical investigation audits (see [Annex J](#)).

## Part 2. Ethical Considerations

- Section 4: Summary of GCP
- Section 5 of the standard is based on the Ethics considerations consistent with the Declaration of Helsinki.
- Informed Consent process

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### 5.4 Registration in publicly accessible database

- A description of the clinical investigation shall be registered in a publicly accessible database before recruitment of the first subject.
- When required by the national regulations, the content shall be updated throughout the conduct of the clinical investigation and the results entered at completion of the clinical investigation.

NIH U.S. National Library of Medicine  
[ClinicalTrials.gov](https://www.clinicaltrials.gov)

Find Studies ▾ About Studies ▾ Submit Studies ▾ Resources ▾ About Site ▾

ClinicalTrials.gov is a database of privately and publicly funded clinical studies conducted around the world.

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## 5.6.2 Initial EC submission

Minimum required documents are outlined:

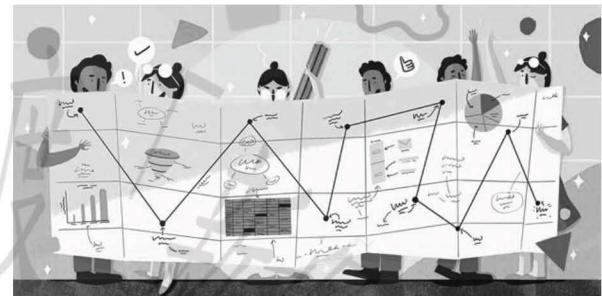
- Clinical Investigation Planning (CIP)
- Investigator Brochure (IB) or equivalent
- Informed consent (IC) document
- Advertising
- CV of principal investigator

## Other documents that may be requested

- Depending on national requirements or investigation design
  - Sample Case Report Form (CRF) and any other data collection tools
  - Information on payment and compensation to subjects
  - Proposed compensation to institution and/or investigator(s)
  - Information on conflict of interest including financial conflict of the investigator insurance certificate

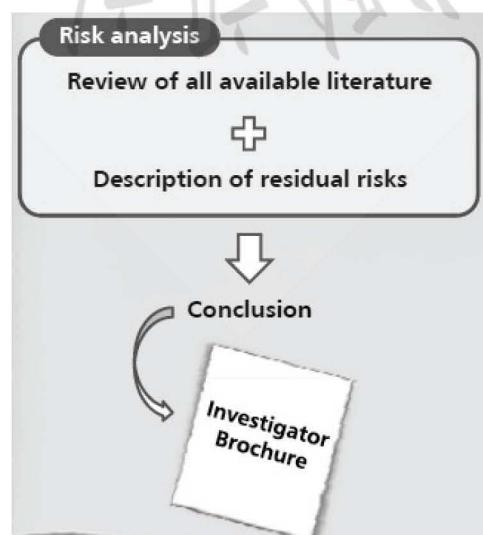
## Part 3 - Clinical Investigation Planning

- Risk assessment
- Justification of investigation design
- Essential documents
- Monitoring plan
- Site selection
- Agreements
- Labelling
- Data monitoring committee



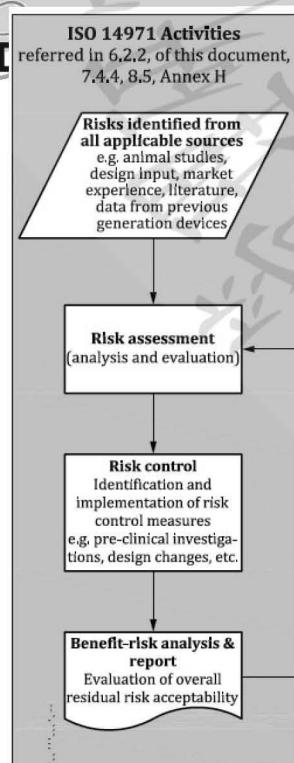
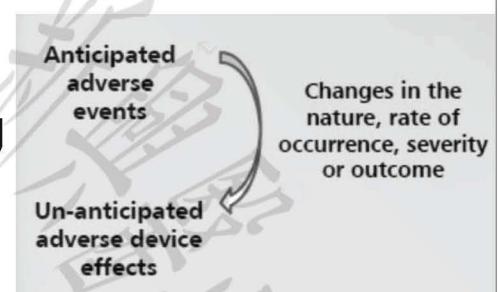
### 6.2 Risk Assessment

- Summary of the risk analysis of the use of the investigational device shall be included in the IB

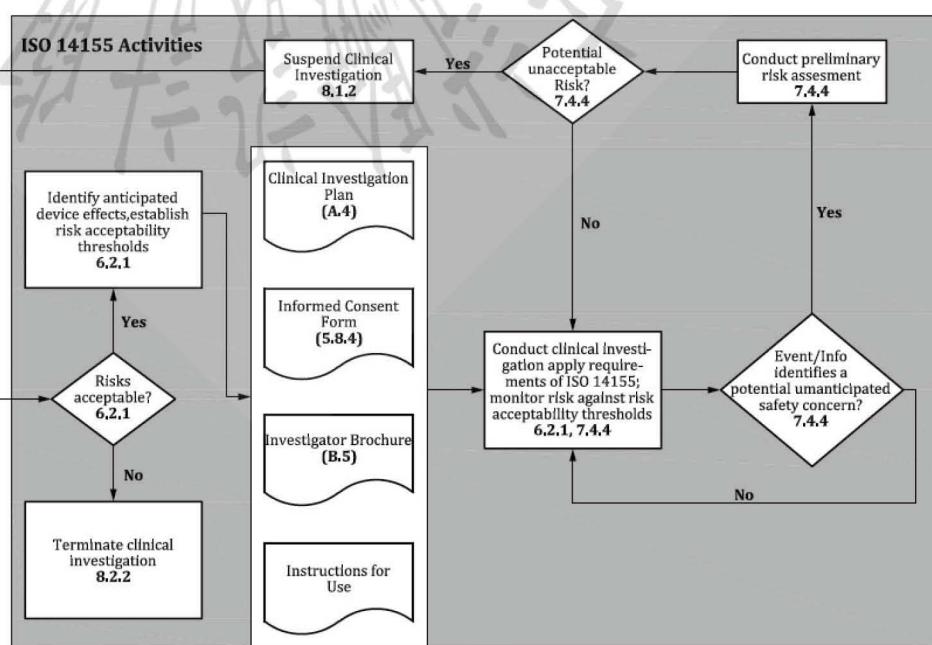


## 6.2 Risk Assessment

- Risk assessment includes
  - Risks associated to the device
  - Risks associated to the requirements of the CIP
    - Any risk associated to clinical procedures
- Risk analysis is used to identify anticipated adverse device effects
  - Documented in CIP, IB and IC
  - Enable compliance with reporting



### Application of ISO 14971 to the management of potential safety concerns in a clinical investigation



## 6.3 Justification for clinical investigation design

- Pre-clinical data
- Pre-clinical evaluation of existing data
- Risk analysis
  - Scientific standards using the principles of GHTF clinical evaluation
  - Design must allow clinically relevant and scientifically valid results

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<b>Regulatory status</b>	<b>PRE-MARKET</b>		<b>POST-MARKET</b>	
<i>Clinical development stage</i>	Pilot stage (I.3.2)	Pivotal stage (I.3.3)	Post-market stage (I.3.4)	
<i>Type of design</i>	Exploratory or confirmatory (I.4.1)	Confirmatory (I.4.2)		Observational (I.4.3)
<i>Descriptors of clinical investigations</i>	First in human clinical investigation (I.5.1) Early feasibility clinical investigation (I.5.2) Traditional feasibility clinical investigation (I.5.3)	Pivotal clinical investigation (I.5.4)	Post market clinical investigation (I.2.2)	Registry <sup>a</sup> (I.5.5) Post market clinical investigation <sup>a</sup> (I.2.2)
<i>Burden to subject</i>	Interventional (I.6.1)		Non-Interventional (I.6.2)	

<sup>a</sup> Registry data may be used for pre-market regulatory purposes (see I.5.5), this may also apply to the post market clinical investigation data.

## 1. Feasibility/pilot study:

- Typically recommended for spinal device designs and investigational protocols where no data are available or no devices with similar designs are available.
- The scope and objective are limited.
- A control may be necessary.
- May not obtain statistical significance, a limited evaluation of the safety and effectiveness data should be made.

**Guidance Document for the Preparation  
of IDEs for Spinal Systems.**  
<http://www.fda.gov/cdrh/ode/87.pdf>.

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## 2. Pivotal study

- Adequate preliminary safety and/or effectiveness information
- Permit initial assessment of device design
- Better define/refine the clinical endpoints
- Establish appropriate assessment tools and success/failure criteria

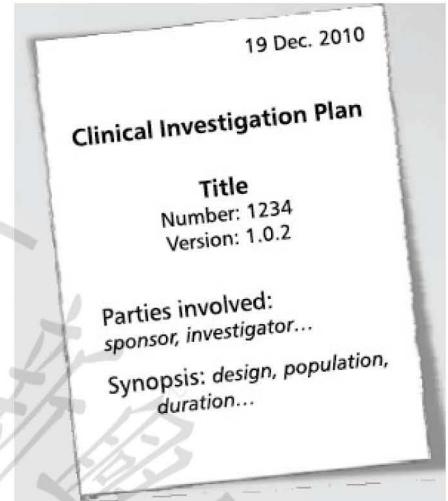
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<http://www.fda.gov/cdrh/ode/87.pdf>.

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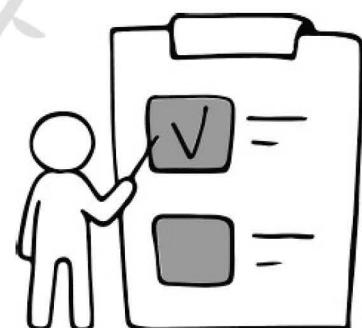
## 6.4 CIP (also in Annex A)

- Clear identification of the document (version, date, number, title, etc.)
- Identification of all the parties involved (sponsor, investigators, institutions, etc.)
- Overall synopsis including relevant information on design, eligibility, subjects involved, duration of the follow up, objectives and endpoints



## 6.4 CIP Annex A

- Identification and description of the investigational device
- Review of the existing literature
- Outline of pre-clinical testing
- Existing clinical data
- Conclusion of the risk analysis
- Objectives and hypothesis of the clinical investigation
  - Intended claims must be defined



## 6.4 CIP

### Annex A

- Design of the clinical investigation: Scientifically valid data
  - Type of investigation (blinded, randomized, open, etc.)
  - Description of methods to avoid bias (randomization process)
  - Primary and secondary endpoints
  - Methods of assessment
  - Specific equipment for the assessment



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## Standardization of radiographic examinations (Basics)



## 6.4 CIP

### Annex A

- Design of the clinical investigation
  - Procedures for replacing subjects if needed
  - Details of investigational device and comparators
  - Identification of the population
  - Overview of all procedures involved
    - E.G. Settings of assessment tools
  - Monitoring plan
    - Reference to or included in CIP



## 6.4 CIP

### Annex A

- Statistical design and analysis
  - Analytical procedures, sample size, bias, missing data, exploratory/sensitivity analysis
- Data management arrangements
  - Especially with electronic data
- Process of amendments
  - Which section
  - What the amendment involves
  - Reason for amendment



## 6.4 CIP

### Annex A

- Handling of deviations
  - Preliminary approval by sponsor, EC (and CA).
  - Documented and reported in emergencies
- Procedure for device accountability
  - Clearly define how to document!
- Statements of compliance (ethics and regulatory)
  - EC submission
  - Regulatory notification

## 6.4 CIP

### Annex A

- Informed consent process
- Safety reporting
- Device Deficiency reporting
  - Must be considered separately from adverse events
- Description of process for vulnerable populations if applicable
- Procedure for early termination or suspension
- Publication policy

## 6.5 Investigator brochure (also in Annex B)

- Must provide the principal investigator with the necessary pre-clinical and clinical information
- Updated throughout the investigation
- Principal investigator must acknowledge receipt and keep data confidential
- Clear identification of the document (version, date, name, etc.)
- Identification of the sponsor or manufacturer (both if different parties)

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## 6.5 Investigator brochure Annex B

- Investigational device information
  - Including material used
- Summary of existing clinical data
- Risk assessment
  - What risks remain?
  - How minimized?
  - Justification
- Regulatory references
  - Classification of the device

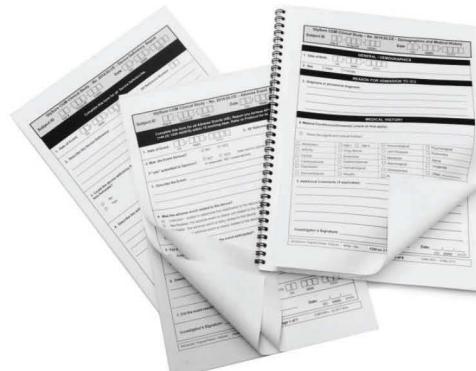


## 6.6 Case Report Form (also in Annex C)

- Must capture all data from enrolled subjects
- Must reflect requirements of the CIP
- Must be amended if needed after amendment of the CIP
- Identification system, related to CIP
  - Identification system defines the relationship
- Each page must have clear identifiers including investigation and subject identifiers

## 6.6 Case Report Form Annex C

- Basic CRF sections depending on CIP design
  - Screening
  - Informed consent documentation
  - Eligibility criteria
  - Baseline visits
  - Treatment
  - Follow-up visits
  - Clinical investigation procedures
  - Adverse events



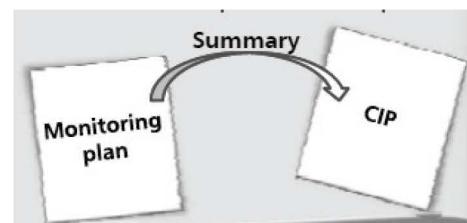
## Basic CRF sections depending on CIP design

- Device deficiencies
- Concomitant medication
- Unscheduled visits
- Subject diary
- Withdrawal or lost follow-up
- End of investigation
- Deviations



## 6.7 Monitoring plan

- Evaluate and document the extend and nature of monitoring based on
  - Design of the investigation
    - Randomized, pre / post-market
  - Complexity
    - No. of procedures, complexity of device
  - Size
    - No. of subjects expected
- Critical data points and endpoints
  - Verification against source documents
- Risk based monitoring plan
  - Adverse event reporting



## 6.8 Investigation site selection

- Qualifications of the principal investigators and adequacy of the sites must be verified and documented in a site selection report
- Rational for selecting a given site must be documented
  - Selection criteria may be based on previous experience.



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## 6.9 Agreements

- Define all roles and responsibilities in writing, signed and dated by all parties
  - Between sponsor and principal investigator/institutions
  - Between sponsor and other involved parties (e.g., investigators, CROs)

Responsibility Matrix						
Title	Project Chartering Committee	Client Representative	Project Manager	Technology Team	Finance Team	Schedule Coordination Team
Scope Statement	✓	✓	✓			
Work Breakdown Structure		✓	✓	✓		✓
Budget		✓	✓		✓	
Quality		✓		✓		✓
Change Management Procedures		✓	✓		✓	✓
Change Approvals		✓	✓			

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## 6.10 Labeling

- Clear indication that the labeling needs to mention the device is for use in a particular clinical investigation
  - May be optional for post-market studies
- Reference to ISO 15223 and EN 1041 as well as additional national regulatory requirements



manufacturer's trade name and address	manufacturer's catalogue code number and product description in different languages	bar code
CE mark (made in compliance with 93/42/EEC Directive on class IIa or IIb medical devices)	CE (*) expiry date, if the product is perishable (year/month)	storage temperature
lot number (indicated by LOT mark)	LOT (*) for professional use only	P (***) for single use only
keep dry	KEEP DRY	keep away from sunlight
CE mark (made in compliance with 93/42/EEC Directive on class I medical devices)	CE (*) see instructions for use	gamma-ray sterilized
titanium	T (*) surgical steel	SS (***) this product contains Chromium: possible allergic reactions
autoclavable at temperature indicated	134°C (*) non-sterile	CA (***) with content or presence of natural rubber latex

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## 6.11 Data monitoring committee

- Sponsor shall consider establishing a data monitoring committee based on:
  - Risk assessment of the device and the clinical investigation requirements.
- Primary function must be described in the CIP
- Responsibilities of the DMC are detailed in written procedures detailing:
  - Frequency of meetings,
  - Handling of emergency situations,
  - Documentation of the meetings.

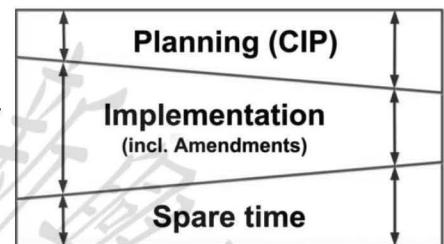
DMC adds credibility to study results

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## Part 4 – Conducting a Clinical Investigation

- Site initiation
- Site monitoring
- Adverse events and device deficiencies
- Documents and documentation
- New site personnel
- Subject privacy and confidentiality
- Document and data control
- Accounting of subjects
- Auditing



### 7.2 Investigation site initiation

- On site visit or investigator meeting or both to ensure:
  - Appropriate training of all site personnel
    - Guarantee for compliance
  - Review investigation requirements
    - CIP, IB, CRF, IFU
    - ISO 14155
    - Other written agreements
  - Review investigator responsibilities initiate and maintain a log
  - Identifying all personnel and their designated authorizations

**Monitoring activities****Activities of the monitor****Frequency of the activities**

## 7.3 Monitoring

- Monitoring plan must ensure compliance with
  - CIP
  - ISO 14155
  - EC and regulatory requirements
- Monitoring plan must ensure:
  - Accuracy and completeness of data
  - Verification against source documents
  - Recording and reporting of adverse event data
  - Necessary discussions on deviations and accurate reporting thereof is verifiable

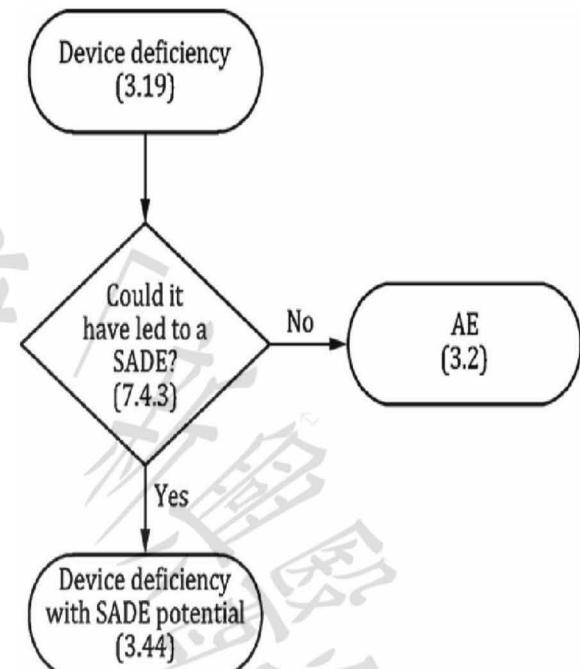
## 7.3 Monitoring

- Remote monitoring can only take place...
  - ... in exceptional situations
  - ... when performed with
    - Appropriate training
    - Necessary meetings
    - Tight procedures
    - Clear guidelines
    - Phone follow-up



## 7.4 Adverse Events and Device Deficiencies

- All adverse events must be recorded and reported appropriately
- Periodic safety reports are needed
- Adverse events classification decision tree is given in Annex F



### 7.4.2 Adverse Events

- Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the investigational device



*Note 1: This includes events related to the investigational device or the comparator.*

*Note 2: This includes events related to the procedures involved.*

*Note 3: For users or other persons this is restricted to events related to the investigational device.*

## Adverse device effect

- Adverse event related to the use of a medical device
  - Includes the device procedure related events

**Note 1:** This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

### Malfunction

A failure of a device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP

**Note 2:** This includes any event that is a result of a use error or intentional misuse.

### Use Error

Act of omission or an act by the user, that results in a different medical device response than intended by the manufacturer or expected by the user

## Serious adverse events

- Adverse event that
  - Led to a death
  - Led to a serious deterioration in the health of the subject that
    - resulted in a life-threatening illness or injury or injury,
    - resulted in a permanent impairment of a body structure or a body function, or
    - required in-patient hospitalization or prolongation of existing hospitalization, or
    - resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function
  - Led to fetal distress, fetal death or a congenital abnormality or birth defect



## Serious adverse device effect

- Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event



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The diagram consists of two arrows pointing towards each other from opposite sides. The left arrow is labeled "Adverse event" and the right arrow is labeled "Device deficiency".

### 7.4.3 Device Deficiencies

- Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance such as malfunction, misuse or use error and inadequate labeling

Device deficiencies include those that might have led to a medical occurrence if either a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate.

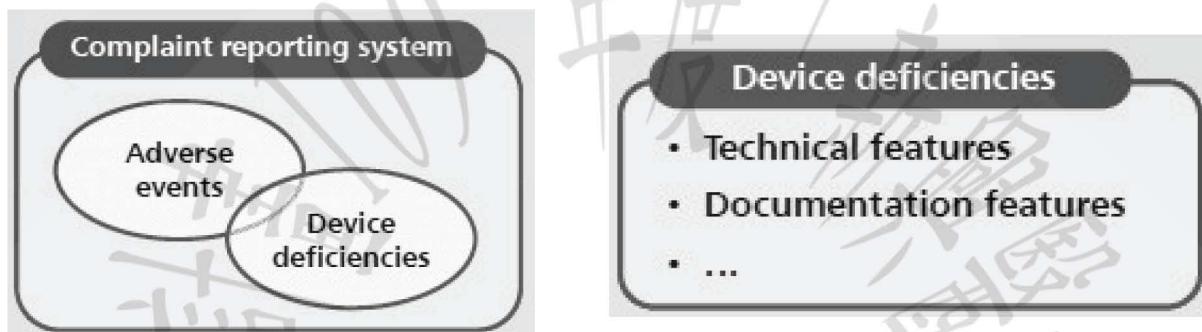
In case a SAE might have happened

Device deficiency has same reporting requirements as a SAE

### 7.4.3 Device Deficiencies

Clinical investigation + Commercial use of a device

- All adverse events need **complaint reporting**
- Complaint reporting includes device deficiencies
- Reference to ISO 13485



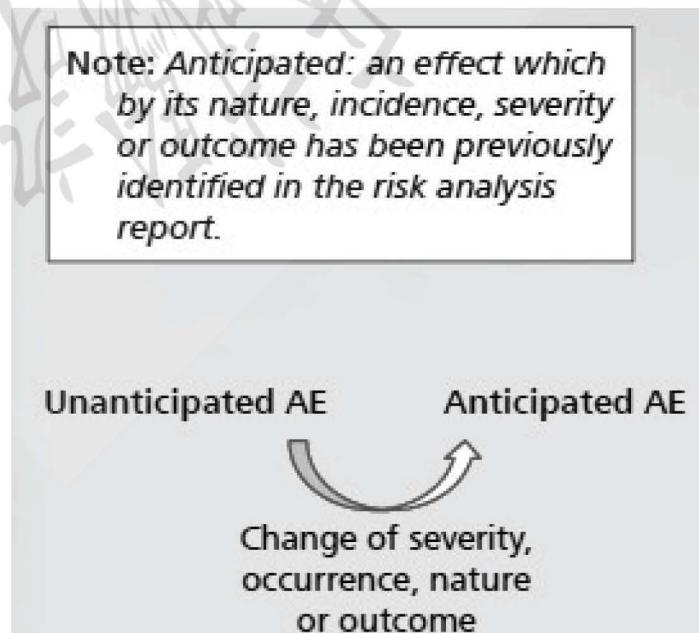
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### 7.4.4 Unanticipated serious adverse device effect

- Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report

*Note: Anticipated: an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.*



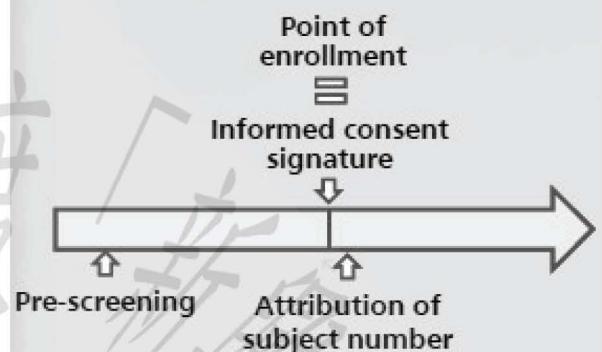
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## 7.5.2 Subject Identification Log

- Log identifying subjects enrolled links identification code to subject name or other means of identification
  - Contains confidential data
  - Must remain on the site

*Note: Additional log identifying pre-screened subjects prior to enrollment may be needed*



## 7.5.3 Source Documents

- Must be created and maintained by the investigation site personnel throughout the duration of the study

**Source documents**

*Printed, optical or electronic documents containing source data.*

**Source data**

*All information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation.*

## 7.7 Subject Privacy and Confidentiality of Data

- All parties must keep data confidential and prevent unauthorized access
- Subject privacy and data protection must be guaranteed in reports and publications
- Permission must be obtained to allow access to source documents by representatives of sponsor, ethics committee and regulatory authorities

Unique identifier for each subject  
Thereby protecting subject's anonymity

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## 7.8 Document and Data Control

### Traceability of Documents and Data



- Traceability of documents
  - Good identification and handling
- Assurance and documentation of accuracy of translations
- Complete history of all changes
- Investigator ensures accurate, complete, legible, and timely data reporting to sponsor
- Copies of source documents or printouts of electronic documents must be signed and dated by a member of the investigation site
- A statement must be produced that these copies or printouts are a true representation of the originals

## 7.8.2 Recording of data

- Written procedures are needed to
  - Establish and document requirements of the system
  - Verify and validate consistency of the system
  - Ensure attributability, completeness, reliability, consistency and logic of the data entered
  - Ensure accurate reports

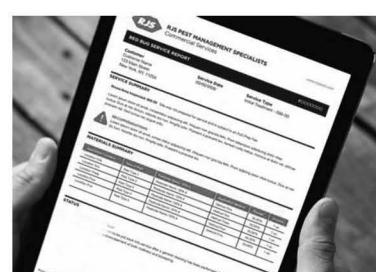


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## 7.8.3 Electronic clinical data systems

- Validation of electronic clinical data systems
- Ensure that data changes are documented and that there is no deletion of entered data (i.e., Maintain an audit trail, data trail, edit trail)
- Maintain a security system that prevents unauthorized access to the data both internally (sponsor) and externally (investigation site)

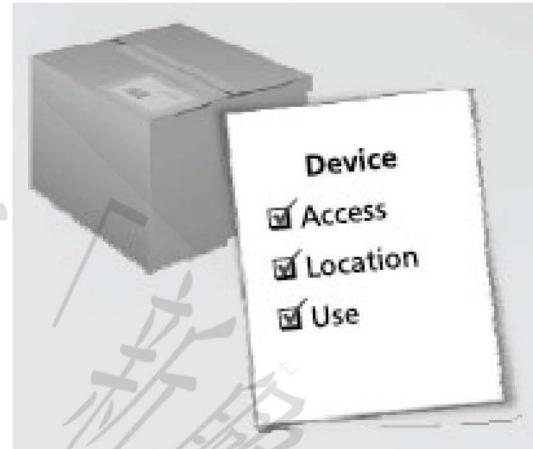


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## 7.9 Device Accountability

- Controlled access
- Sponsor keeps records of location of devices from shipment to return or disposition
- Principal investigator or authorized designee keeps records of receipt, use, return and disposition of devices

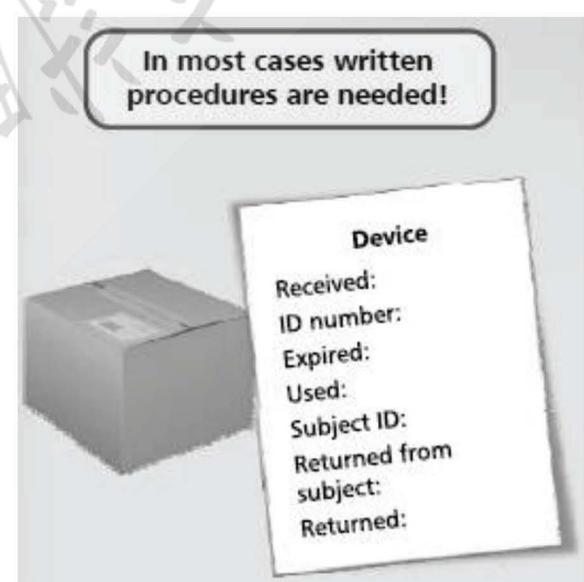


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### Device accountability records include

- Date of receipt
- Identification of each investigational device (batch number, serial number or unique code)
- Expiry date, if applicable
- Date of use with the subject's identification
- Date returned/explanted from subject, if applicable
- Date of return of unused, expired or malfunctioning investigational devices, if applicable



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## 7.10 Accounting for Subjects

- All subjects enrolled must be accounted for and documented.
  - Any subjects that have signed the informed consent form
- Reasons for withdrawal must be documented.
- If withdrawal is due to device safety or performance, attempts should be made to follow-up subject outside the clinical investigation.

