醫材臨床試驗之法規遵循與研究倫理

工研院生醫所 商業發展組/法規事務部

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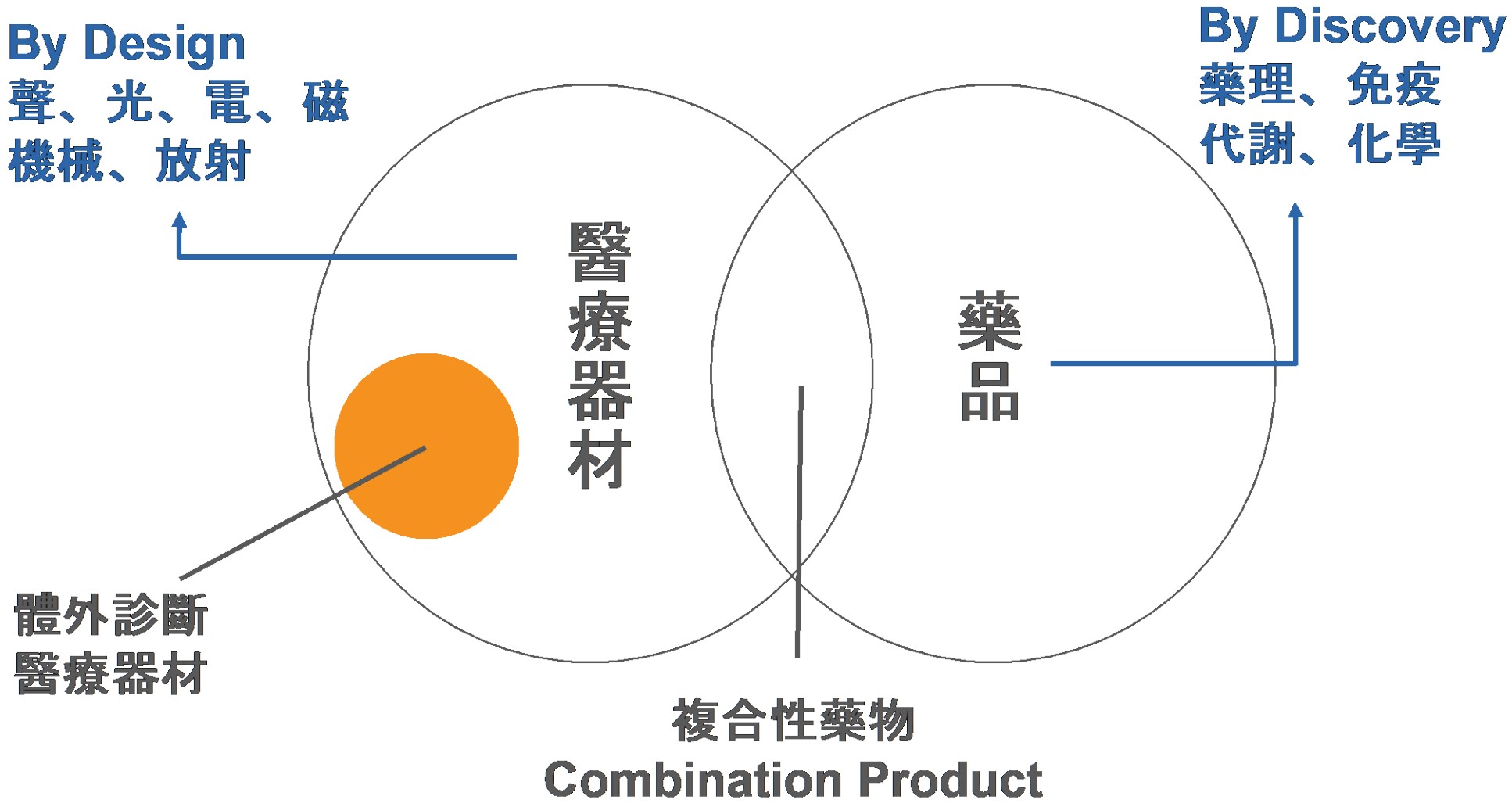
醫療器材 vs 藥品


By Design
聲、光、電、磁
機械、放射
By Discovery
藥理、免疫
代謝、化學
醫療器材
藥品
體外診斷
醫療器材
複合性藥物
Combination Product

醫療器材分類-TFDA vs US FDA

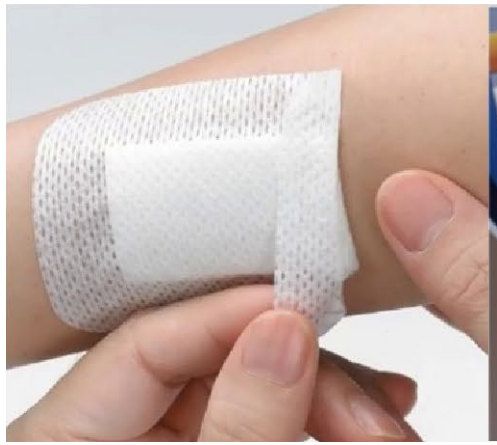
TFDA 分類代碼	FDA CFR 21 Parts	分類類別
A	862	臨床化學及臨床毒理學 Chemistry、Toxicology
B	864	血液學及病理學 Hematology、Pathology
C	866	免疫學及微生物學 Immunology、Microbiology
D	868	