## 7.11 Auditing

- Audits are not mandatory but considered useful
  - Routinely under the quality process
  - To assess effectiveness of the monitoring
  - To assess the reasons for serious or repeated deviations or when there is suspicion of fraud
  - Prior to regulatory inspection
  - Upon request on regulatory authorities

## 7.11 Auditing

- Auditors must be qualified by training and experience
- Audits are done according to written procedures
- Audits are based on an audit plan
  - What to audit?
  - How to perform an audit?
  - What is the frequency of the audits?
  - What is the form and content of the audit report?

## 7.11 Auditing

- How detailed an audit plan must be is based on complexity of the clinical investigation and seriousness of the findings
- Audit results must be documented in writing and communicated to relevant parties
  - e.g., clinical trial manager, investigator...

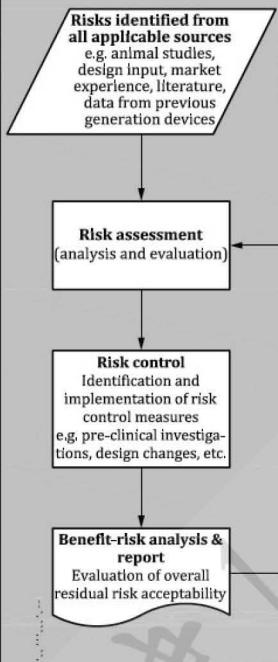
## Part 5 - Clinical Investigation Close Out

- Suspension or Premature Termination of the Clinical Investigation
- Routine Close Out

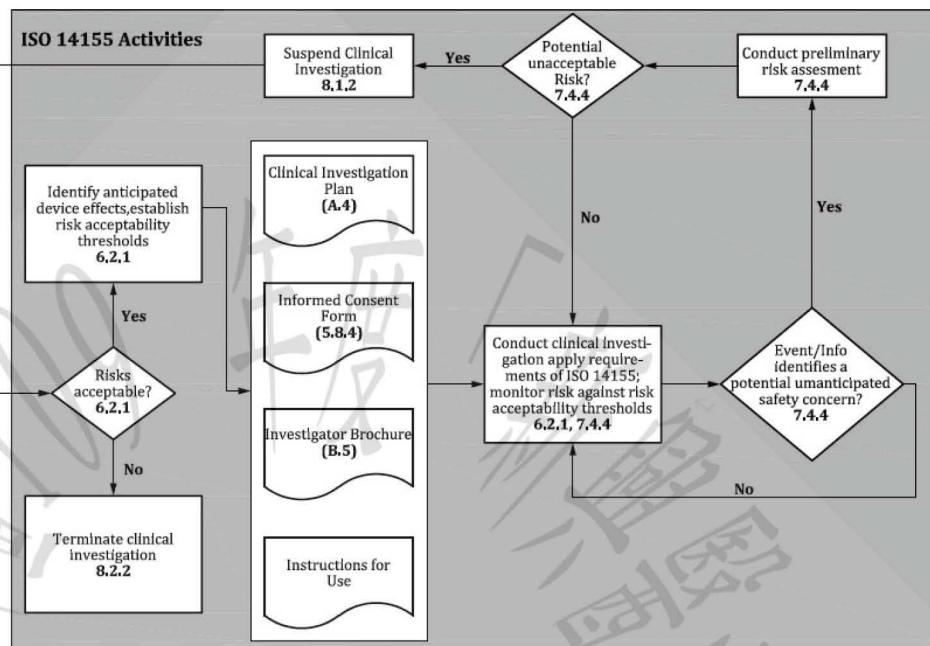
### 8.5 Feeding results into risk management

- A formal review of risk information should be carried out upon completion of the clinical investigation and fed into the risk analysis and clinical evaluation report with an update of the risk/benefit conclusions in both documents.

**ISO 14971 Activities**  
referred in 6.2.2, of this document,  
7.4.4, 8.5, Annex H



## Application of ISO 14971 to the management of potential safety concerns in a clinical investigation



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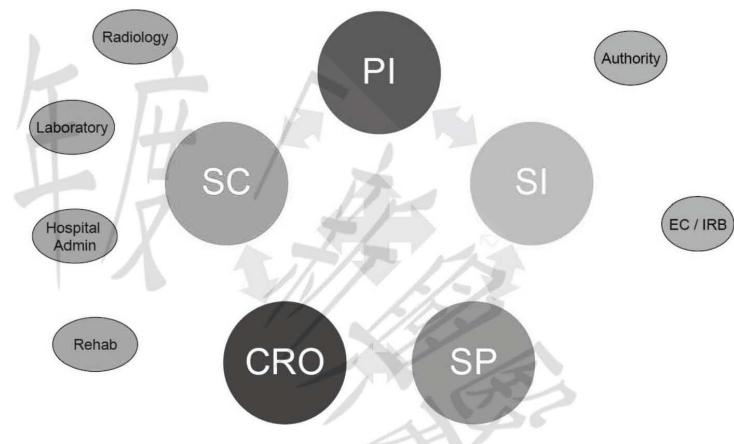
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## Part 6 - Responsibilities of Sponsor

- Quality Assurance
- Selection of Clinical Personnel
- Documents and Materials Preparation
- Conduct of the Clinical Investigation
- Monitoring
- Safety Evaluation and Reporting
- Outsourcing of Duties and Functions
- Communication with Regulatory Authorities

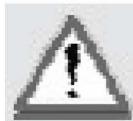
## Monitor initiates each investigation site to ensure:

- Principal investigator and team receive and understand contents of
  - CIP
  - IB
  - Informed Consent
  - CRFs
  - Instructions for Use
  - Agreements



## Monitor initiates each investigation site to ensure:

- PI and team receive and understand all documents and materials, and are familiar with the use of the device training on the responsibilities of PI
- Before the start of the investigation



Training must be documented

## 9.2.4.5 Monitoring – Routine On-Site Monitoring Visit

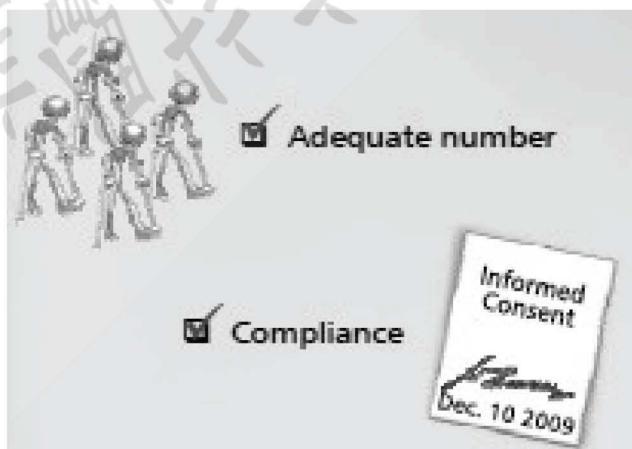
- Monitor performs routine on-site monitoring to ensure:
  - Only authorised individuals are participating in the clinical investigation
  - Investigational device is used, according to instructions from the sponsor
  - Investigator's request for modification to the device or the CIP must be promptly notified to the sponsor
  - Investigation site resources remain adequate

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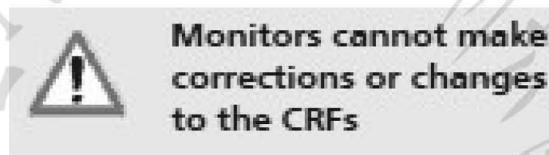
Monitor performs routine on site monitoring to ensure:

- Continued access to adequate number of subjects
- Continued availability of investigational devices
- Compliance with informed consent process



## 9.2.4.5 Monitoring – Routine On-Site Monitoring Visit

- Source documents and clinical investigation records are accurate, complete, up-to-date, stored and maintained appropriately
- CRFs and queries are completed in a timely manner and are consistent with source documents
- Appropriate correction methods are applied to CRF

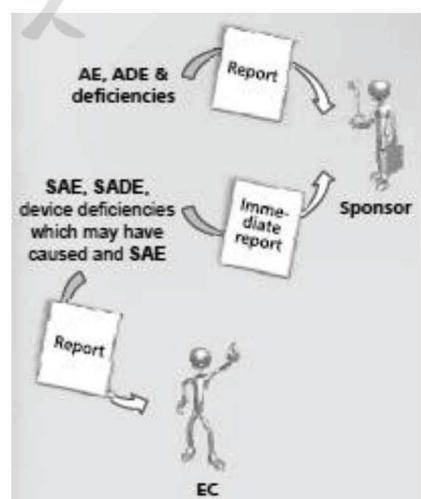


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## 9.2.4.5 Monitoring – Routine On-Site Monitoring Visit

- Monitor performs routine on site monitoring to ensure:
  - Adverse events, adverse device effects and device deficiencies are reported to sponsor
  - Serious adverse events and device deficiencies that could have led to a serious adverse device effect are reported to sponsor without delay and to the EC
  - Deviations are reported to the EC



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## 9.2.4.5 Monitoring – Routine On-Site Monitoring Visit

- Monitor performs routine on site monitoring to ensure:
  - Storage, accountability and traceability of investigational devices is appropriate
  - Investigator files are maintained accurately and completely
  - Documentation of maintenance and calibration of equipment
  - Ensure laboratory normal values, certifications, accreditations of labs are in the investigator file

## 9.2.4.6 Monitoring – Routine On-Site Monitoring Visit

- Monitor performs routine on site monitoring to ensure:
  - Documentation of subjects withdrawal, and appropriate discussion thereof,
  - Documentation of subjects noncompliance and related discussions
  - Continue training of investigation site personnel on the relevant updates of documents
  - Follow-up of any corrective and preventive actions implementation
  - Necessary close out activities

## 9.2.6 Clinical investigation close-out

- Sponsor

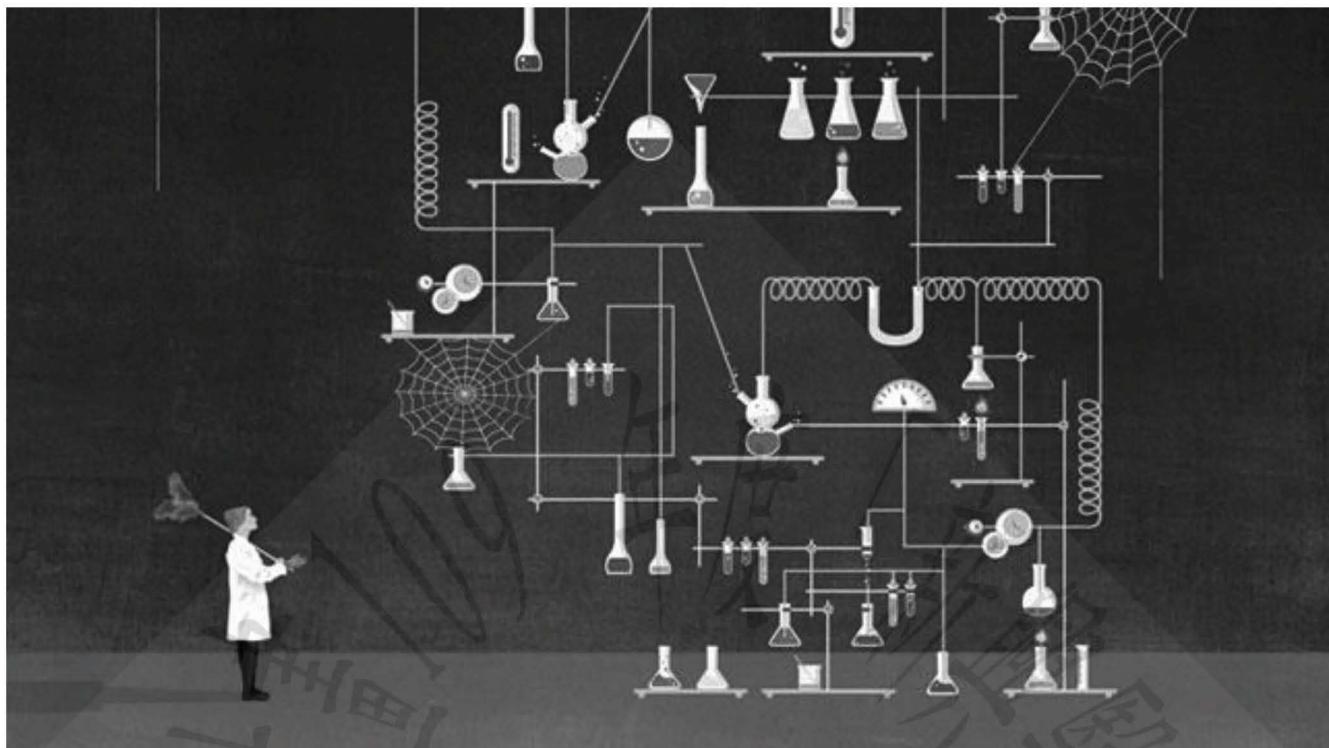


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## Part 7 - Responsibilities of the Principal Investigator

- Qualifications of the Principal Investigator
- Qualification of the Investigation Site
- Communication with the EC
- Informed Consent Process
- Compliance with the CIP
- Medical Care of Subjects
- Safety Reporting



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Thank you

Reference:

Clinical investigation of medical devices for human subjects — Good clinical practice (ISO 14155:2020)

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# 伴隨式體外診斷試劑之 臨床試驗設計

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前輔大醫學系專任教授

## FDA Approval

Dossier

Design

Analytic performance Clinical performance

Efficacy

Safety

TFDA

確認宣稱屬實

Reviewers



# 伴隨式體外診斷試劑之 臨床試驗設計

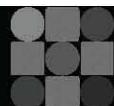
Design

Clinical  
performance

表一、美國上市之伴同性體外診斷醫療器材

技術平台	IVD產品名	製造商	上市許可時間 相對應之藥品	主要證據
免疫組織化學	HERCEPTEST	Dako Denmark, A/S	1998年 Trastuzumab	—*
	PATHWAY ANTI-HER-2/NEU(4B5) Rabbit Monoclonal PrimaryAntibody	Ventana Medical Systems, Inc.	2000年 Trastuzumab	比對研究
	DAKO EGFR PharmDx Kit	Dako North America, Inc.	2004年 Cetuximab	投藥之臨床試驗
	InSite Her-2/neu Kit	Biogenex Laboratories, Inc.	2004年 Trastuzumab	比對研究
	DAKO C-KIT PharmDx	Dako North America, Inc.	2005年 imatinib mesylate	比對研究
原位雜交	Bond Oracle Her2 IHC System	Leica Biosystems	2012年 Trastuzumab	比對研究
	INFORM HER-2/NEU	Ventana Medical Systems, Inc.	1997年 Trastuzumab	—*
	PATHVYSIS HER-2 DNA Probe Kit	Abbott Molecular Inc.	1998年 Trastuzumab	—*
	HER2 FISH PharmDx Kit	Dako Denmark, A/S	2005年 Trastuzumab	比對研究
	SPOT-LIGHT HER2 CISH Kit	Life Technologies, Inc.	2008年 Trastuzumab	比對研究
聚合酶鏈鎖反應	HER2 CISH PharmDx Kit	Dako Denmark, A/S	2011年 Trastuzumab	比對研究
	INFORM HER2 DUAL ISH DNA Probe Cocktail	Ventana Medical Systems, Inc.	2011年 Trastuzumab	比對研究
	VYSIS ALK Break Apart FISH Probe Kit	Abbott Molecular Inc.	2011年 Crizotinib	投藥之臨床試驗
	COBAS 4800 BRAF V600 Mutation Test	Roche Molecular Systems, Inc.	2011年 Vemurafenib	投藥之臨床試驗
	therascreen KRAS RGQ PCR Kit	Qiagen Manchester, Ltd	2012年 Cetuximab	投藥之臨床試驗

\*：已過時，無參考價值。



# 伴隨式體外診斷試劑

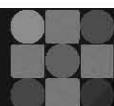
companion diagnostic (CDx)

## \* Clinical utility

- In a clinical utility study, the ability of the test to improve outcomes is evaluated, often with a randomized controlled trial (RCT).
- Using a patient characteristic to select patients for a clinical trial with the expectation that the selected patients are more likely to reveal a treatment effect than unselected patients is called enrichment
- Market-ready assay test kit (MRT) or companion diagnostic (CDx) for predictive biomarkers or treatment selection biomarkers

# 伴隨式體外診斷試劑

companion diagnostic (CDx)



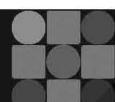
- ★ CDx 須和藥物一起共同研發 (co-development)。在這種情況下，藥物的有效性及安全性就會和體外診斷醫療器材的有效性及安全性緊緊結合在一起。而如果兩者皆符合有效性及安全性的要求，那麼IVD應和藥物應該一起被核准，而且使用同一標示 (labeling)。
- ★ 審查的基本原則是，對於分析確效我們著重 於評估該IVD是否能正確而可靠地檢測欲檢測之分析物;在評估臨床確效時著重於檢測結果是否與預期的臨床表現有關，以及相關性之可靠程度。



# Prospective study: Vysis ALK as an example

## ★ Prospective

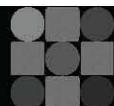
The use of single-agent XALKORI in the treatment of locally advanced or metastatic ALK-positive NSCLC was investigated in 2 multi-center, single-arm studies (Studies A and B). Patients enrolled into these studies had received prior systemic therapy, with the exception of 15 patients in Study B who had no prior systemic treatment for locally advanced or metastatic disease. In Study A, ALK-positive NSCLC was identified using the Vysis ALK Break-Apart FISH Probe Kit. In Study B, ALK-positive NSCLC was identified using a number of local clinical trial assays. The primary efficacy endpoint in both studies was Objective Response Rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST). Response was evaluated by the investigator and by an independent radiology review panel. Duration of Response (DR) was also evaluated. Patients received 250 mg of XALKORI orally twice daily. Demographic and disease characteristics for Studies A and B are provided in Table 4.



# Clinical utility study

## ★ Prospective

- ★ **A prospectively designed cohort study of consecutively or randomly sampled subjects is desirable for obtaining a study population that is representative of the target population of subjects to whom the test will be applied in clinical practice.**



# Clinical utility study

- ★ **Prospective**

- All-comers randomized trial (marker stratified randomization)
- Enrichment design: enrollment is restricted to subjects with an market-ready assay test kit (MRT) result

- ★ **Prospective-retrospective**

- Archived material examined for a prespecified study objective

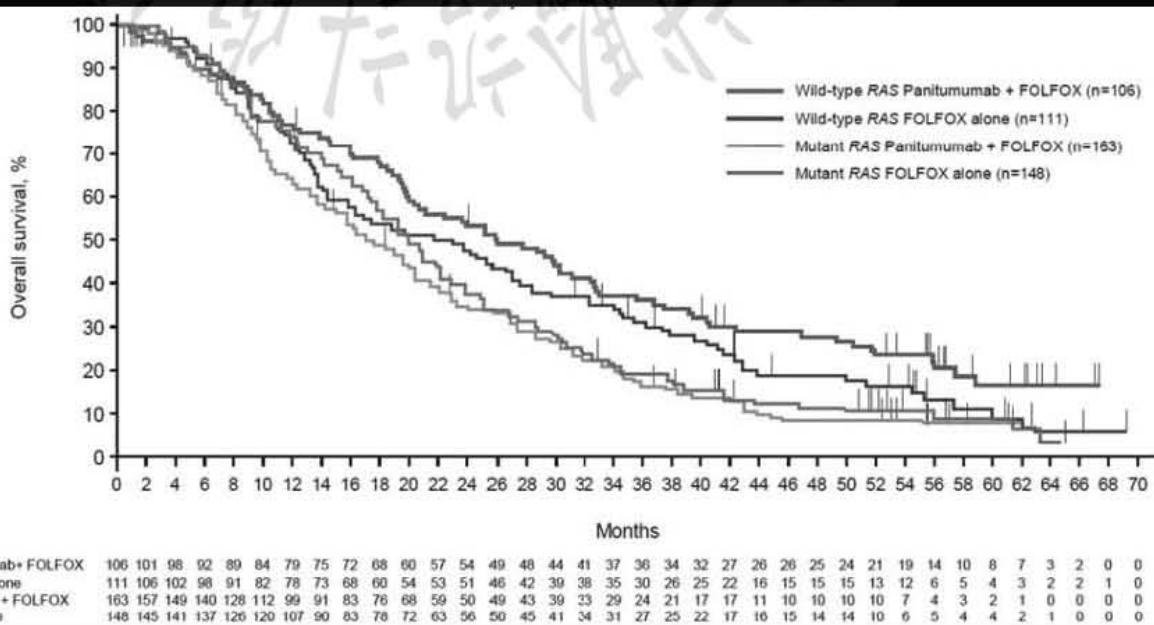
# Retrospective study

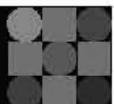
- ★ The safety and effectiveness of the XXX testing was evaluated in a retrospective study designed to demonstrate that the XXX testing correctly detects the presence of YYY mutants in ZZZ cancer patients for the purpose of clinically validating the use of the test companion diagnostic test for WWW drug.

# Retrospective study: Roche cobas® KRAS as an example

- ★ **Samples:** Roche study NO16968 was a randomized phase III trial comparing capecitabine (Xeloda) plus oxaliplatin (XELOX) with bolus fluorouracil/leucovorin (FU/LV) as adjuvant therapy for stage III colon cancer.
- ★ **Clinical outcomes of patients enrolled in Roche study NO16968 were not reviewed, and were not the basis of this PMA submission.**

# Retrospective study: Illumina NGS as an example





## 伴同性體外診斷醫療器材

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<sup>2</sup>輔仁大學醫學系，台北，台灣

### 摘要

過去幾年來，診斷方法的進展顯著地改善了藥品在臨床上的使用，因為診斷的結果會決定病患的治療方針，如應使用或不該使用某一藥物，或者須改變藥物的劑量。理想上，這種「伴同性體外診斷醫療器材（in vitro companion diagnostic device）」須和藥物一起共同研發（co-development）。在這種情況下，藥物的有效性及安全性就會和體外診斷醫療器材的有效性及安全性緊緊結合在一起。而如果兩者皆符合有效性及安全性的要求，那麼IVD應和藥物應該一起被核准，而且使用同一標示（labeling）。審查的基本原則是，對於分析確效我們著重於評估該IVD是否能正確而可靠地檢測欲檢測之分析物；在評估臨床確效時著重於檢測結果是否與預期的臨床表現有關，以及相關性之可靠程度。但有時候，藥物與IVD並無法同時共同研發。在這種情況下，審查過程會困難些，然而，對於有效性及安全性的評估原則是不會改變的。（生醫2013;6(2):98-102）

關鍵字：伴同性體外診斷醫療器材（in vitro companion diagnostic device）、共同研發（co-development）、標示（labeling）

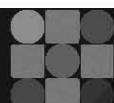
## Potential for bias

- ★ **Retrospective, convenience sampling of subjects that happen to have available specimens and reference results can introduce selection bias.**
- ★ **Selection of subjects and testing of specimens should be conducted in a such a way that the association between test result and clinical reference result is not confounded by analytical variables (day, user, reagent lot, specimen collection site, specimen testing site, etc.) or other ancillary variables that may be associated with both test result and clinical reference result.**



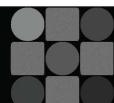
# CDx: major problem

- ★ A well-characterized market-ready assay test kit (MRT) is often desired for patient enrollment in device-drug pivotal clinical trial(s) so that FDA can ensure that appropriate clinical and analytical validation studies are planned and carried out for CDx.
- ★ Such a requirement may be difficult or impractical to accomplish.



# CDx: bridging study

- ★ A local lab tests (LLTs) instead of market-ready assay test kit (MRT) may be used for patient enrollment in the clinical trial.
- ★ A concordance study will be required to assess the agreement between MRT and LLT in order to bridge the clinical data (e.g. overall survival) from LLT to MRT and to evaluate the drug efficacy in MRT intended use population.
- ★ After approval, MRT will become CDx.



# CDx: bridging study

- ★ Test inaccuracy in clinical evaluation
- ★ Example: cobas® KRAS Mutation Test

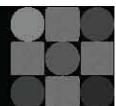
Data Source <sup>Ref</sup>	Comparator Method	PPV (95% CI)	NPV (95% CI)	Attenuation Factor (95% CI)
Cetuximab <sup>1</sup>	Sanger Sequencing	0.858 (0.811, 0.902)	0.975 (0.946, 0.994)	83.3% (77.7, 88.3)
Cetuximab <sup>6</sup>	FDA-approved Test	0.957 (0.927, 0.981)	0.945 (0.909, 0.978)	90.2% (85.6, 94.4)
Panitumumab <sup>4, 7</sup>	FDA-approved Test	0.949 (0.914, 0.977)	0.956 (0.927, 0.981)	90.4% (86.1, 94.4)

## Clinical performance study

A clinical performance study was conducted to generate data to support the clinical utility of the *therascreen*® KRAS RGQ PCR Kit (referred to as KRAS Kit) as a companion diagnostic test that aids in the identification of patients for treatment with cetuximab (Erbitux®). The objective of the study was to assess whether K-Ras status as determined by the *therascreen* KRAS RGQ PCR Kit can be used to select patients with metastatic colorectal cancer (mCRC) who will benefit from cetuximab treatment.

CA225025 (ClinicalTrials.gov number NCT00311262) was a randomized, multicenter, open-label, Phase 3 study of cetuximab plus best supportive care (BSC) versus BSC alone in patients with previously treated, K-Ras mutation-positive epidermal growth factor receptor (EGFR) - expressing, recurrent or metastatic colorectal cancer (mCRC). The study was conducted by the National Cancer Institute's National Clinical Trials Group (NCIC CTG).

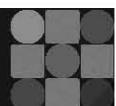
Banked tumor samples from patients in study CA225025 were tested with the KRAS Kit to identify two subgroups: K-Ras mutation-positive and K-Ras mutation-negative (wild-type), according to whether at least one or none of seven K-Ras mutations in codons 12 and 13 of exon 2 in the K-Ras oncogene was detected. In retrospective analyses, efficacy data from study CA225025 were stratified by K-Ras subgroup.



# Clinical performance study

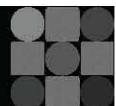
- ★ **Clinical performance study = Clinical validation study**
  - diagnostic accuracy of a test include the percentage of correct diagnoses (sensitivity, specificity), the predictive value of the test (negative, positive), diagnostic likelihood ratios (positive, negative), and, for a continuous test result, the receiver operating characteristic (ROC) plot

# Clinical performance study



## Spectrum effect

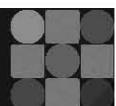
- ★ When diagnosing presence or absence of disease, performance (e.g., sensitivity, specificity) can tend to be overstated when subjects at the extreme ends of the disease spectrum are enrolled preferentially.
- ★ Subjects in between these two groups, often the most difficult to diagnose, are excluded from study, which can result in overstated test performance.



# Clinical performance study

## Comparison study

- ★ The reference result can be regarded as the endpoint of the study against which the test is evaluated for performance.
- ★ As mentioned, to avoid the potential for bias in test evaluation, the user of the test should be masked to the reference standard result, and vice versa.



# Clinical performance study

## Comparison study

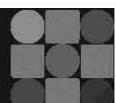
- ★ Accuracy may be determined by comparing the experimental methods to well-established reference or gold standard methods.
- ★ Because comparative methods are potentially less accurate, it may be beneficial to use a combination of comparative methods.



# Clinical performance study

## Comparison study

- ★ **Example: C difficile cytotoxin B**
- ★ **Comparing the molecular kit with 2 nonmolecular tests (cytotoxicity assay and toxigenic culture)**
- ★ **A total of 187 stool specimens are tested. Of these, 128 samples for one control, and 59 samples are tested for the other control.**



# Clinical performance study

## Comparison study

- ★ **Example: KRAS**
- ★ **100 clinical specimens (50 positive for mutations and 50 negative for mutations) from an outside reference laboratory that used a clinical acceptable method are analyzed.**

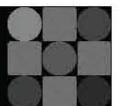


# Clinical performance study

- ★ A negative cell line and 7 KRAS positive cell lines that included the 7 most common mutations assayed. In addition, 10 clinical specimens (5 positive for mutations and 5 negative for mutations) from an outside reference laboratory that used a clinical acceptable method are also analyzed.

## Sample size ? Roche cobas® KRAS as an example

cobas® KRAS Mutation Test	Comparator Method							
	Sanger Sequencing				FDA-approved Test			
	Mutation Detected	No Mutation Detected	Invalid	Total	Mutation Detected	No Mutation Detected	Invalid	Total
Mutation Detected	124	34	5	163	139	9	15	163
No Mutation Detected	4	268	2	274	10	248	16	274
Invalid	0	19	5	24	0	5	19	24
Total	128	321	12	461	149	262	50	461
PPA (95% CI)	96.9% (92.2%, 98.8%)				93.3% (88.1%, 96.3%)			
NPA (95% CI)	88.7% (84.7%, 91.8%)				96.5% (93.5%, 98.1%)			
OPA (95% CI)	91.2% (88.1%, 93.5%)				95.3% (92.8%, 97.0%)			



# Sample size ?

	比對方法 得到陽性結果	比對方法 得到陰性結果
測試方法 得到陽性結果	A	B
測試方法 得到陰性結果	C	D
Overall Agreement = $(A+D) \div (A+B+C+D)$		

# Sample size ?

一個常見的問題是，到底要測試多少樣本數才足夠評估呢？我們由表一來看，當表一的B=C=0的時候，由 $O_A$ 的95%信賴區間來看，只要測試陽性樣本及陰性樣本數各31個， $O_A$ 就可達到85%了。如果採用 $O_A \geq 88\%$ 為標準，那麼測試陽性樣本及陰性樣本數則各需50個才能達到標準。由此看來，臨床與實驗室標

# 體外診斷醫療器材和實驗室研發之 檢驗法的比對研究

曾嵌元<sup>1,2</sup>

<sup>1</sup>國泰綜合醫院病理暨檢驗醫學部，台北，台灣

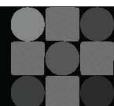
<sup>2</sup>輔仁大學醫學系，台北，台灣

## 摘要

新的「體外診斷醫療器材（in vitro diagnostic device; IVD）」和新的「實驗室研發的檢驗法（laboratory developed test; LTD）」在運用於臨床之前，都必須先透過驗證（validate）或查證（verify）來證明其有效性（efficacy）。在這方面，「比對研究（comparative study）」是常用的方法之一。此方法看來很簡單，但充滿了陷阱。本文即是介紹「比對研究」的概念和方法，並指出在分析比對結果時，應如何評估整體一致性（overall agreement;  $O_A$ ）、陽性一致性（positive agreement;  $P_A$ ）和陰性一致性（negative agreement;  $N_A$ ）。（生醫 2013;6(1):21-24）

## Risk categories

- ★ For tests that categorize the risk of a future clinical event, the risk categories can be compared on cumulative probabilities (absolute risks) for the event at follow-up times, that is, the survival curve.
- ★ If a study is enriched for the condition (e.g., a case-control retrospective study), the cumulative probabilities for a given test result will be distorted because they depend on the incidence rate for the condition.



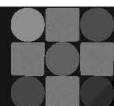
# Qualitative assays

- ★ Clinical sensitivity and specificity are measures of accuracy
- ★ The ability of a test to identify or recognize the presence of disease is its diagnostic sensitivity;
- ★ The ability to recognize the absence of disease is its diagnostic specificity.

INTERNATIONAL  
STANDARD

ISO  
20916

First edition  
2019-05



生物醫學 2011年第4卷第4期：179-186

## 體外診斷醫療器材的臨床試驗

曾嶽元<sup>1,2</sup>

In vitro diagnostic medical device  
Clinical performance studies using  
specimens from human subjects  
Good study practice

Dispositifs médicaux de diagnostic in vitro — Études des performances cliniques utilisant des prélèvements de sujets  
— Bonnes pratiques d'étude

<sup>1</sup>國泰綜合醫院病理暨檢驗醫學部，台北，台灣

<sup>2</sup>輔仁大學醫學系，台北，台灣

### 摘要

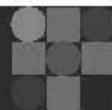
高風險體外診斷用新醫療器材必須通過臨床試驗（clinical trial）評估後始得上市。一般而言，臨床試驗由試驗委託者發起，經過資訊收集、概念形成、資源整合、團隊建立後，即可研擬試驗並撰寫計畫書。試驗乃根據研究之目的而設計，必須通過倫理審查後方得執行。數據的收集和統計需根據事先擬定的方法而行。臨床試驗的目的是提供有效的科學證據給審核機關及其諮詢委員會（advisory committee），希望經過評估其體外診斷用新醫療器材技術後，得到「合理的保證其安全及有效性（reasonable assurance of safety and effectiveness）」之結論。（生醫2011;4(4):179-186）

關鍵字：體外診斷醫療器材（in vitro diagnostic device; IVD）、臨床試驗（clinical trial）、安全性（safety）、有效性（efficacy; effectiveness）

Reference number  
ISO 20916:2019(E)

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# 伴隨式體外診斷試劑之 臨床試驗設計

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前輔大醫學系專任教授



# Clinical evaluation under MDR 2017/745

Dipl.-Ing. Windah Hsu  
Certifier, TÜV Rheinland Taiwan Ltd.  
2020-09-18



## 醫療器材條例

歐盟醫療器材條例(MDR, 2017/745)關於臨床評估要求事項

MDR第10條製造商義務的臨床評估要求

MDR第61條的臨床評估要求

MDR附錄十四的臨床評估和上市後臨床追蹤

臨床評估報告概述



## 個人簡介—徐文達 Personal Profile



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## MDR CER Introduction

### Disclaimer 免責聲明

Please note that this Power Point Presentation is for general purpose only. It is not intended to be an exhaustive training materials of the European Medical Devices Regulations nor to provide quality management, regulatory advice & product requirements to the audience. Materials presented in the presentation should not be considered a substitute for actual regulatory requirements, quality management and products standards of medical devices. It is best practice to consult current edition of referenced statute, regulation and/or code for precise wordings.



特請注意，此份演講稿僅適用於一般用途。並非歐盟醫療器材條例的完整訓練教材，亦非提供觀眾關於品質管理、法規及產品要求的定論。此份文稿提到的內容不應視為實際醫療器材法規要求、品質管理和產品標準的替代品。閱者務必參考所引述的法規、條例和/或規章、標準的最新版本。

## 製造商的義務 Obligation related to device

Article 10(1) to Article 10(8)

Articles	Content	Referred to
10 (1)	Devices shall be designed and manufactured in accordance to the requirements of MDR.	
10 (2)	System of risk management	Annex I Sec. 3
10 (3)	Clinical evaluation and PMCF	Article 61, Annex XIV
10 (4)	Technical documentation	Annex II & Annex III
10 (5)	Custom-made device	Annex XIII Sec.2
10 (6)	Declaration of conformity & CE-marking	Article 19 & 20
10 (7)	UDI system, registration obligation	Article 27, Article 29 &31
10 (8)	Documentation retention, at least 10 year, 15y for implant.	

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## 臨床資料 – Clinical data

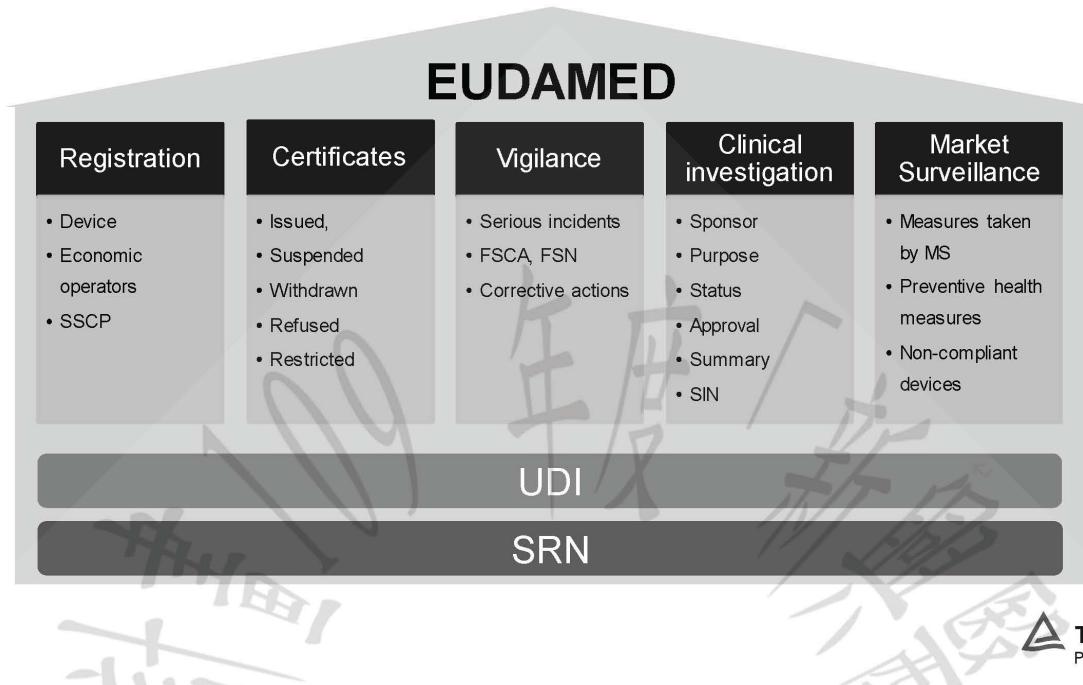
Article 2 (48)

- Information concerning safety or performance from the use of device and is sourced from:
  - Clinical investigation
  - Clinical investigation, studies reported in scientific literature of equivalence device
  - Reports published in literature on other clinical experience of either the device concern or equivalence device
  - Clinically relevant information by PMS, PMCF

6



## 歐洲醫療器材資料庫 – Eudamed



## 臨床證據 Clinical Evidence

MDR, article 2 (51)

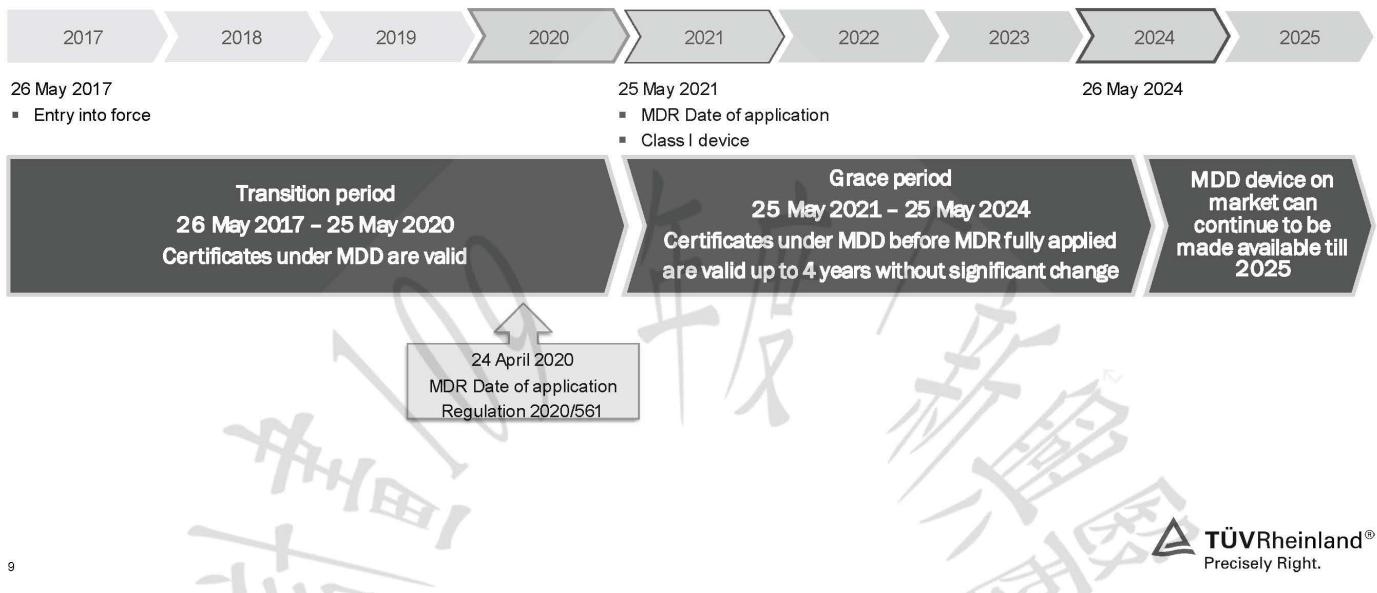
means clinical data and clinical evaluation results pertaining to a device of a sufficient amount and quality to allow a qualified assessment of whether the device is safe and achieves the intended clinical benefit(s), when used as intended by the manufacturer;

『是指關於目標器材之臨床資料和臨床評估結果，具有足夠數量和品質，當目標器材依循製造商之預期使用時，承受合格評鑑（人員 / 程序），係稱器材是否安全與達到預期臨床效益。』



## Transition timeline

- Article 120



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## (f) Clinical evaluation in Article 10(9)

CEN/TR 17223:2018, Table 1.

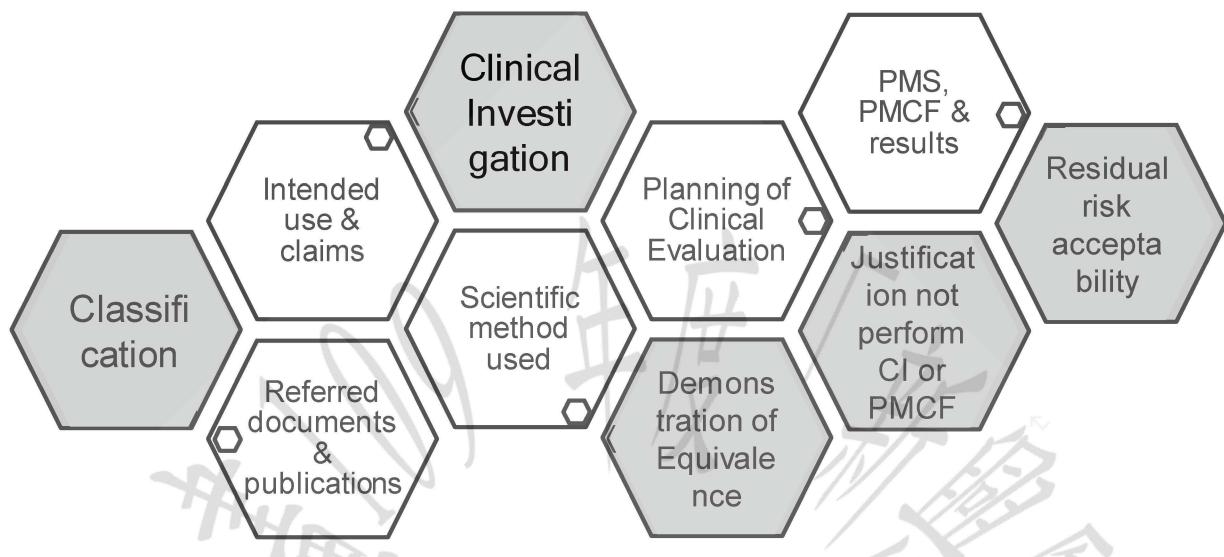
MDR Annex XIV Part A

- Clinical evaluation in accordance with Article 61 and Annex XIV, including post-market clinical follow-up (PMCF).
  - Clinical evaluation plan.
  - Identify and appraise clinical data. Generate clinical data by clinical investigation if necessary.
  - Analyse relevant clinical data to reach a conclusion.
- Related clauses in EN ISO 13485,
  - 7.3.7 As part of design and development validation, the organization shall perform clinical evaluations or performance evaluations of the medical device in accordance with applicable regulatory requirements.



## Clinical evaluation: Review tasks of the Notified Body

Clinical Evaluation is an ongoing process, CER is a living document



## Responsibility of Medical Device Manufacturer 醫療器材製造商責任

MDR, Article 63

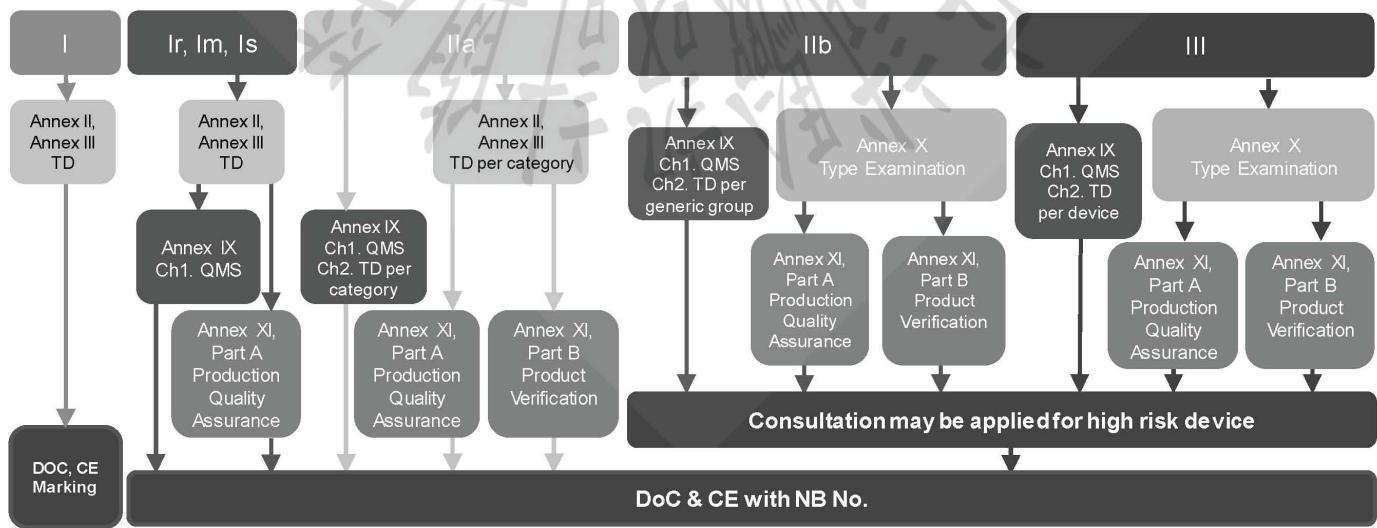


# Informed consent 知情同意



- What should clinical evidence support?
- Quantification of clinical benefits:
  - Clinical relevant of these changes should be discussed & justified
  - Parameters should be directly clinically relevant
  - In certain cases, benefits can be assumed when validated surrogate endpoints are met
- The probability of the patient experiencing one or more benefit(s)
- The duration of effect(s)

## Overview 概觀



## 主動式醫材 Active device – Rule 12 and Rule 13

Annex VIII

■ Class I ■ Class IIb  
■ Class IIa ■ Class III

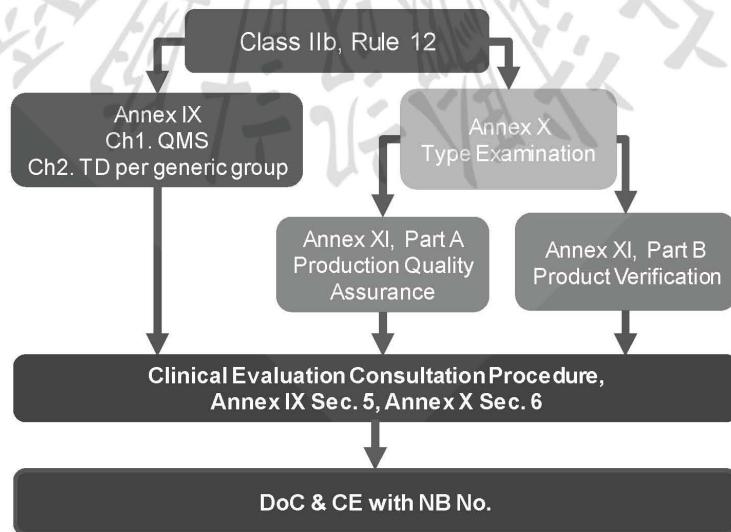


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### Class IIb, Rule 12

Article 52



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## Clinical Evaluation & Clinical Investigations

### MDR Chapter VI

§	Title	§	Title
61	臨床評估	72	實施臨床調查
62	臨床調查要求，展現器材符合	73	臨床調查電子系統
63	知情同意	74	器材有CE標示的臨床調查
64	對無行為能力者之臨床調查	75	臨床調查重大修改
65	對未成年人之臨床調查	76	EU成員國矯正措施及資訊交流
66	對孕婦/哺乳期婦女之臨床調查	77	結束/暫停/提前終止應提供資訊
67	補充國家措施	78	臨床調查循序評鑑程序
68	緊急情況下臨床調查	79	審查循序評鑑程序
69	損害賠償	80	記錄/報告臨床調查期間不良事件
70	申請臨床調查	81	實施細則
71	成員國評估	82	臨床調查其它要求

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## 臨床評估 – Clinical Evaluation

MDR Article 2 (44)

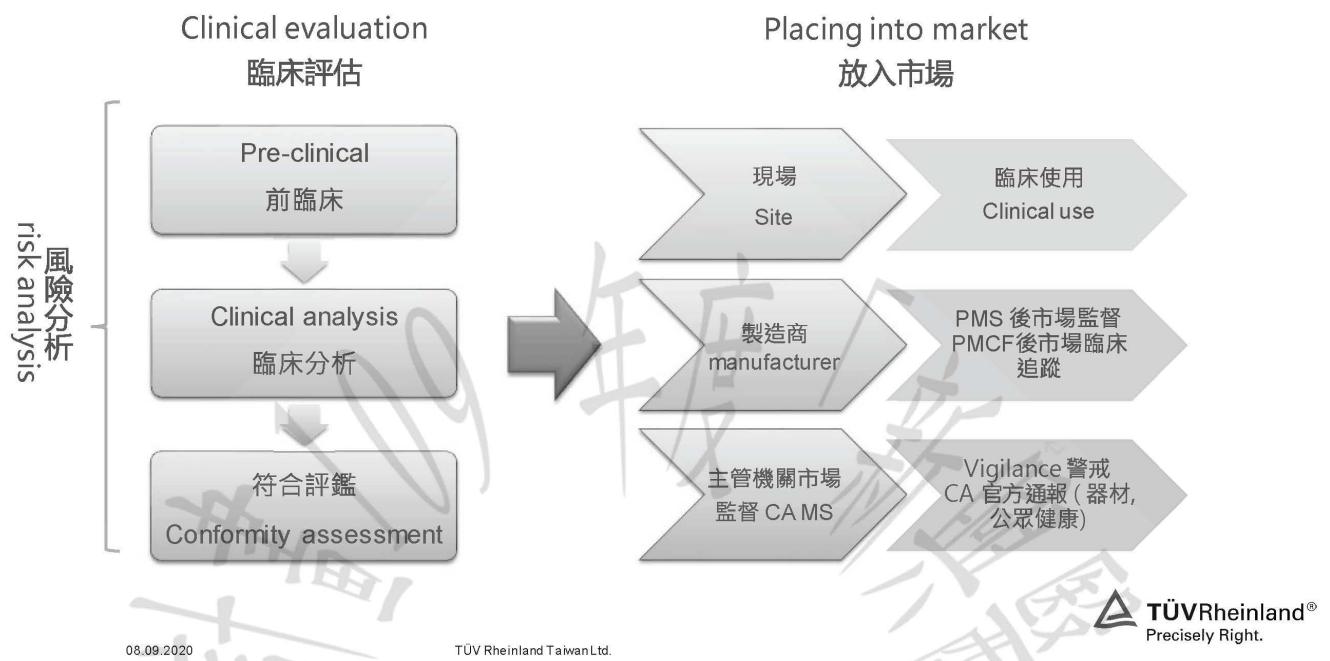
### Clinical Evaluation

A systematic & planned process to continuously generate, collect, analyse & assess the **clinical data** pertaining to a device in order to verify the safety & performance, including clinical benefits, of the device when used as intended by the manufacturer.

『以系統化、妥善規劃的程序，持續地產出、收集、分析及評鑑係稱器材的**臨床資料**，以查證按製造商預期使用器材方式的安全、性能及臨床效益』

# Clinical Evaluation & Clinical Investigations– life cycle 壽命周期

MDR Chapter VI



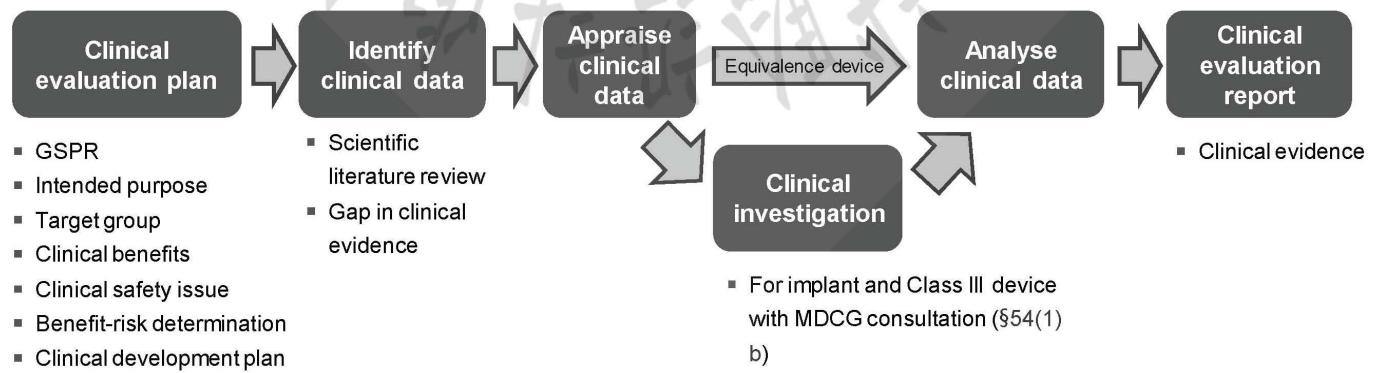
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## 臨床評估 – Clinical evaluation

Article 61, Annex XIV part A



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## 臨床試驗 – Clinical Investigation, exception

### Article 61

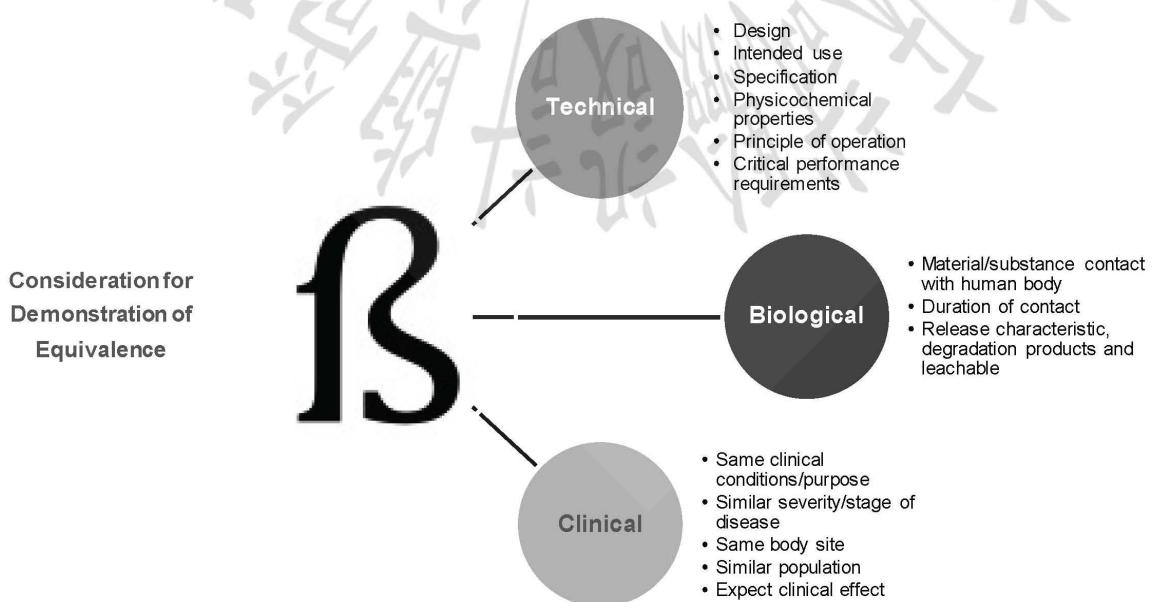
- In the case of implantable device and Class III devices, clinical investigation shall be performed.
- Exception:
  - Already market device, modification by same manufacturer
  - Have lawfully placed on the market in accordance with MDD/AIMDD
  - Suture, staples, dental fillings, dental braces, tooth crowns, screws, wedges, plates, wires, pins, clips, connectors.
- Equivalent device:
  - Been demonstrated by the manufacturer to be equivalent to the marketed device and
  - Clinical evaluation of the marketed device is sufficient to demonstrate the conformity of the device.
  - A contract in place allows manufacturer full access to the TD of the marketed device

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## 實質相等性比對 – Demonstration Equivalence

### Annex XIV



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## Clinical Evaluation & Clinical Investigations

Article 61, Annex XIV Part A

- Based on clinical data providing sufficient clinical evidence
- Confirmation of conformity with GSPR under the normal conditions of the intended use of the device
- Evaluation of the undesirable side-effects
- The acceptability of the benefit-risk-ratio
- Design phase, follow-up of clinical application phase

時機

執行

開發階段

器材壽命  
週期

後續追蹤

初次符合  
評鑑

器材設計

23

08.09.2020

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## MDCG 醫療器材協調委員會

MDR, Chap. VIII

§ 106 歐盟專家委員會諮詢過程適用高風險醫療器材特殊要求：

- 第III級植入式器材，或
- 管理或移除藥品的IIb級主動式器材

雙重安全保障機制：

□第一重：上市前臨床諮詢機制

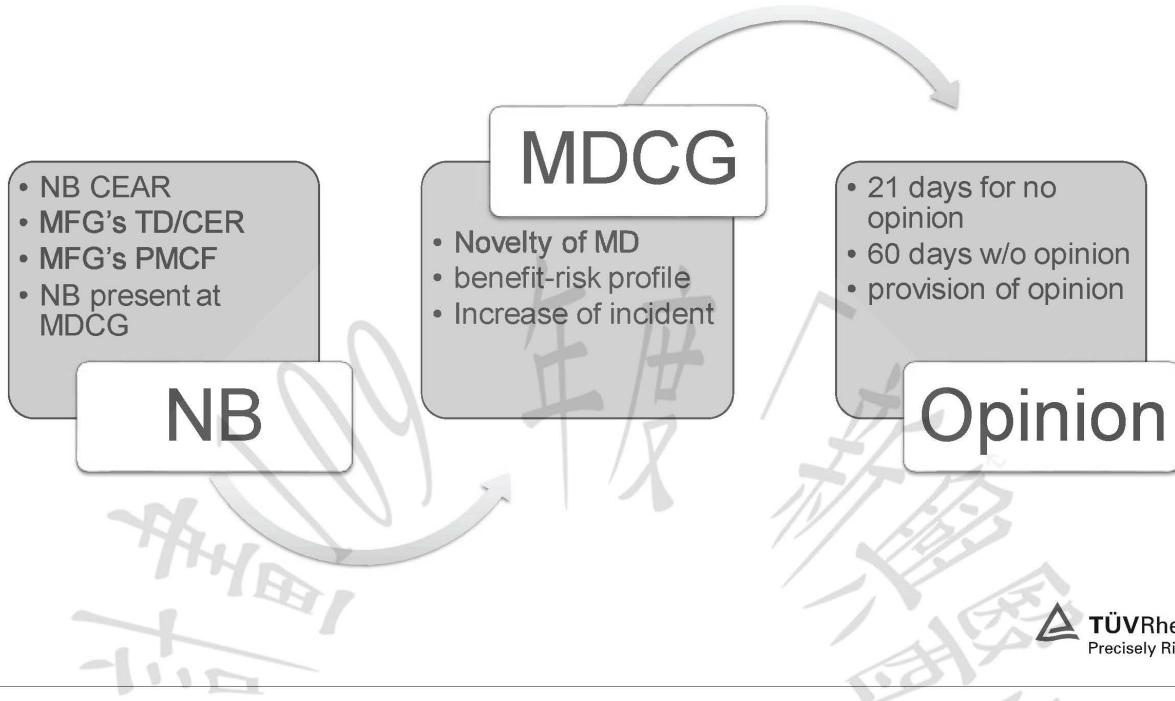
- 公告機構(NB)完成評鑑臨床評估報告及相關資訊後，提供給專家協調委員會(MDCG)評斷

□第二重：上市後審查機制

- 臨床評估評鑑內容包括足夠證據，係由特定目標群體獲得之
- 應考慮利益—風險比率，變通治療方案

## Technical Documentation – Consultation Procedure

MDR Annex IX, cl. 5.1; Annex X, cl. 6



25 2020/9/8

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## 歐盟醫療器材條例MDR—臨床調查轉換時程

2017	2019	2020	2021	2022	2023	2024	2025	2027
維持進行中的臨床調查，準備轉換 後市場臨床追蹤計劃與措施 (依循MEDDEV 2.7/1, 第4版) 更新臨床評估報告 鑑別/考慮“State of the art” [現今科技水準]	extension 展延期	執行後市場監督(PMS) 後市場臨床追蹤 (PMCF) 延續臨床調查，陸續轉換為MDR 凡是符合 MDD / IVDD的產品 期限屆滿前，徹底出清庫存	市場上皆為符合 MDR 2017/745 IVDR 2017/746 器材					

2020/9/8

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## 臨床資料 – Clinical data

There are indispensable minimum requirements regarding clinical data

Good clinical practice (GCP) must be followed for all clinical investigations (before & after CE approval).

There is no exemption from adherence to GCP! Unethical clinical data is not acceptable.

WMA declaration of Helsinki, current version 2018

“statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data”

- A PMCFs is medical research that involves human subjects
- A PMCFs requires handling of identifiable human data
- To be deferred between anonymized & pseudo-anonymized data

Refer to EN ISO 14155:2020

## Clinical literature 臨床文獻 find the evidence

PubMed.gov

lung ventilator

X

Search

48,623 results

Use more than one database

PubMed.gov

ventilatory impairment

X

Search

2,598 results

Use MeSH terms

PubMed.gov

ventilatory insufficiency

X

Search

3,055 results

Vary search terms

PubMed.gov

emergency ventilator|

X

Search

12,811 results

# Ventilatory equipment standard

DEUTSCHE NORM		Februar 2020	DEUTSCHE NORM	Februar 2020	
	DIN EN ISO 80601-2-79	DIN		DIN EN ISO 80601-2-80	DIN
ICS 11.040.10	Mit DIN EN ISO 80601-2-80:2020-02 Ersatz für DIN EN ISO 10651-6:2011-06		ICS 11.040.10	Mit DIN EN ISO 80601-2-79:2020-02 Ersatz für DIN EN ISO 10651-6:2011-06	
<b>Medizinische elektrische Geräte – Teil 2-79: Besondere Festlegungen für die grundlegende Sicherheit und die wesentlichen Leistungsmerkmale von Heimbeatmungsgeräten zur Atemunterstützung von Patienten mit Atmungsbeeinträchtigungen (ISO 80601-2-79:2018); Deutsche Fassung EN ISO 80601-2-79:2019</b>	Medical electrical equipment – Part 2-79: Particular requirements for basic safety and essential performance of ventilatory support equipment for ventilatory impairment (ISO 80601-2-79:2018); German version EN ISO 80601-2-79:2019		<b>Medizinische elektrische Geräte – Teil 2-80: Besondere Festlegungen für die grundlegende Sicherheit und die wesentlichen Leistungsmerkmale von Heimbeatmungsgeräten zur Atemunterstützung von Patienten mit Atmungsinsuffizienz (ISO 80601-2-80:2018); Deutsche Fassung EN ISO 80601-2-80:2019</b>	Medical electrical equipment – Part 2-80: Particular requirements for basic safety and essential performance of ventilatory support equipment for ventilatory insufficiency (ISO 80601-2-80:2018); German version EN ISO 80601-2-80:2019	
Appareils électromédicaux – Partie 2-79: Exigences particulières pour la sécurité de base et les performances essentielles des équipements d'assistance ventilatoire en cas de trouble ventilatoire (ISO 80601-2-79:2018); Version allemande EN ISO 80601-2-79:2019	Appareils électromédicaux – Partie 2-80: Exigences particulières pour la sécurité de base et les performances essentielles des équipements d'assistance ventilatoire en cas d'insuffisance ventilatoire (ISO 80601-2-80:2018); Version allemande EN ISO 80601-2-80:2019				

29 9/8/2020 Please insert footnote

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## 臨床評估 – Clinical evaluation – qualified persons

### MEDDEV 2.7/1, rev. 4

- Research methodology (including clinical investigation design, biostatistics)
- Information management (scientific background, librarianship, medical database, as Embase, MedLine)
- Regulatory requirements
- Medical writing (medical sector experiences, training of medical writing, systematic review & clinical data appraisal)

relevant knowledge of device

- Device technology & its application
- Diagnosis & management of diagnosed conditions, knowledge of medical alternatives, treatment standards & technology

Training & experiences

- 5 years professional experiences after higher education in respective field
- 10 years professional experiences other degree



30 9/8/2020 Please insert footnote

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## Clinical Evaluation Report (sample contents)

臨床評估報告 (樣式)

- 1) Summary of the CER
- 2) Scope of the clinical evaluation
- 3) Clinical background, current knowledge & state of the art
- 4) Device under evaluation
- 5) Clinical evaluation report conclusion
- 6) Date of next clinical evaluation
- 7) Qualification of the responsible evaluators
- 8) Date & signatures
- 9) reference

31 9/8/2020

Please insert footnote



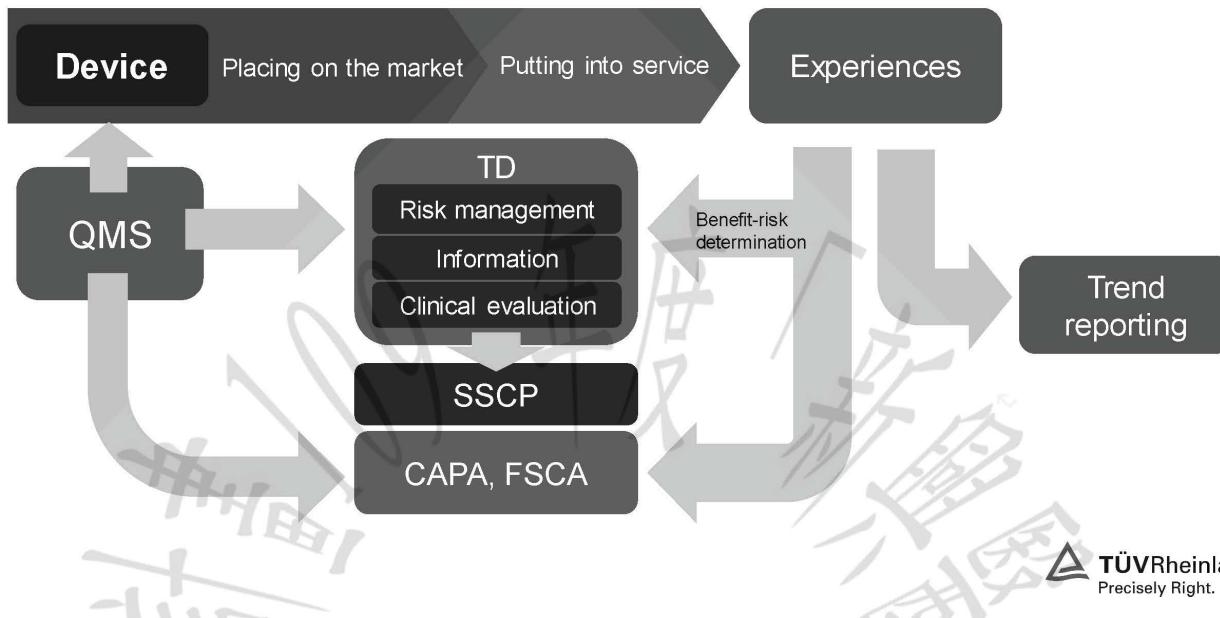
## 上市後監督 – Post market surveillance, PMS

Article 2 (60), Annex III

- Proactively collect and review experience gained from devices placing on the market, make available on the market or put into service.
- Identify any necessary corrective or preventive actions.
- Experiences included
  - serious incidents, PSURs, and FSCA
  - records of non-serious incidents and undesirable side-effects;
  - trend reporting;
  - literature, databases etc.;
  - feedbacks and complaints,
  - publicly available information

## 上市後監督 – Post market surveillance, PMS

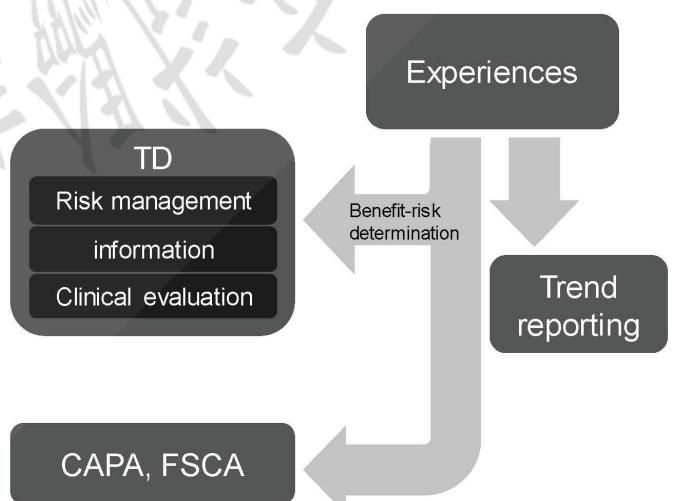
Article 83



## 上市後監督計畫 – PMS Plan

Article 83, Annex III

- Method for Information collection & processing
- Indicator & threshold for benefit-risk analysis
- Method/tools to investigate compliant.
- Identified if corrective action necessary
- Method for trend report handling
- Communication with EO, NB, CA, users
- Reference to relevant procedure
- PMCF plan



## 上市後臨床追蹤 – Post market clinical follow-up

### Annex XIV part B

- Continuous process updates clinical evaluation, be addressed in PMS plan
- Manufacturer shall proactively collect and evaluate clinical data, with the aim of confirming the safety and performance.
- Plan:
  - Method and procedures of PMCF such as information gathering and evaluation.
  - Rationale of the method and procedures
  - Reference to clinical evaluation and risk management
  - Objectives
  - Evaluation of clinical data to equivalent or similar devices
  - Reference such as standards, regulations, guidelines harmonized standards and CS

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## 上市後臨床追蹤計畫 – PMCF Plan

### Annex XIV, part B

- Aim to confirm the safety & performance of the device
- Identifying unknown side-effects
- Monitoring known side-effects & contraindications
- Ensure benefit-risk ratio
- The plan shall include
  - Method and procedure for collecting and evaluating clinical experiences
  - Rationale for the method and procedure
  - Objective
  - Evaluation on similar device or equivalent device
  - References to procedures and applicable standards
  - Time schedule

Clinical data

TD

Risk management

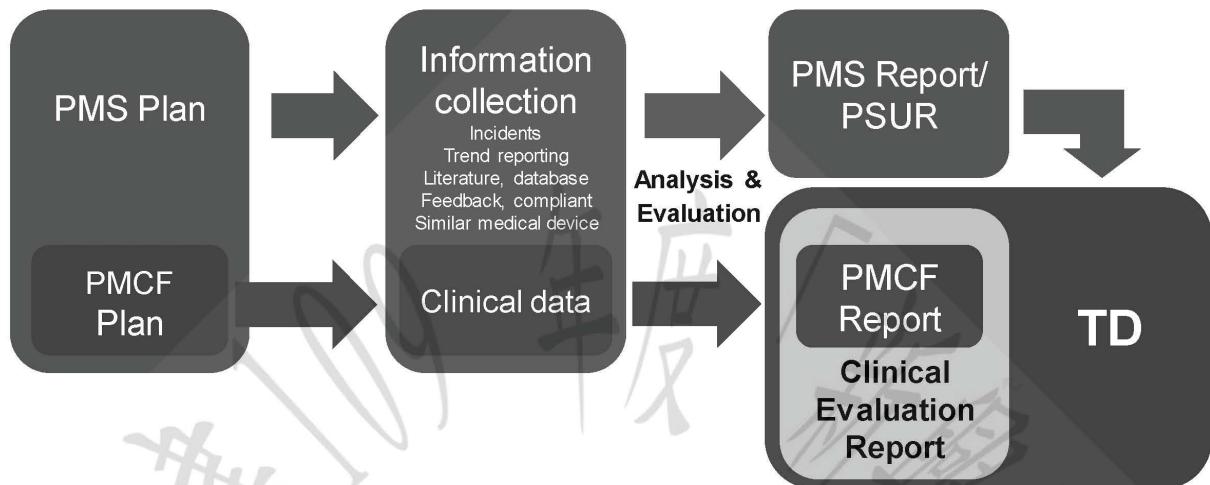
Clinical evaluation

36



## 上市後監督與上市後臨床追蹤 - PMS/PMCF

Annex XIV, part B



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## 上市後監督報告與定期安全性報告 – PMS report & PSUR

Article 85, 86

<b>Report</b>	PMS report	Periodic Safety Update Report, PSUR		
<b>Class of Device</b>	<b>Class I</b>	<b>Class IIa</b>	<b>Class IIb</b>	<b>Class III</b>
<b>Update Frequency</b>	When necessary	Every 2 years	Annually	Annually
<b>Requirements</b>	Summarizing the results and conclusions of PMS, corrective action taken			
<b>Submit for assessment</b>	N/A	Class III and Implant shall send to NB via EUDAMED for evaluation. Otherwise assessment conduct during TD assessment.		
<b>Specific requirements</b>	N/A	a. Conclusion of benefit-risk determination b. Main finding in PMCF c. Sale volume, estimate evaluation the size population use the device		

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## 警示與嚴重事故通報 – Vigilance & reporting of incident

Article 2 (64)-(66)

### Incident

malfunction or deterioration in characteristics or performance on device made available on the market, including use-error due to ergonomic features, as well as any inadequacy in the information supplied by the manufacturer and any undesirable side-effect;

### Serious incident

means any incident that directly or indirectly led, might have led or might lead to any of the following:

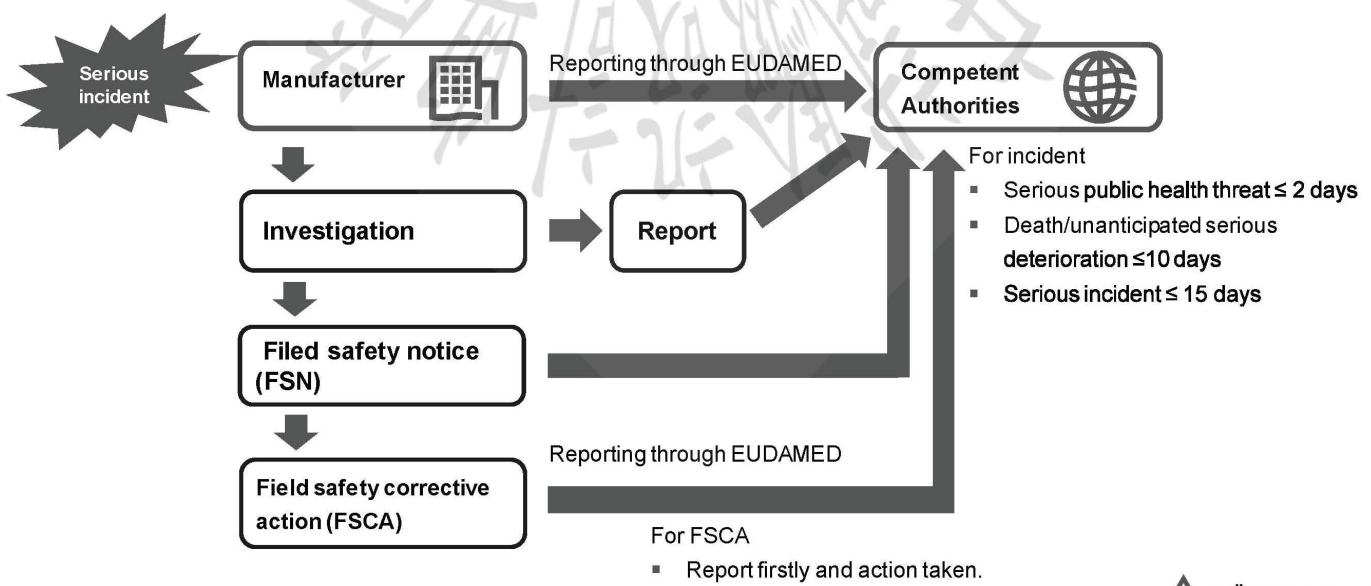
- Death of patient
- Serious deterioration of a patient's or user's or other person's state of health
- Serious public health treat

39

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## 嚴重事故通報與現場安全矯正措施 – Serious incident reporting and FSCA

Article 87, 89,

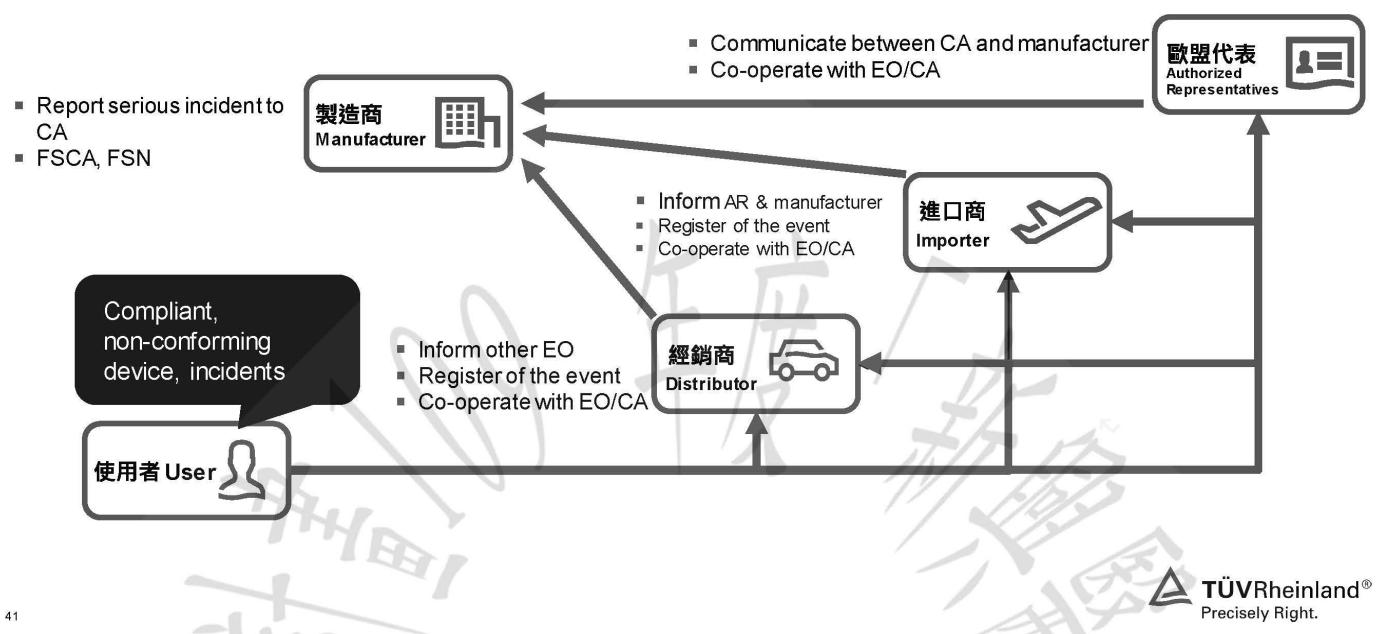


40

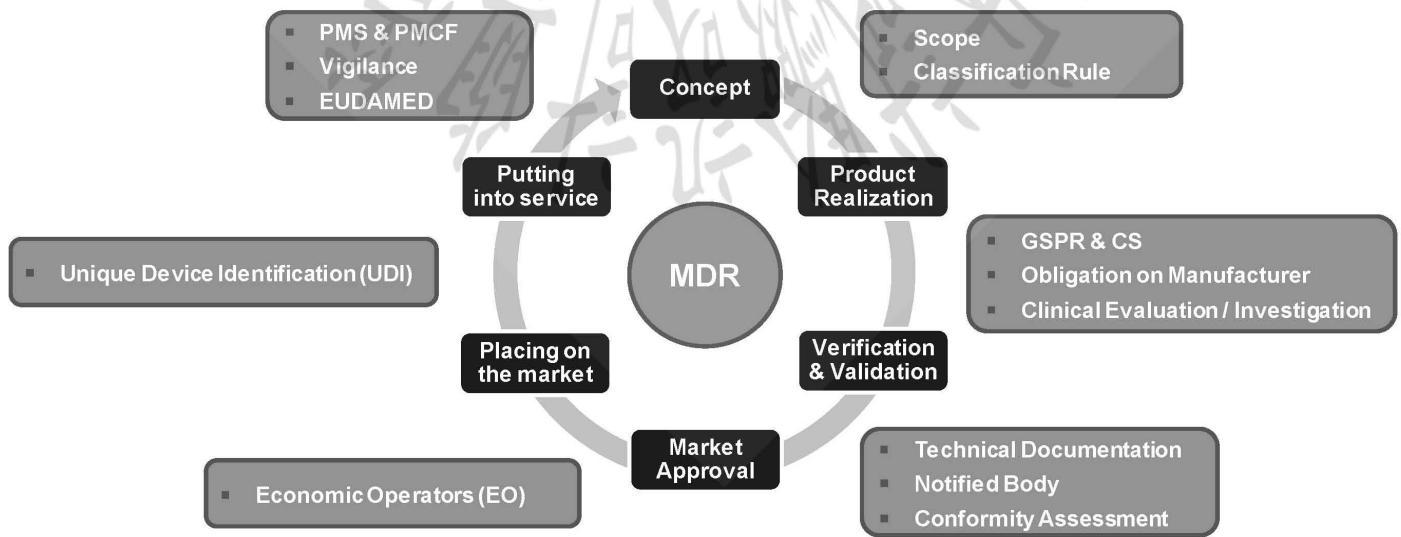
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## 經營者的義務 – General obligation of EO

Article 11, 13, 14



## 醫療器材生命週期 – MDR



# Q & A

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Thanks for your attention

Windah Hsu, [Windah.Hsu@TUV.com](mailto:Windah.Hsu@TUV.com)  
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# 臨床試驗實務分享： 以AI判讀肝臟腫瘤

How to Do AI Researches: My Experiences

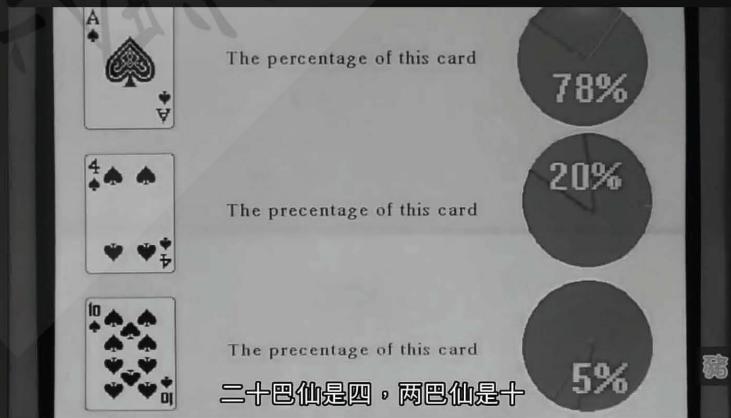
雙和醫院 影像醫學部主任 呂岳勳 2020 Sep. 18th

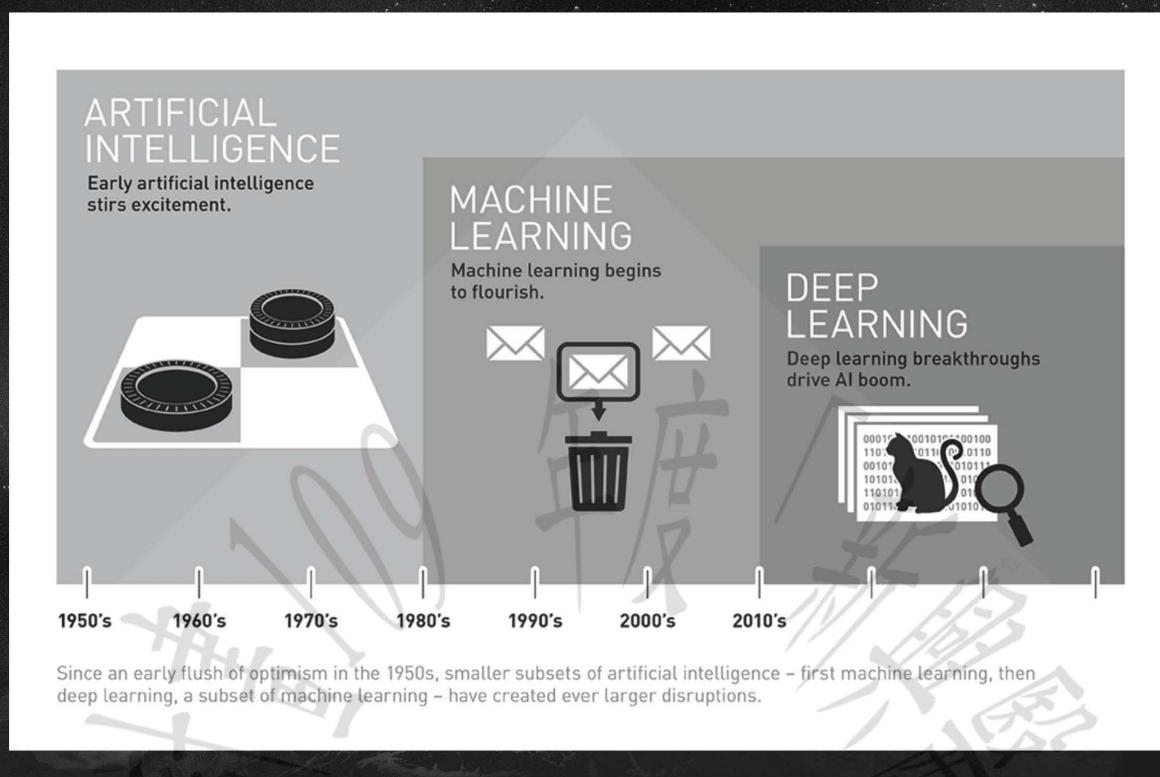
呂岳勳

- 雙和醫院影像醫學部
- 神經放射醫學會監事
- 陽明大學醫務管理所碩士
- 陽明大學醫學系兼任助理教授
- 臺北醫學大學專任講師

# 緣起與發想

開個6給他





## 風起雲湧的AI

### 放射診斷科醫師即將絕跡？AI 將奪走人類的工作

2019-08-10 09:02 / u讀小編 | 收藏 9 | 分享

AI 將奪走人類的工作：放射診斷科醫師即將絕跡

沒有護理師忙進忙出的身影、沒有消毒水嗆鼻的味道，就連一個患者也沒有。只有一排人坐在電腦前，仔細觀察螢幕畫面——這不是對未來的想像，而是目前放射診斷科的實況。

可能是因為日本人特別熱衷健康檢查，與歐洲相比，日本接受CT、MRI等放射檢查的患者非常多。放射檢查的機器過去十分昂貴，近年價格降低，因此一些規模比較小的診所也會設置。過去放射檢查很花時間，一個上午只能拍攝兩張照片；現在由於性能大幅改善，拍攝一張照片只需要六分鐘。此外，不僅照片的解析度提升，每次拍攝都能取得數百甚至數千張照片。

放射診斷科醫師的工作為觀察放射檢查的照片，判斷患者是否罹患癌症、動脈瘤等疾病。

然而即使放射檢查的機器變得普遍，放射診斷科醫師並未隨之增加，反而人才短缺。事實上許多診所無法聘請專屬的放射診斷科醫師。過去診所必須委託大醫院診斷，但大醫院的放射檢查亦日漸頻繁，實在無力負擔。因此各地開始出現大大小小負責診斷照片的檢查中心，提升診所的效率——開始我提到的實況，正是這些檢查中心的樣貌。

Fig. 1: Trends: Deep Learning vs Machine Learning vs Pattern Recognition

# Why Liver? Why Not Brain?

- The Major Researches in AI are .....
- Relative less incidence of liver disease in Western world
- What important things are .....

IRB & MOU

# IRB



表08-02-2初審審  
研究基本資料表計  
查意見...0180509  
畫相關...0180509

表08-03-1研究計  
畫基本...0180509  
查案件...0180509



簡易審查案件範圍  
核對表...0180509

表08-04-1中文計  
畫書摘...0180509

中文計畫摘要相關  
文件修...0180509



計劃書  
ver1.1-20180509

計畫書相關文件修  
正前 / ...0180509

個案報告表  
Ver1.1-20180509

個案報告表相關文  
件修正...0180509

# IRB

5. 委員審查意見五：研究計畫基本資料表 page 2「資料庫研究」欄位勾選「否」，page 3「召募受試者方式」勾選「使用資料庫，未召募受試者」，中文計畫書摘要表 page 3「受試者召募流程」說明「無召募受試者，資料來源為院內資料庫」，互相矛盾，建議修正研究計畫基本資料表「資料庫研究」欄位勾選為「是」，後續填寫為「院內影像資料庫」。

計畫主持人回覆：謝謝委員指點，已經修正

# MOU

什麼是「備忘錄（MOU）/意向書（LOI）」？

根據《梅里亞姆-韋伯氏法律辭典》（Merriam-Webster's Dictionary of Law, 1996）之定義，MOU應解釋為：「一種由一方當事人根據《詐欺防止條例》試圖強制執行另一項口頭協議時（作為附註）使用的紀錄，係用以證明另一方當事人同意了一項合約，且該紀錄無須包含前述合約所有的條款。（a record (as a note) which is used by a party seeking to enforce an otherwise oral agreement in accordance with the Statute of Frauds to prove that the other party agreed to a contract and which need not contain all the terms of the contract itself.）」

LOI的意涵根據《梅里亞姆-韋伯氏法律辭典》則定義為「一種書函，其中呈現了訂立正式協議（作為合約）或採取某種具體行動的意向。（a letter in which the intention to enter into a formal agreement (as a contract) or to take some specified action is stated）」

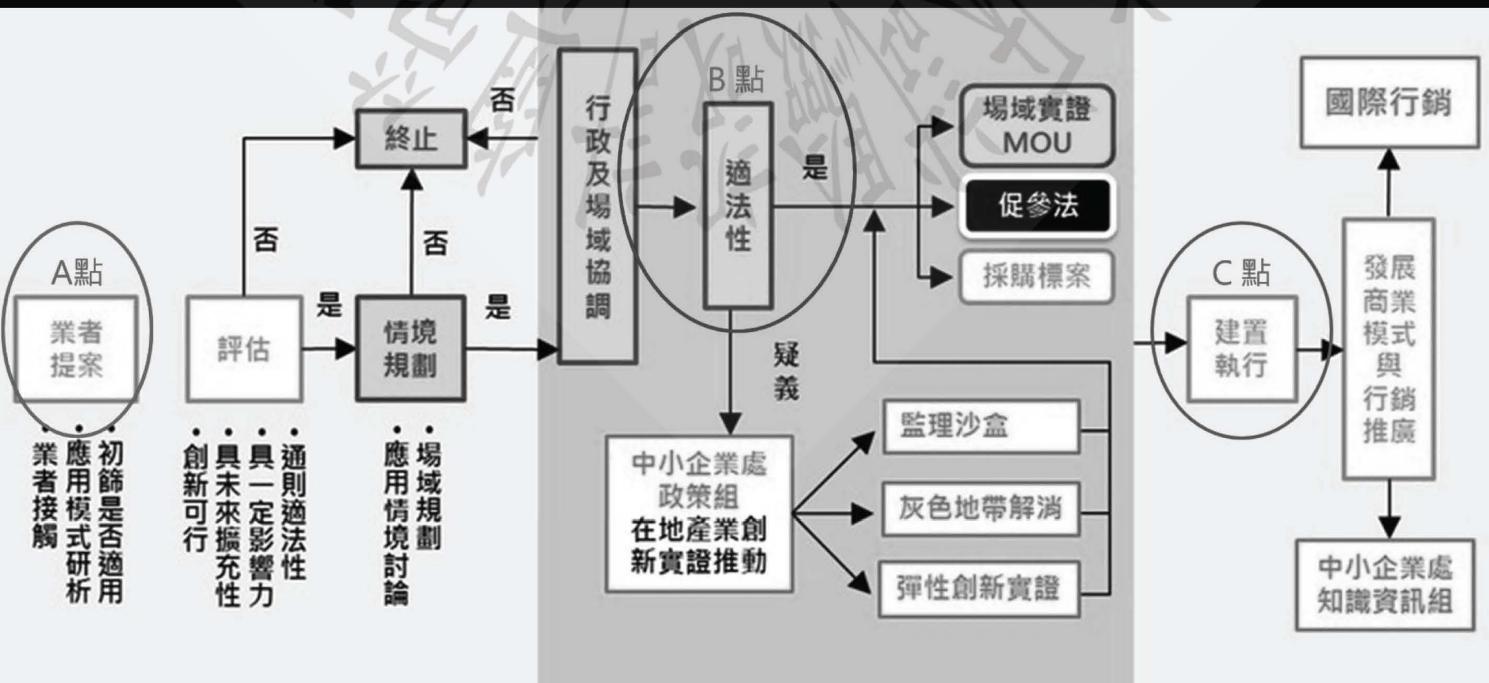
不過根據美國法律，MOU和LOI的是相同的（註1）。兩者經常被使用在成形中的談判上，因此MOU/LOI內的失效日期十分重要，因為這是各方同意若未達成協議就中止談判的時點（註2）。

## 什麼環境做什麼事情？時空與政治問題

供應商力量整合、形成艦隊



## Who Paid the Bill?



# The Server

## Its Cost?

- IBM PowerPC 8
- GPU NVIDIA P40x2
- RAM: 512Gmb



Nvidia  
P40

Dell

製造商部份 DPP88  
Dell 部份 489-BBCO

以 NVIDIA Tesla GPU 加速器加速您最嚴苛的 HPC、超大規模 (Hyperscale) 和企業資料中心工作負載。

現在科學家能在從能源探勘到機器學習等各種不同的應用中，以最高比 CPU 快的速度處理數 Petabyte 的資料。此外，Tesla 加速器能提供較以往任何裝置更快速執行更大型模擬場景的效能。對於部署 VDI 的企業來說，Tesla 加速器是能協助任何使用者隨時隨地加速虛擬桌面的完美選擇。

Dell 價格

NTD 573,577



# Now

品名	規 格	產地	保固	單位	單 價	數量	小 計
個人電腦	Intel i7-9700 中央處理器 華碩 STRIX-B360F-GAMINI 1151 主機板 振華 SF-750F 14MG 750W 電源供應器 Micron DDR4-2666 16GB 桌機用記憶體*2 隻 TOSHIBA MD04ACA400 4TB 3.5 吋硬碟 ADATA XPG SX8200 PRO 256G M.2 PCIe 固態式硬碟 華碩 DUAL RTX2080TI-O11G-GAMING 顯示卡 BE QUIET BASE600 靜音黑機殼	全球(含中國)	3 年	台	64900	1	64900
作業系統	WIN10 專業版			套	4990	1	4990
Total NT\$							69890

合計新臺幣：陸萬玖仟捌佰玖拾元整

## 速率決定步驟與深水區



**3DSlicer**

**Original author(s)** The Slicer Community [↗](#)

**Stable release** 4.10.2 / 22 May 2019; 15 months ago

**Written in** C++, Python, Qt

**Operating system** Linux, macOS, Windows

**Size** 200MB

**Available in** English

**Type** Scientific visualization and image computing

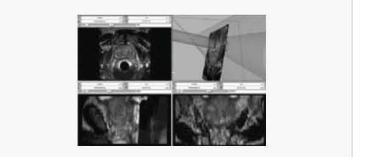
**License** BSD-style

**Website** [www.slicer.org](http://www.slicer.org) [↗](#)

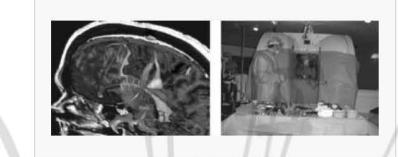
# 3DSlicer



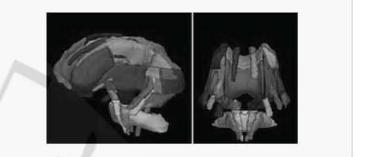
Hardware accelerated volume rendering with nVidia drivers, (on Windows and Linux only).



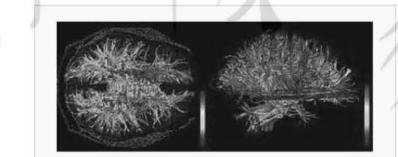
ProstateNav Module for MRI guided robot assisted biopsy of the prostate.



Left: 3D rendering. Right: Open MR system



Visualization of some atlas-based ROIs which correspond to major anatomical fiber tracts. The atlas was provided as part of a download of DTI studio [↗](#).





## Data Prepare

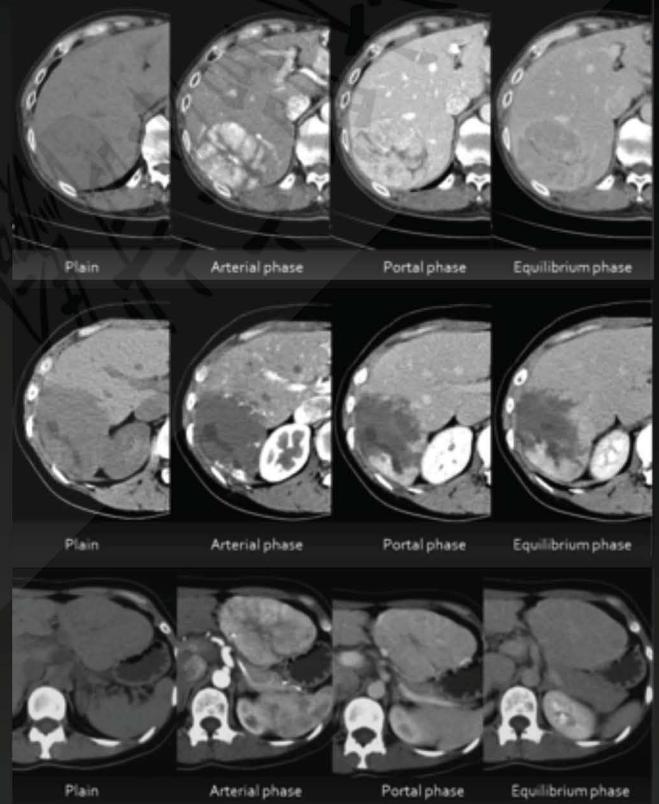


```

keras_script.py
39
40 import keras.backend as K
41 from itertools import product
42 import functools
43 import tensorflow as tf
44 # Custom loss function with costs
45
46 def w_categorical_crossentropy(y_true, y_pred, weights):
47     nb_cl = len(weights)
48     final_mask = K.zeros_like(y_pred[:, 0])
49     y_pred_max = K.max(y_pred, axis=1)
50     y_pred_max = K.reshape(y_pred_max, (K.shape(y_pred)[0], 1))
51     y_pred_max_mat = K.equal(y_pred, y_pred_max)
52     for c_p, c_t in product(range(nb_cl), range(nb_cl)):
53         # final_mask += (weights[c_t, c_p] * y_pred_max_mat[:, c_p] * y_true[:, c_t])
54         final_mask += (K.cast(weights[c_t, c_p],tf.float32) * K.cast(y_pred_max_mat[:, c_p] ,tf.float32)* K.cast(y_true[:, c_t],tf.float32))
55     return K.categorical_crossentropy(y_pred, y_true) * final_mask
56
57 weights = np.ones((2,2))
58 weights[:, :] = 50
59
60 ncce = functools.partial(w_categorical_crossentropy, weights=weights)
61 ncce.__name__ = 'w_categorical_crossentropy'
62
63 import argparse
64 parser = argparse.ArgumentParser(description='Training script for training a script 3D CNN network.')
65
66 parser.add_argument('--snapshot', help='Resume training from a snapshot.', type=str)
67 parser.add_argument('--batch-size', help='Size of the batches.', default=32, type=int)
68 parser.add_argument('--gpu', help='Id of the GPU to use (as reported by nvidia-smi).')
69 parser.add_argument('--epochs', help='Number of epochs to train.', type=int, default=50)
70 parser.add_argument('--steps', help='Number of steps per epoch.', type=int, default=1000)
71 parser.add_argument('--snapshot-path', help='Path to store snapshots of models during training (defaults to \'./snapshots\')', default='./snapshots')
72 parser.add_argument('--tensorboard-dir', help='Log directory for Tensorboard output', default='./logs')
73 parser.add_argument('--initial-epoch', help='Epoch at which to start training.', type=int, default=0)
74 parser.add_argument('--train-key', help='Path to the file contains keys of training set.', type=str)
75 parser.add_argument('--val-key', help='Path to the file contains keys of validating set.', type=str)
76 parser.add_argument('dataref', help='Path to the data reference file.', type=str, default='')
77
78 args = parser.parse_args()
79
80 # Parameters
81 params = {'dim': (24,24,24),
82            'batch_size': args.batch_size,
83            'n_classes': 2,
84            'n_labels': 2}

```

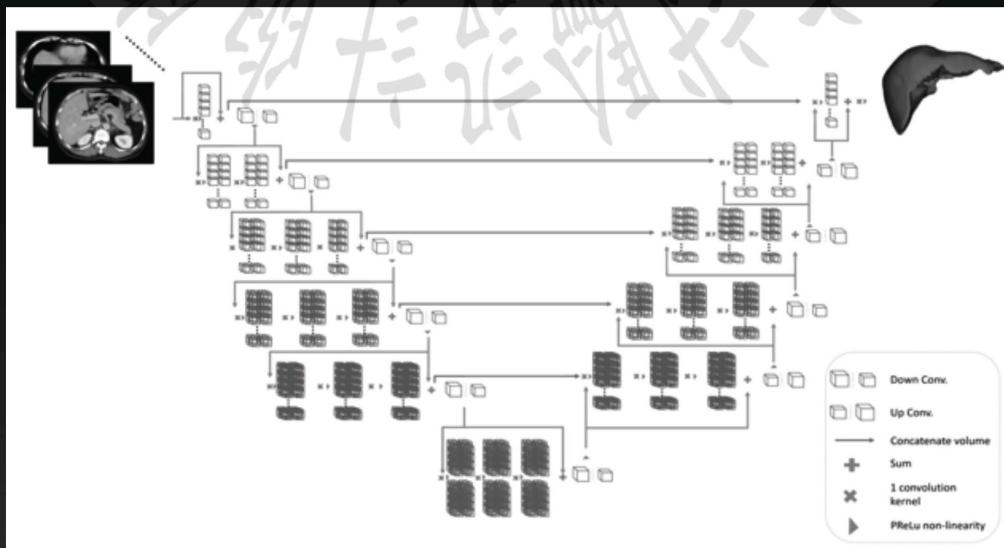
- Typical Imaging Findings



# RDS - Rate Determining Step



## V-NET



# TensorFlow

- TensorFlow提供了一個Python API，以及C++、Haskell、Java、Go和Rust API。第三方包可用於 C#、Julia、R 和 Scala。
- TensorFlow的底層核心引擎由C++實現，通過 gRPC 實現網路互訪、分散式執行。雖然它的Python/C++/Java API共用了大部分執行程式碼，但是有關於反向傳播梯度計算的部分需要在不同語言單獨實現。目前只有Python API較為豐富的實現了反向傳播部分。所以大多數人使用Python進行模型訓練，但是可以選擇使用其它語言進行線上推理。
- TensorFlow在Windows和Linux上支援使用 Bazel 或 CMake 構建，在某些平台上也支援直接使用 GNU Make 進行編譯

# Keras

- Keras包含許多常用神經網路構建塊的實現，例如層、目標、啟用功能、最佳化器和一系列工具，可以更輕鬆地處理圖像和文字資料。其程式碼代管在GitHub上，社群支援論壇包括GitHub的問題頁面和Slack通道。
- 除標準神經網路外，Keras還支援卷積神經網路和遞迴神經網路。其他常見的實用公共層支援有Dropout、批次歸一化和池化層等。
- Keras允許用戶在智慧型手機（iOS和Android）、網頁或Java虛擬機器上製作深度模型，還允許在圖形處理器和張量處理器的叢集上使用深度學習模型的分散式訓練。

## Materials and Methods

- Collect arterial and venous phase of liver CT image data for hepatocellular carcinoma (HCC), hemangioma and focal nodular hyperplasia (FNH).
- HCC was diagnosed by pathologic finding, hemangioma and FNH were diagnosed by experted radiologist with dynamic CT images or Primovist MRI.
- Total patients are 123, the numbers of each tumors are 55 for HCC, 60 for Hemangioma and 14 for FNH.

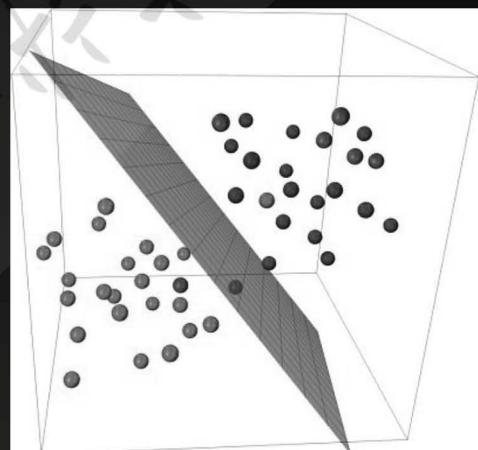
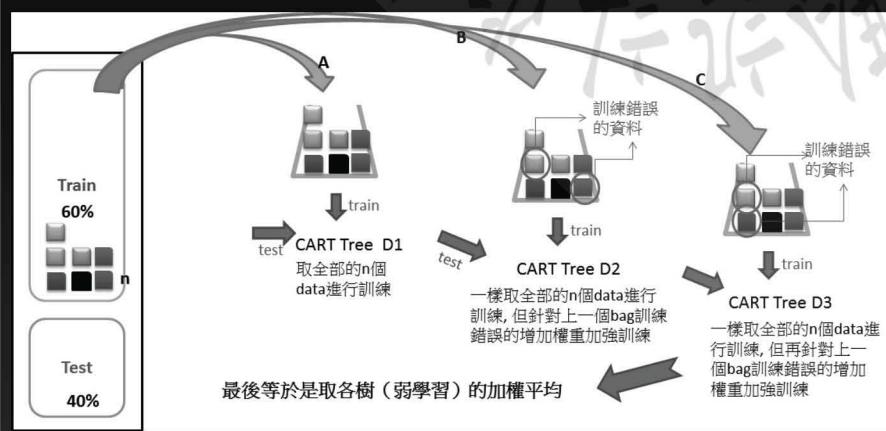
## Random Forest Learning

- We use random forest learning method and choose 52 features those are not only original metrics but also generated from aggregating (ex, mean HU value of arterial tumor subtract mean HU value of venous tumor) between each other. Model was validated by 5-folds cross validation.

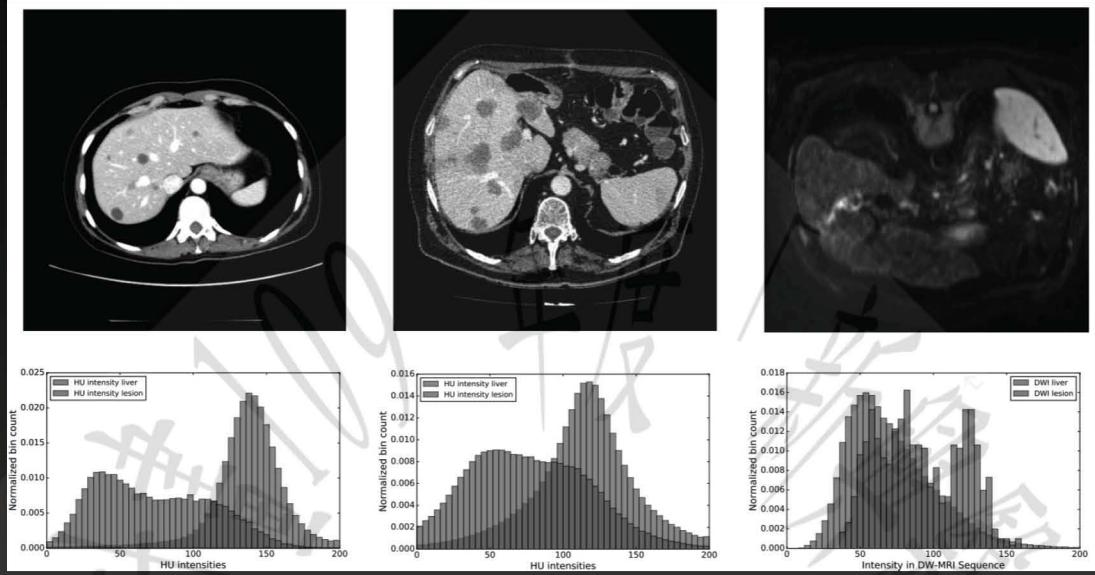
# The Features Used

- ※ Average HU value
- ※ Standard deviation of HU value
- ※ Skewness of HU value
- ※ Kurtosis of HU value
- ※ Signal to noise of HU value
- ※ Min of HU value
- ※ Quantile 10p, 25p, 50p, 75p, 90p
- ※ Max of HU value
- ※ Interquartile range

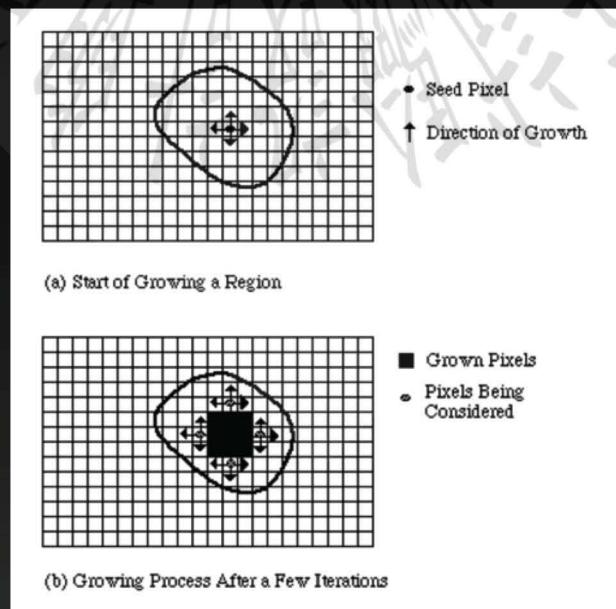
## Random Forests and SVM



# Density (HouseField Unit) Distribution



## Region Grow

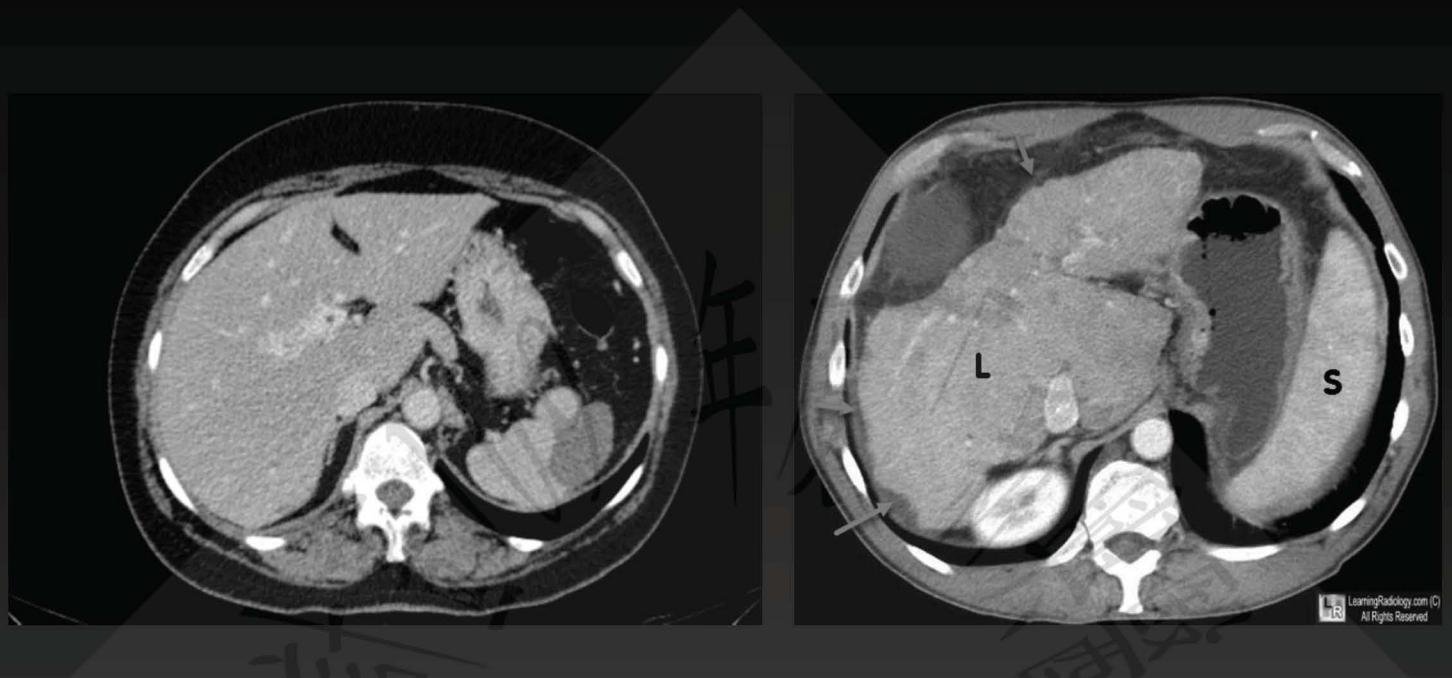


# Object

- We developed a tool for liver parenchyma segmentation; whether in noncirrhotic liver parenchyma or cirrhotic liver parenchyma.
- We developed a tool for classification of three hepatic tumors in segmented liver image. These tumors included HCC (hepatocellular carcinoma), Hemangioma, and FNH (focal nodular hyperplasia)

結果與分析

# Normal and Cirrhotic Liver



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## Normal Liver and Liver Cirrhosis

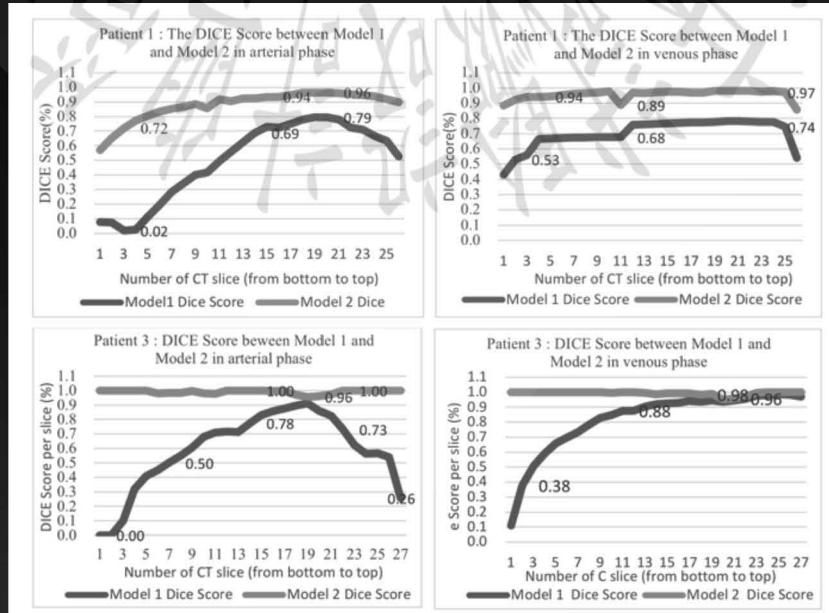
	Group 1	Not for train	Group 2
	Non-cirrhosis Liver	Cirrhosis patient	Non-cirrhosis and Cirrhosis Liver
Number of training dataset	40 (40%)	33 (33%)	73 (73%)
Number of testing dataset	19 (19%)	8 (8%)	27 (27%)
Total	59 (59%)	41 (41%)	100 (100%)

Table 1.: The number of patient in each group and condition.

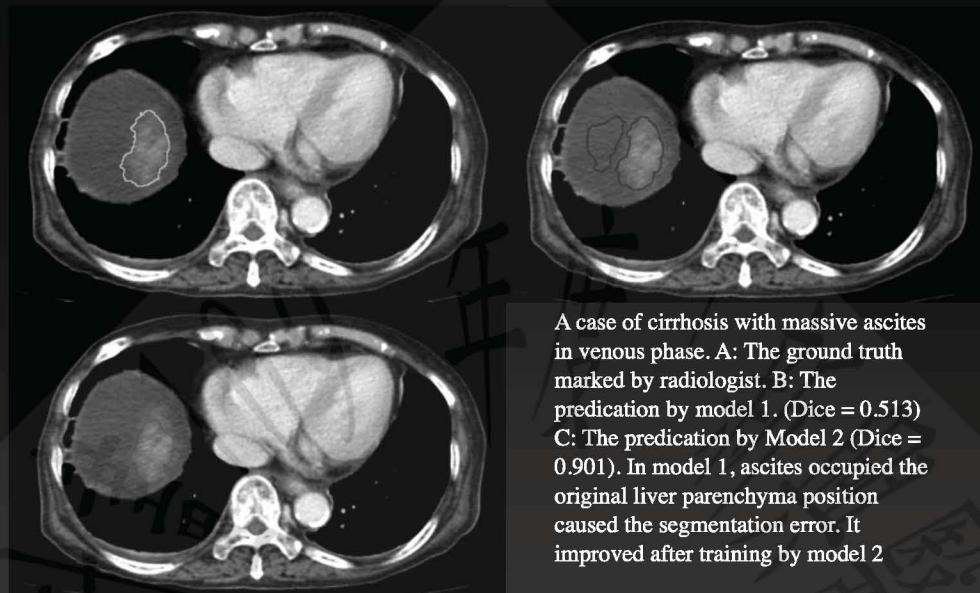
# The DICE Distribution

A	B	C	D	E	F	G	H	I
file name	Cirrhosis_001A	Cirrhosis_003A	Cirrhosis_004A	Cirrhosis_005A	Cirrhosis_006A	Cirrhosis_007A	Cirrhosis_008A	Cirrhosis_009A
liver:dice	0.9904	0.9995	0.9995	0.9872	0.9930	0.9961	0.9986	0.9969
TPR	0.9878	0.9999	0.9991	0.9974	0.9866	0.9923	0.9973	0.9938
FNR	0.0122	0.0001	0.0009	0.0026	0.0134	0.0077	0.0027	0.0062
TNR	0.9998	1.0000	1.0000	0.9985	1.0000	1.0000	1.0000	1.0000
FPR	0.0002	0.0000	0.0000	0.0015	0.0000	0.0000	0.0000	0.0000
Accuracy	0.9994	1.0000	1.0000	0.9984	0.9991	0.9995	0.9998	0.9998
speed	5.1577	4.6450	4.9780	4.0941	5.2471	4.0024	5.9690	6.3387
shape	(49, 512, 512)	(40, 512, 512)	(39, 512, 512)	(32, 512, 512)	(44, 512, 512)	(31, 512, 512)	(53, 512, 512)	(56, 512, 512)
file name	Cirrhosis_001V	Cirrhosis_003V	Cirrhosis_004V	Cirrhosis_005V	Cirrhosis_006V	Cirrhosis_007V	Cirrhosis_008V	Cirrhosis_009V
liver:dice	0.9880	0.9980	0.9997	0.9873	0.9989	0.9945	0.9988	1.0000
TPR	0.9875	0.9960	0.9994	0.9997	0.9979	0.9891	0.9975	1.0000
FNR	0.0125	0.0040	0.0006	0.0003	0.0021	0.0109	0.0025	0.0000
TNR	0.9996	1.0000	1.0000	0.9994	1.0000	1.0000	1.0000	1.0000
FPR	0.0004	0.0000	0.0000	0.0006	0.0000	0.0000	0.0000	0.0000
Accuracy	0.9993	1.0000	1.0000	0.9994	0.9999	0.9998	0.9999	1.0000
speed	12.5058	8.9872	10.4695	10.4615	9.3928	10.6480	9.8558	9.5226
shape	(106, 512, 512)	(87, 512, 512)	(88, 512, 512)	(89, 512, 512)	(89, 512, 512)	(83, 512, 512)	(91, 512, 512)	(85, 512, 512)

## DICE Distribution



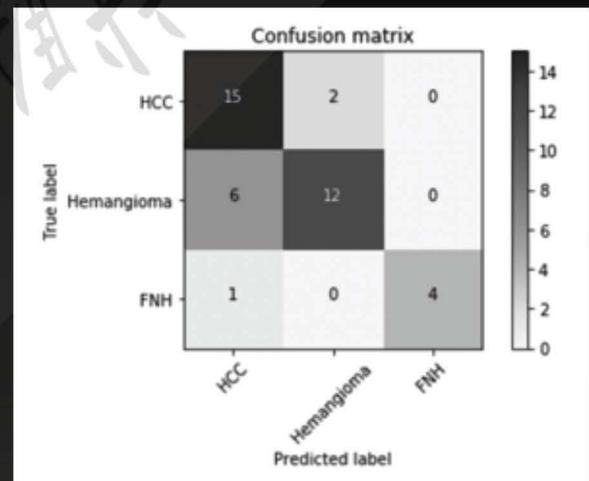
# Ground Truths and Different Models



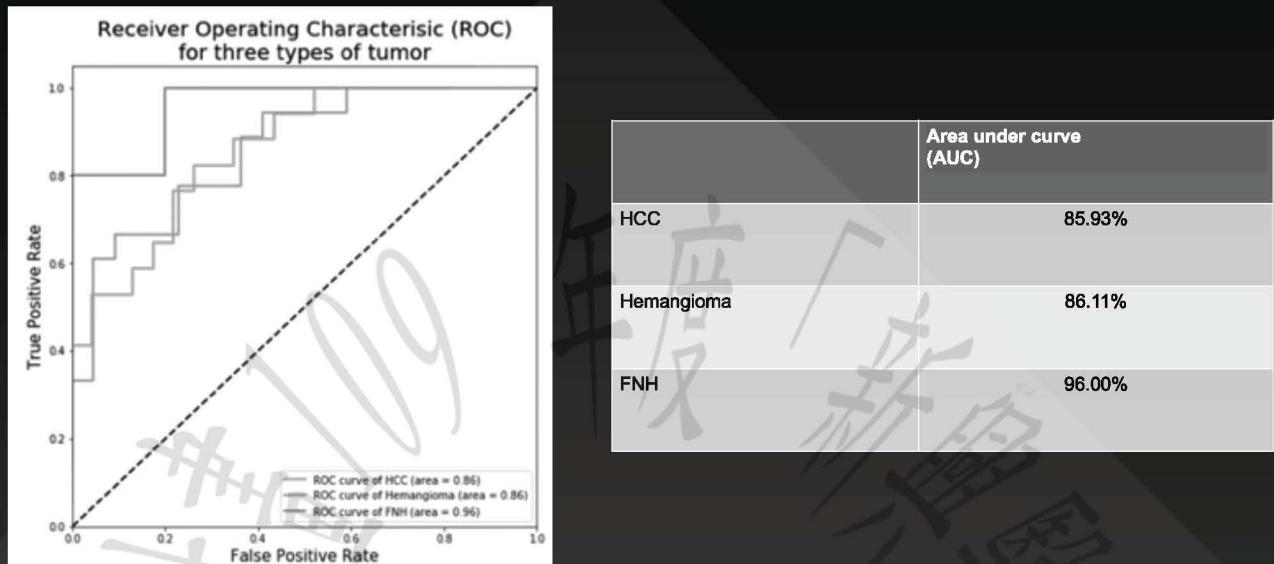
## Results

	True positive rate	True negative rate	False positive rate	False negative rate
HCC	68.18%	88.88%	11.11%	31.81%
Hemangioma	85.71%	76.92%	23.07%	14.28%
FNH	100%	97.22%	0.02%	0.00%

	Case number:123
Accuracy rate	77.50%
Precision rate	79.86%
Recall rate	77.50%
F1-score	77.50%



# Results: The AUC Curve



## Tumors Marked

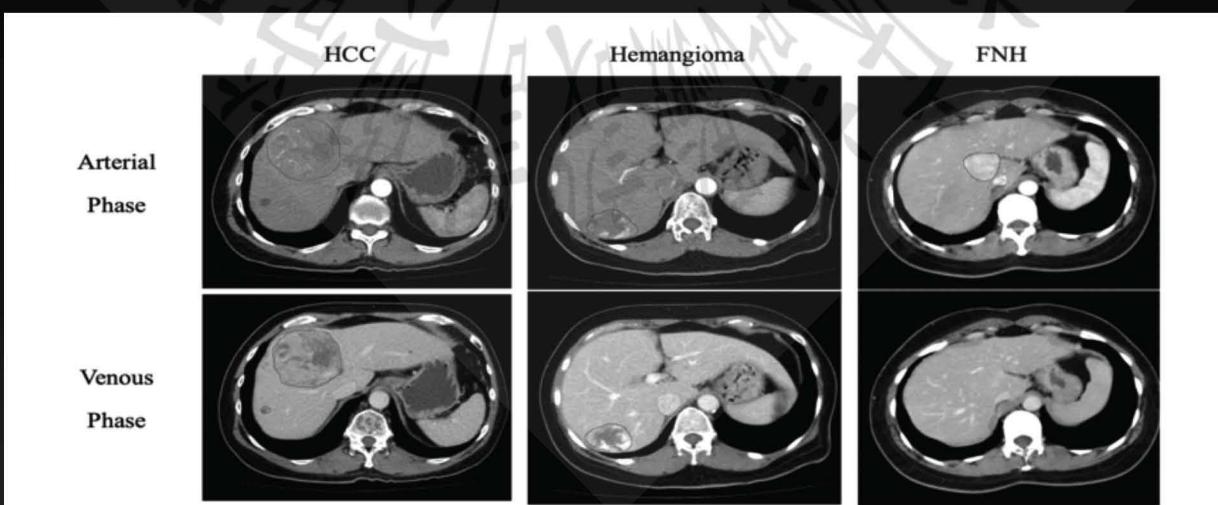
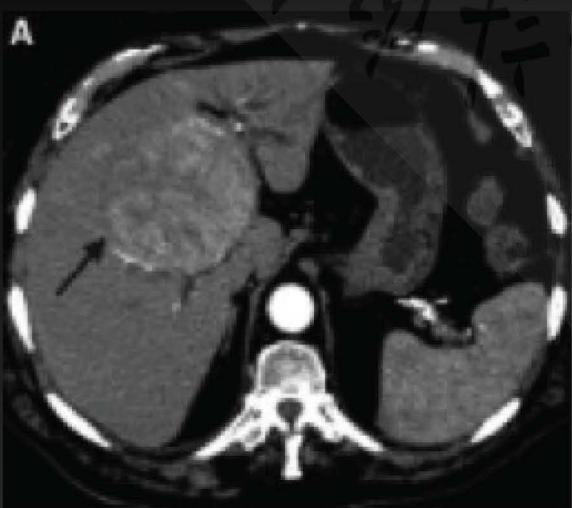


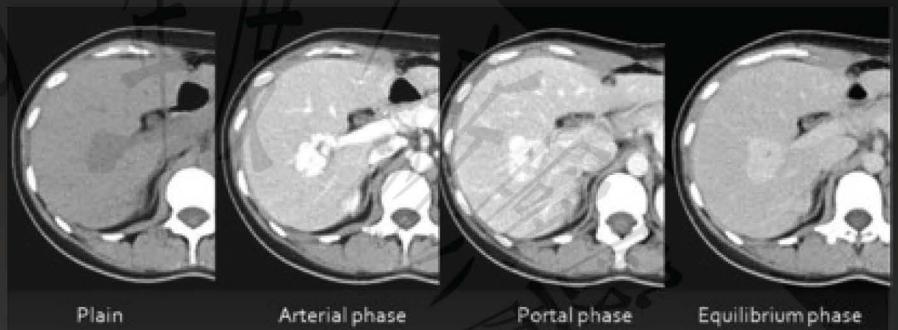
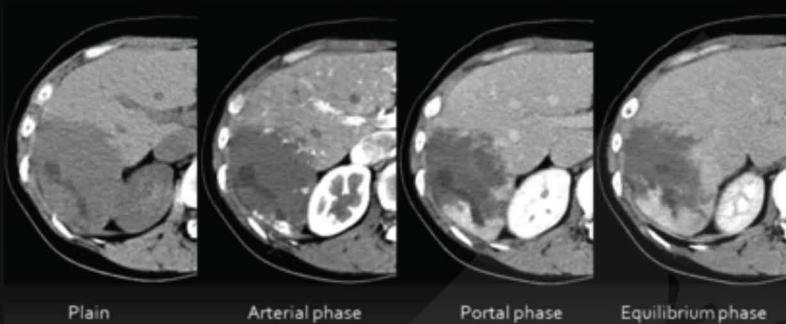
Figure 1: The demonstration of three type tumors. Ground truth is applied by three radiologists. Machine learning is arranged to learn the architecture and intensity of tumors. The arterial and venous phases images are subtracted after image registration.

# Human Eyes & AI Eyes

HCC



# Hemangiomas



## The Results

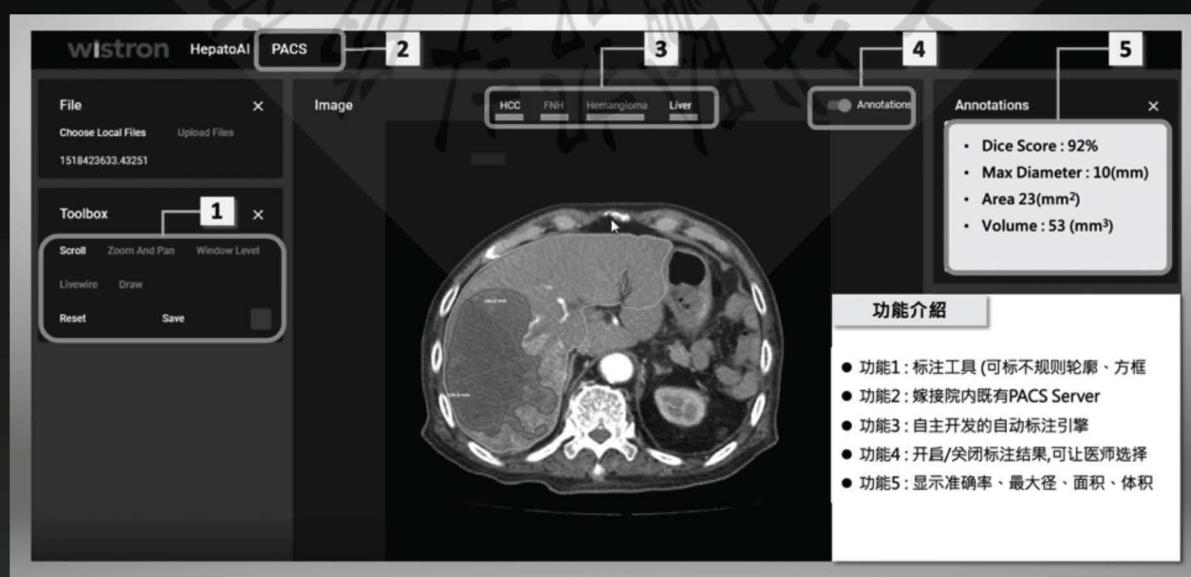
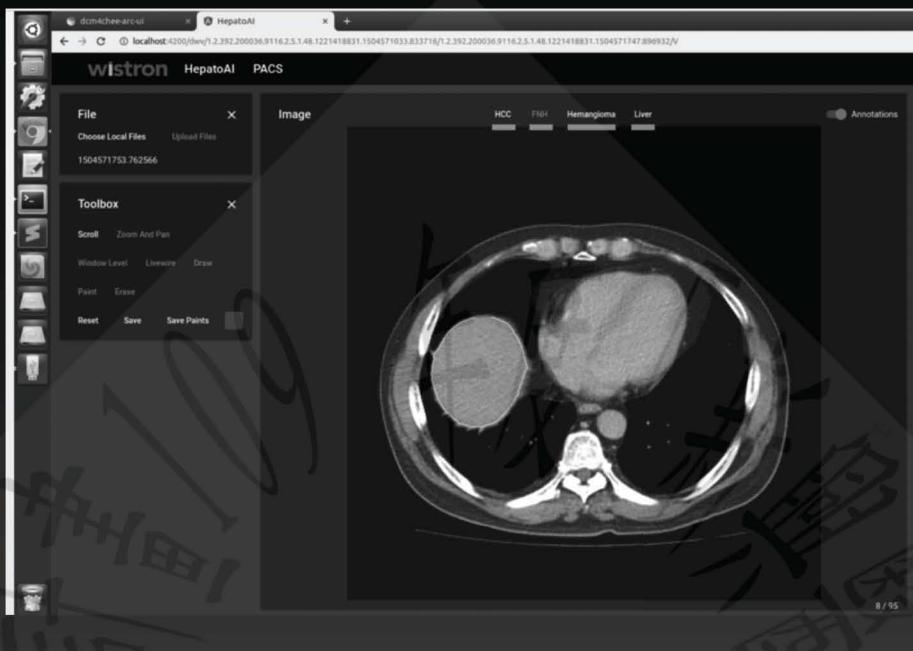
- We found a model including various conditions could help in the correctness of model. To make an automatic pipeline tool, we recommended further liver and tumor segmentation model should involve the cirrhotic liver group in proper weights.
- Our semi-automatic pipeline with automatic liver segmentation and classifier have good property to separate three types of tumor under arterial and venous phase, dynamic CT image.

你要什麼？你的長官要什麼？

2019 台北國際醫療暨健康照護展



# Prototype of API



# 我得到了什麼？

- Know - How
- 對流程的熟悉
- Algorithms
- 連結

未來的挑戰

# 風往哪裡吹？

- 巨量1.0 計畫：台大，北榮，北醫 - 三年大科技部計畫 (2018-2020)
- 巨量2.0: Something happened.
- 國內有哪些廠商有興趣呢？

## 人力與物力

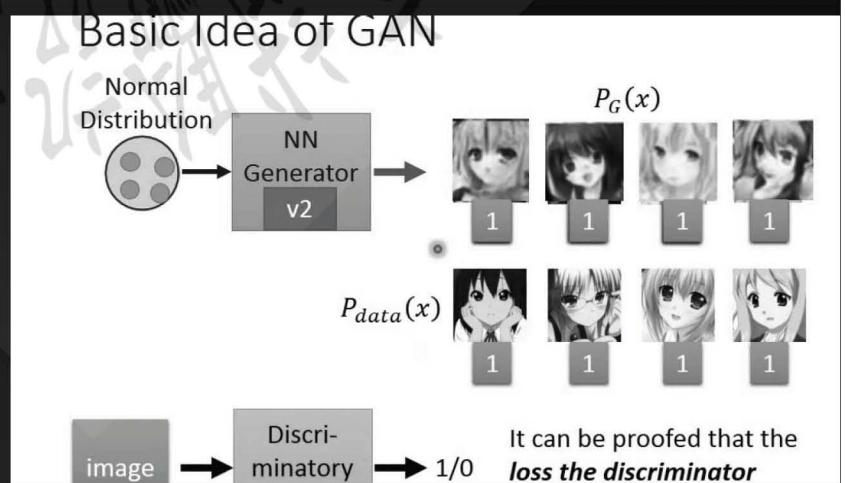
- We have much much much “Data”
- We don't have time
- How much is the hourly rate?
- Like it or Not?

# 落地

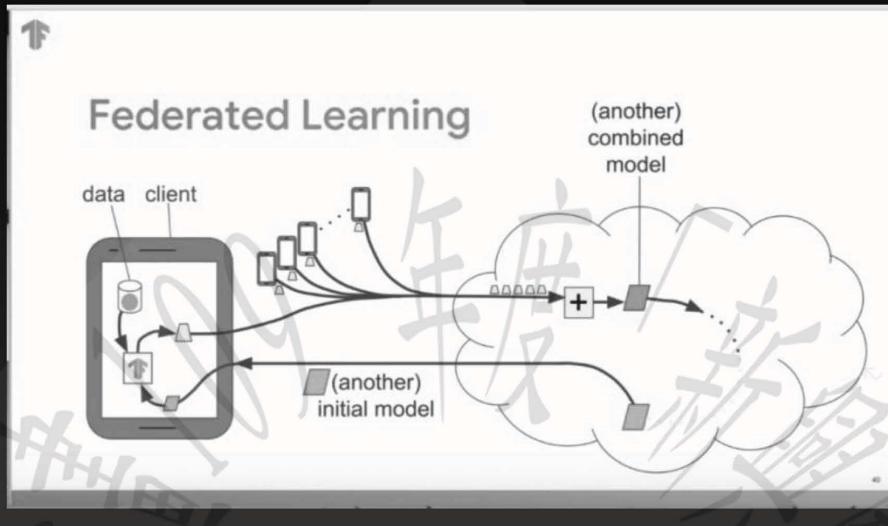
- 結果
- 論文
- 產品化
- 落地
- 你要什麼，公司要什麼？

## One More Thing

- GAN -
- Generative Adversarial Network



# Federated Learning



結語：如果你也想做AI研究

# Main Issue of Current Neural Network Techniques

- Weak in theory and reasoning - black boxes after black boxes
- Empirical (try and error)
- Biological Neural Network learning does not process error backpropagation
- Sensitive to clutter

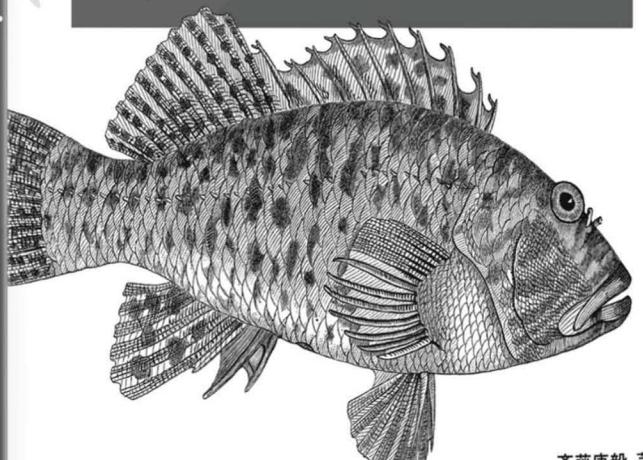
## 延伸閱讀

- Deep Learning : 用Python進行深度學習的基礎理論實作



Deep  
Learning

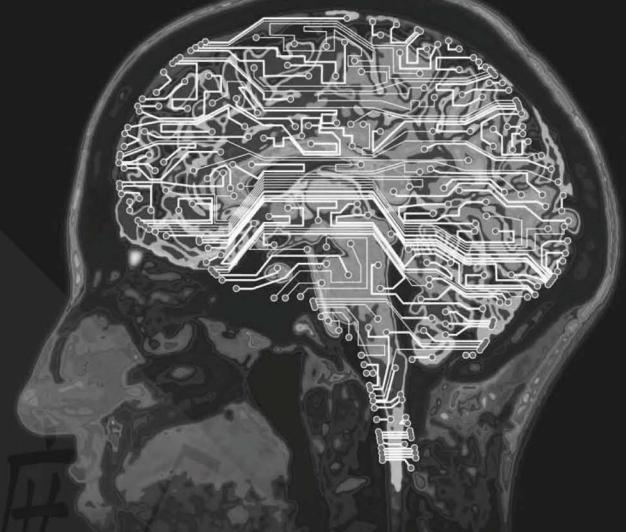
用 Python 進行深度學習的基礎理論實作



文廣出版社

## 延伸閱讀

- Deep Learning for Medical Image Analysis

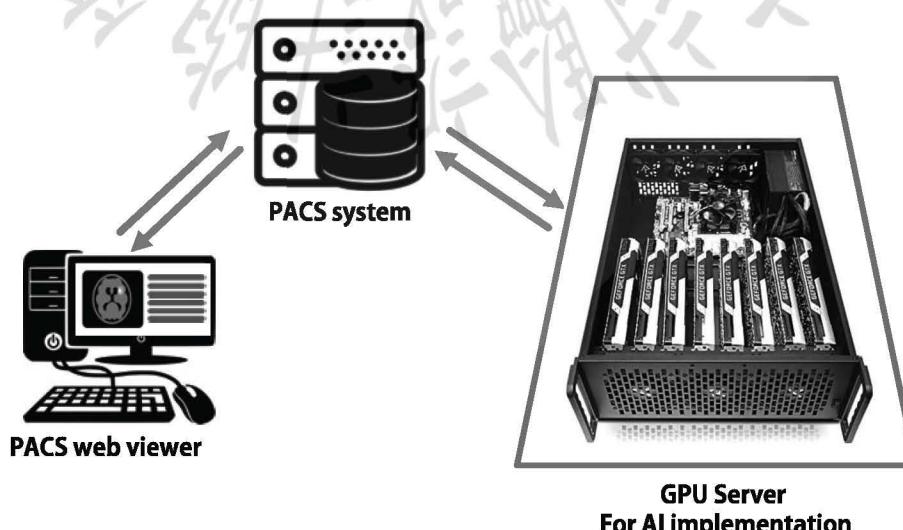


## Deep Learning for Medical Image Analysis

Edited by  
S. Kevin Zhou  
Hayit Greenspan  
Dinggang Shen



## 雙和醫院影像醫學部



# 雙和醫院影像醫學部

臺北醫學大學  
TAIPEI MEDICAL UNIVERSITY

Stanford Center for Artificial Intelligence  
in Medicine & Imaging

Stanford MEDICINE

ASL MRI

PET-CBF

DL-ASL

→

雙和醫院放射科  
陳彥廷醫師

利用深度學習(DL-ASL model)由MRI產生PET  
腦血流影像，並實用於史丹佛與北醫醫院

Prof. Greg Zaharchuk  
MD, PhD

Thank You For Your  
Attention



# 人工智能醫療器材之臨床試驗統計方法 – 以AI判斷糖尿病嚴重度與骨頭年齡為例

Chin-Fu Hsiao

Institute of Population Health Sciences  
National Health Research Institutes

1

## AI醫療現況

- 人工智能(Artificial Intelligence, AI)與大數據等新興概念在醫療健康產業發展神速。多家電子廠商，亦藉由雲端服務所提供之大數據增值之應用，紛紛加入AI產品之開發
- AI技術在醫療設備領域的應用主要集中在醫學影像、輔助診斷、藥物研發、健康管理、疾病預測等幾大領域

2

# 相關法規

- **Classification**

Software as a Medical Device (SAMD):

Clinical Evaluation (12/2017)

- **Clinical Performance Assessment**

Clinical Performance Assessment: Considerations for

Computer-Assisted Detection Devices Applied to

Radiology Images and Radiology Device Data in

Premarket Notification (510(k)) Submissions (01/2020)

- **Software Validation**

Guidance for the Content of Premarket Submissions for

Software Contained in Medical Devices (05/2005) <sup>3</sup>

# 相關法規

- **Cybersecurity**

Postmarket Management of Cybersecurity in Medical

Devices (12/2016)

Content of Premarket Submissions for Management

of Cybersecurity in Medical Devices (10/2018)

# Statistical Considerations

## Null Hypothesis ( $H_0$ ):

No difference in the response exists between treatment and control groups

### **Alternative Hypothesis ( $H_a$ ):**

A difference of a specified amount ( $\Delta$ ) exists between treatment and control

**Significance Level ( $\alpha$ ): Type I Error**

The probability of rejecting  $H_0$  given that  $H_0$  is true

**Power =  $(1 - \beta)$ : ( $\beta$  = Type II Error)**

The probability of not rejecting  $H_a$  given that  $H_a$  is true

5

# Test of Hypothesis

- Two sided vs. One sided  
e.g.  $H_0: \text{Trt} = \text{Con}$        $H_0: \text{Trt} \leq \text{Con}$
  - Classic test       $z_\alpha$  = critical value  
  
If  $|z| > z_\alpha$       If  $z > z_\alpha$   
Reject  $H_0$       Reject  $H_0$   
 $\alpha = .05, z_\alpha = 1.96$        $\alpha = .05, z_\alpha = 1.645$

where  $z$  = test statistic



6

# Typical Design Assumptions

1.  $\alpha = .05$  (two-sided),  $.025$  (one-sided)
2. Power =  $.80$  (IIT),  $.90$  (Sponsor)  
Should be at least  $.80$  for design

7

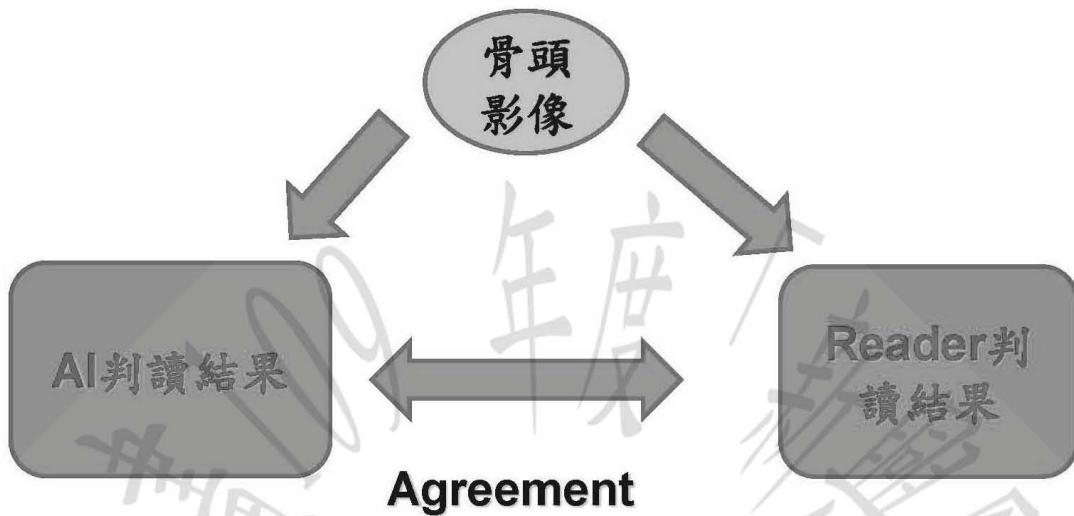
# Typical Design Assumptions

## Two Sided

Significance Level		Power	
$\alpha$	$Z_{\alpha/2}$	$1 - \beta$	$Z_\beta$
0.05	1.96	0.80	0.84
		0.90	1.282
		0.95	1.645

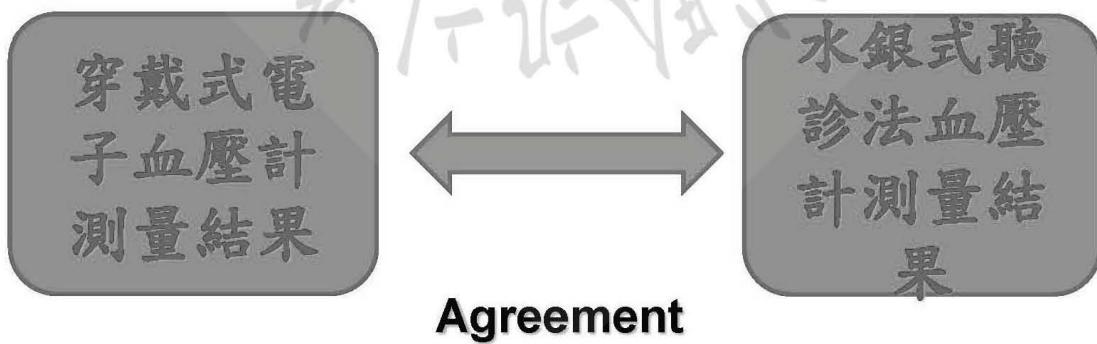
8

# 骨頭年齡



9

# 穿戴式電子血壓計



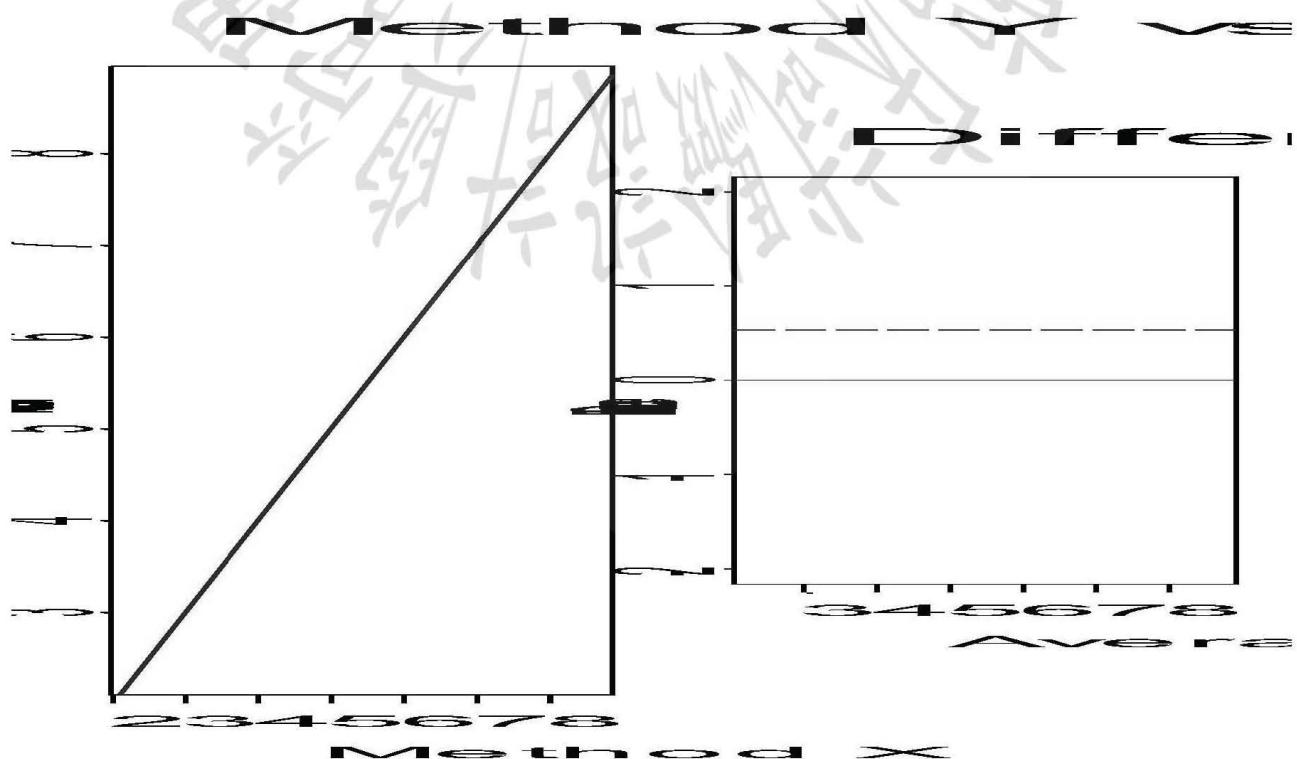
10

# Validating a New Assay

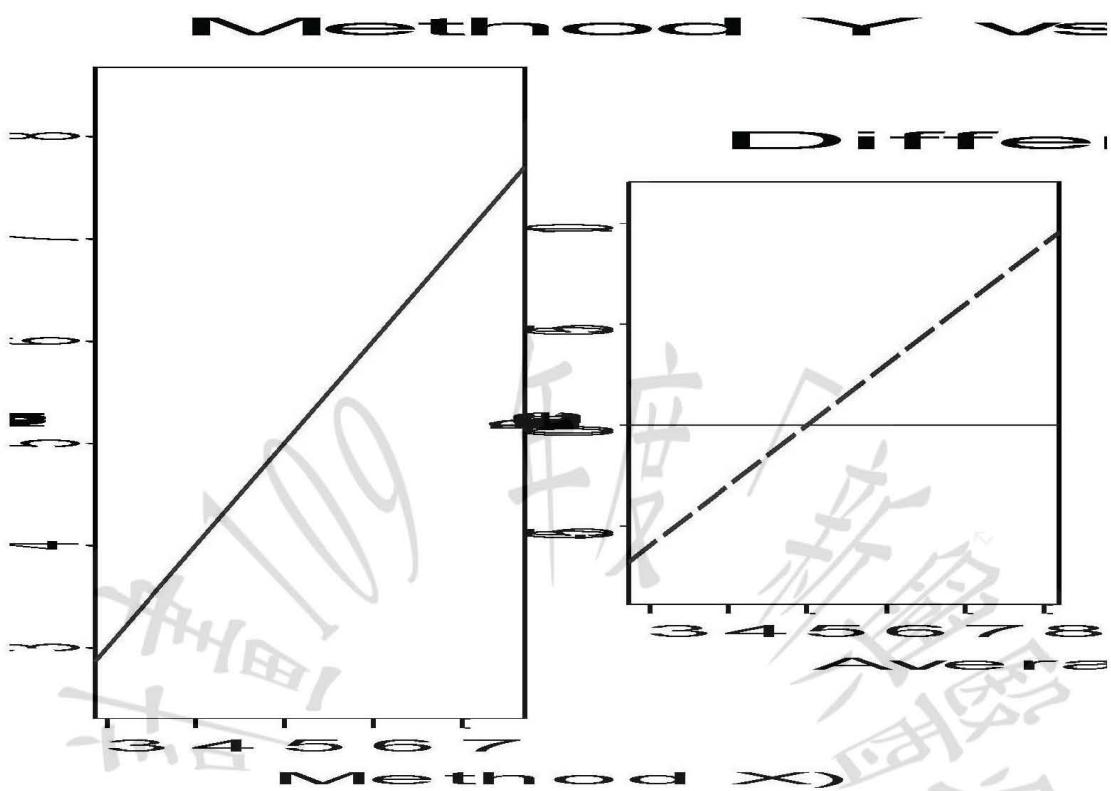
- Purposes
  - To show that the new assay has good agreement with the reference assays
  - To show that the assay performs similarly with different types of specimen
- Premises of methods comparison studies
  - A linear relationship between the two assays
  - LOD, dynamic range have to be already established
  - Appropriate transformation to normalize the data
- Analysis
  - To detect constant bias and proportional bias

11

## Constant Bias



# Proportional Bias



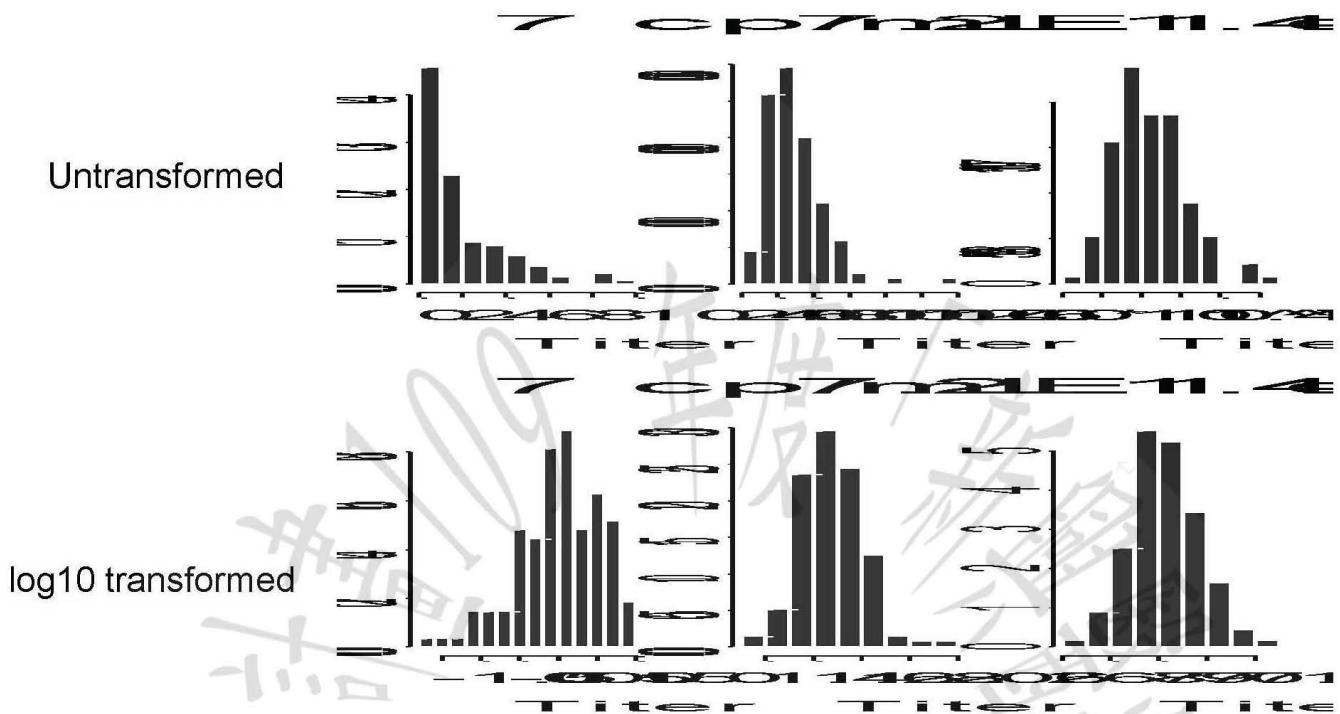
13

## Data Characteristics

- A wide dynamic range
- Skewed distribution (non-normal): typically log<sub>10</sub> transformation for the data
- Heteroscedasticity: variance is higher at higher titer levels
  - log<sub>10</sub> transformation may not achieve homogeneity in variance (variance at lower end may increase)
  - Other transformation:  $\log\left(x + \sqrt{x^2 + \kappa}\right)/2$

14

**log10 transformation may remove some skewness**



15

## Statistical Methods

- Correlation coefficient
- Other coefficients
- t-test
- Bland-Altman plot
- Ordinary least squares regression
- Passing-Bablok regression
- Deming regression

16

# Correlation Coefficient (R or R<sup>2</sup>)

- Measures linear relationship between two assays
- Does not measure agreement: cannot detect constant or proportional bias
- Correlation coefficient can be artificially high for assays that cover a wide range: how high is high? 0.95? 0.99? 0.995?

17

## Sample Size Calculation

$$n = \frac{(z_{\alpha/2} + z_{1-\beta})^2}{[FZ(\rho_1) - FZ(\rho_0)]^2},$$

$$FZ(\rho) = \frac{1}{2} \ln \left[ \frac{1+\rho}{1-\rho} \right]$$

$\rho_0$ : correlation coefficient  
under the null

$\rho_1$ : correlation coefficient  
under the alternative

18

# Other Coefficients

- **Concordance coefficient (Lin, 1989)**
  - Measures the strength of relationship between two assays that fall on the 45° line through the origin
- **Gold-standard correlation coefficient (St.Laurent 1998)**
  - Measures the agreement between a new assay and a gold standard

$$\rho_C = \rho \times \frac{2\sigma_1\sigma_2}{\sigma_1^2 + \sigma_2^2 + (\mu_1 - \mu_2)^2}$$

$$X_i = G_i + \varepsilon_i$$

$$\rho_G = \frac{\sigma_G^2}{(\sigma_G^2 + \sigma_e^2)}$$

19

## Paired t Test

- Paired t-test on the difference in the measurements by two assays
- Can only detect constant bias
- Cannot detect proportional bias

# Paired t Test

New-Reference  $\sim N(\Delta, \sigma^2)$

$$H_0 : \Delta \geq \Delta_M \quad \text{vs.} \quad H_a : \Delta < \Delta_M$$

$$n = \frac{\sigma^2(z_\alpha + z_{1-\beta})^2}{(\Delta - \Delta_M)^2}$$

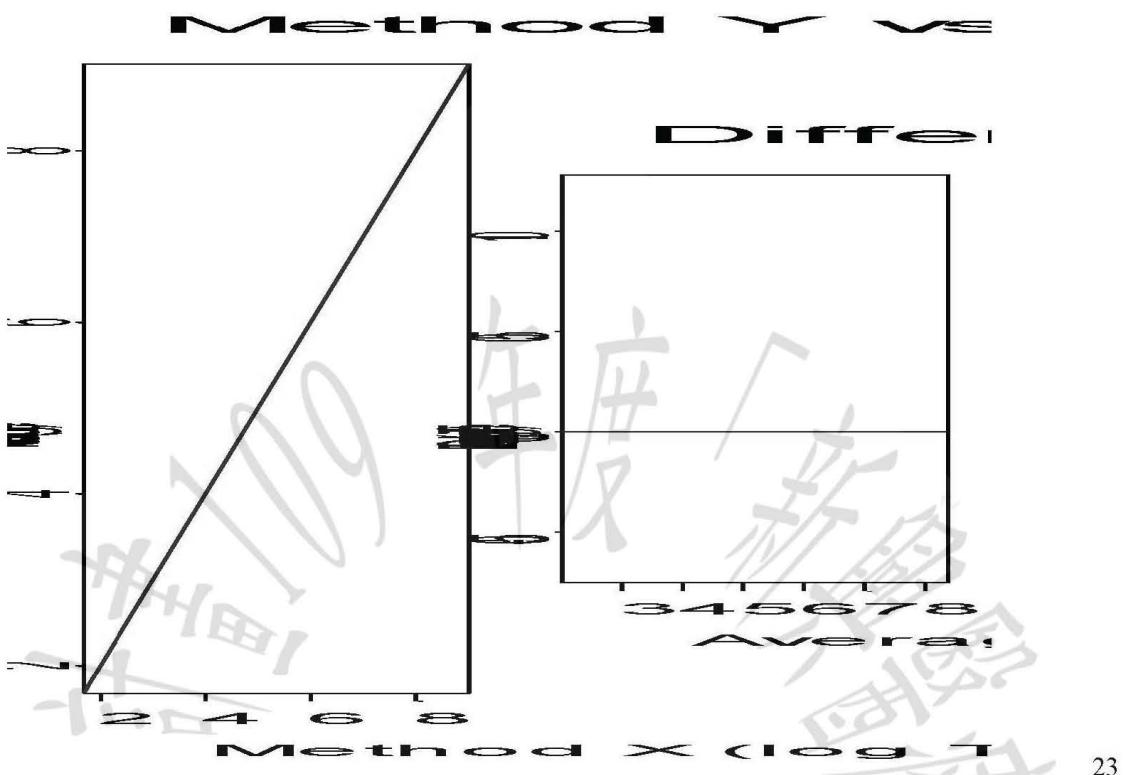
21

## Bland-Altman Graphical Analysis (Bland and Altman, 1986)

- Plot the Difference of the two assays ( $D = X - Y$ ) vs. the Average of the two assays ( $A = (X+Y)/2$ )
- Visually inspect the plot and see if there are any trends in the plot  $\rightarrow$  proportional bias
- Summarize the bias between the two assays by the mean, SD, 95% CI  $\rightarrow$  constant bias
- Modification: regress  $D$  with  $A$ , test if slope = 0 (Hawkins, 2002)

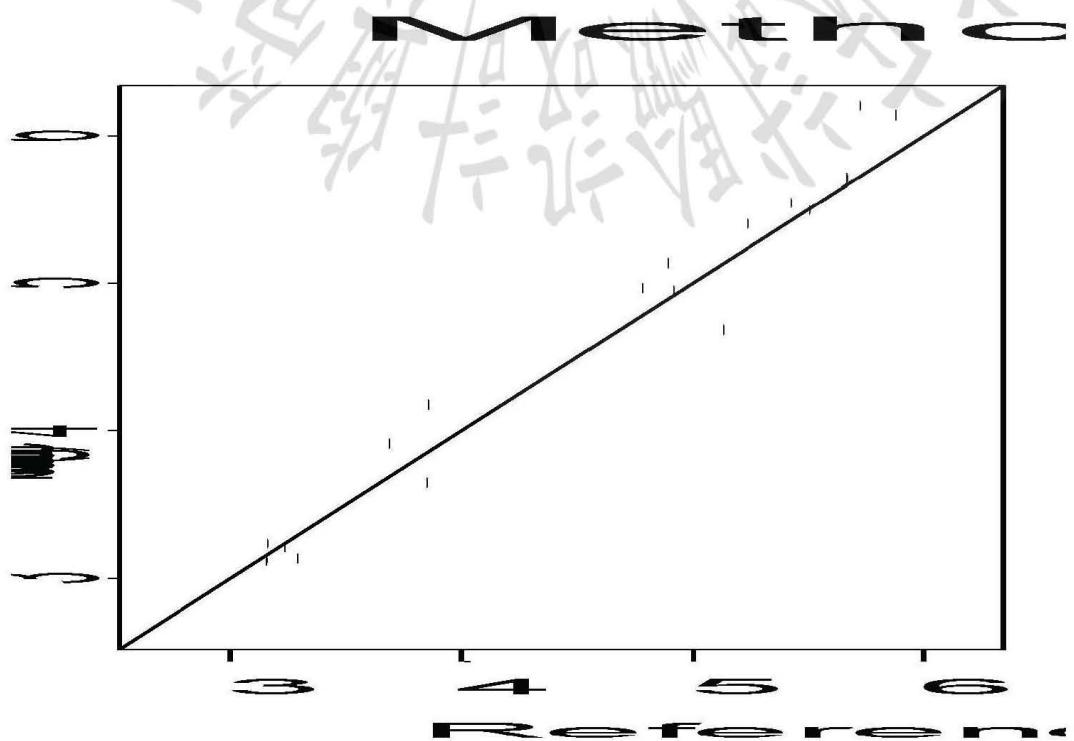
22

# Bland-Altman Plot



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## Methods Comparison for Two HIV-1 Assays

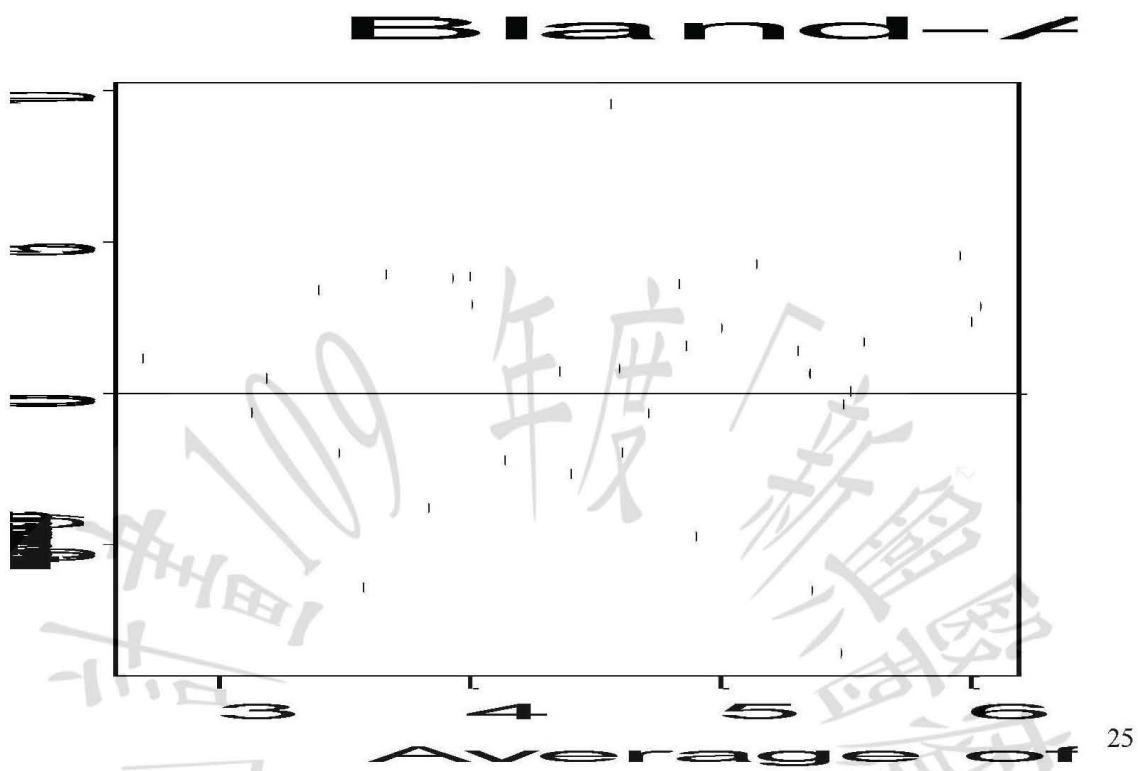


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# Bland-Altman Plot

(potential outliers in the data)



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## Methods for Agreement

- The agreement is often evaluated by using the Pearson correlation coefficient, the paired t-test, the least square analysis of slope ( $=1$ ) and intercept ( $=0$ ), none of these can fully assess the desired reproducibility characteristics

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# Methods for Agreement

- The Pearson correlation coefficient only measures precision of a linear relationship, not accuracy
- Both the paired t-test and least squares analysis can falsely reject (accept) the hypothesis of high agreement when the residual error is very small (large)

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## Lin's Concordance Correlation Coefficient

- CCC is based on the differences between the observations made by two observers on the same subject, and thus it evaluates the agreement between two readings by measuring the variation from the  $45^\circ$  line through the origin
- CCC includes components of both precision (degree of variation) and accuracy (degree of location or scale shift)

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## Lin's CCC

- $Y$  represents a measure from a candidate test or method and  $X$  represents the corresponding measure from the gold standard test or method
- $n$  observations ( $Y_k, X_k$ ) are selected from a bivariate population with means  $\mu_Y$  and  $\mu_X$ , variances  $\sigma^2_Y$  and  $\sigma^2_X$ , and correlation  $\rho$  (the Pearson correlation coefficient)

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## Lin's CCC

The degree of concordance between the two measures can be characterized by the expected value of their squared difference

$$E(Y - X)^2 = (\mu_Y - \mu_X)^2 + \sigma^2_Y + \sigma^2_X - 2\rho\sigma_Y\sigma_X$$

If every pair from the bivariate population is in exact agreement, the above expectation would be 0

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## Lin's CCC

Measures the strength of relationship between two assays that fall on the 45° line through the origin

$$\rho_C = \rho \times \frac{2\sigma_Y \sigma_X}{\sigma_Y^2 + \sigma_X^2 + (\mu_Y - \mu_X)^2}$$

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## Lin's CCC

$$\begin{aligned}\rho_C &= \rho \times \frac{2\sigma_Y \sigma_X}{\sigma_Y^2 + \sigma_X^2 + (\mu_Y - \mu_X)^2} \\ &= \rho \times \frac{2}{\frac{(\mu_Y - \mu_X)^2}{\sigma_Y \sigma_X} + \frac{\sigma_Y}{\sigma_X} + \frac{\sigma_X}{\sigma_Y}} \\ &= \rho \times \frac{2}{(v^2 + w + \frac{1}{w})}\end{aligned}$$

$$= \rho \times C_b,$$

$$C_b = 2(v^2 + w + w^{-1})^{-1}, \quad v^2 = (\mu_Y - \mu_X)^2 / (\sigma_Y \sigma_X), \quad w = \sigma_Y / \sigma_X$$

# Lin's CCC

- The measure of accuracy ( $C_b$ ) evaluates how far the best-fit line deviates from the concordance line in the scale of 1 (no deviation) to (but not including) 0 (very far away)
- The quantity  $w$  is the scale shift
- The quantity  $v$  is the location shift relative to scale

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## Hypothesis Testing

The null and alternative hypotheses are

$$H_0 : CCC \leq CCC_0 \text{ vs. } H_a : CCC > CCC_0$$

Under  $H_a$ , we expect  $CCC = CCC_1$ .

Let

$$\lambda_0 = \frac{1}{2} \ln\left(\frac{1+CCC_0}{1-CCC_0}\right), \quad \lambda_1 = \frac{1}{2} \ln\left(\frac{1+CCC_1}{1-CCC_1}\right).$$

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# Sample Size Calculation

## The power

$$1 - \beta = 1 - \Phi \left[ \frac{(\lambda_0 - \lambda_1) + \Phi^{-1}(1-\alpha)\sigma_0}{\sigma_1} \right]$$

$$\sigma_0 = \sigma(\rho_0, v_0, w_0, n)$$

$$\sigma_1 = \sigma(\rho_1, v_1, w_1, n)$$

$$\begin{aligned}\sigma(\rho, v, w, n)^2 &= \frac{1}{n-2} \left\{ \frac{(1-\rho^2)CCC^2}{(1-CCC^2)\rho^2} + \frac{2CCC^3(1-CCC)v^2}{\rho(1-CCC^2)^2} \right. \\ &\quad \left. - \frac{CCC^4v^4}{2\rho^2(1-CCC^2)^2} \right\}\end{aligned}$$

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## Example

The screenshot shows the nQuery software interface. The main window displays the following input parameters:

Input Item	Value ( $K_0$ )	Value ( $K_1$ )
Correlation coefficient, $\rho$	0.970	0.980
Mean difference, $(\mu_1 - \mu_0)/\sigma_0$	0.150	0.050
Scale ratio, $\sigma_1/\sigma_0$	1.150	1.050
Null hypothesis concordance, $K_0$	0.894	
Variance term, $V(K_0)$	0.643	
Alternative concordance, $K_1$		0.955
Variance term, $V(K_1)$		0.804

The right side of the screen shows a help panel with the following information:

- correlation coefficient which is lowered by differences in the means or scales of the two measurements.**
- Suggestion:** Enter the value you wish to disprove.
- Acceptable Entries:**  $-1 < K_0 < 1, K_0 \neq K_1$
- Aid:** Select Compute Effect Size from the Assistants menu or click on the button to compute a value for  $K$  and its variance term based on the correlation coefficient, and differences in means or scale of the measurements.

At the bottom of the interface, there is a status bar with the text "nQuery" and a date/time stamp "下午 11:23 2020/9/13".

# Example

The screenshot shows the nQuery software interface with the following details:

**AOT2-1 / Test for Lin's Concordance Correlation Coefficient assuming Continuous Outcome**

	1	2	3	4	5	6	7	8
Test Significance Level, $\alpha$	0.025							
1 or 2 Sided Test?	1	2	2	2	2	2	2	2
Null hypothesis concordance, $K_0$	0.894							
Variance term, $V(K_0)$	0.643							
Alternative concordance, $K_1$	0.955							
Variance term, $V(K_1)$	0.804							
Power (%)	80							
n	30							

Calculate sample size  Run ▶

**AOT2S-1**

	Correlation coefficient, $p$	0.970	0.980
Mean difference, $(\mu_1 - \mu_2)/\sigma_0$	0.150	0.050	
Scale ratio, $\sigma_1/\sigma_0$	1.150	1.050	
Null hypothesis concordance $K_0$	0.894		

Output Specify Multiple Factors AOT2S-1

Test for Lin's Concordance Correlation Coefficient assuming Continuous Outcome-1 | Test Significance Level,  $\alpha: 0.025000000$

在這裡輸入文字來搜尋

Help Notes

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下午 11:26 中 2020/9/13

# Diagnostic Accuracy

# Assumption

The true condition status is one of two mutually exclusive states: “the condition is present (e.g., disease)” or “the condition is absent (e.g., non-disease).”

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## A Basic 2x2 Count Table

	Test Positive (T=1)	Test Negative (T=0)	Total
True Present (D=1)	$s_1$	$s_0$	$n_1$
True Absent (D=0)	$r_1$	$r_0$	$n_0$
Total	$m_1$	$m_0$	$N$

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# Sensitivity

- The sensitivity ( $Se$ ) of a test is its ability to detect the condition when it is present
- $Se = P(T=1|D=1)$
- $Se = s_1/n_1$

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# Specificity

- The specificity ( $Sp$ ) of a test is its ability to exclude the condition in patients without the condition
- $Sp = P(T=0|D=0)$
- $Sp = r_0/n_0$

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# A 2x2 Probability Table

	Test Positive (T=1)	Test Negative (T=0)	Total
True Present (D=1)	$Se = s_1/n_1$	$FNR = s_0/n_1$	1
True Absent (D=0)	$FPR = r_1/n_0$	$Sp = r_0/n_0$	1

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## Mammogram Results

Cancer Status	Positive	Negative	Total
Present	29	1	30
Absent	19	11	30
Total	48	12	60

$$Se = 29/30 = 0.967$$

$$Sp = 11/30 = 0.367$$

$$FPR = 19/30 = 0.633$$

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# IDx-DR (DEN 180001)

- 一項多中心隨機對照前瞻性臨床研究比較IDx-DR與眼科醫師判讀糖尿病視網膜病變的能力
- 專家確認了198名患有輕度以上糖尿病視網膜病變(More than mild DR, mtmDR)，IDx-DR系統能夠正確地識別198名參與者中的173人患有mtmDR，其靈敏性高達87%
- 專家確認的621名無mtmDR進展參與者中，IDx-DR識別了556名參與者，特異性為90%

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## General Confidence Interval

A  $100(1-\alpha)\%$  confidence interval for  $\theta$  (sensitivity or specificity) is

$$(\hat{\theta} - z_{1-\alpha/2} \sqrt{\hat{\text{Var}}(\hat{\theta})}, \hat{\theta} + z_{1-\alpha/2} \sqrt{\hat{\text{Var}}(\hat{\theta})})$$

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# Required Sample Size

- Sensitivity:  $n$  will be the number of required patients with the condition
- Specificity:  $n$  will be the number of required patients without the condition

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## Hypothesis Testing

The null and alternative hypotheses are

$$H_0 : \theta \leq \theta_0 \text{ vs. } H_a : \theta > \theta_0$$

Under  $H_a$ , we expect  $\theta = \theta_1$ .

$$n = \frac{[Z_{1-\alpha} \sqrt{\theta_0(1-\theta_0)} + Z_{1-\beta} \sqrt{\theta_1(1-\theta_1)}]^2}{(\theta_1 - \theta_0)^2}$$

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# Example

Under null,  $Se_0 = 0.85$

Under alternative,  $Se_1 = 0.90$

$\alpha = 0.025$ , power=80%

We can derive that  $n=362$  with condition.

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Thanks for your attention!

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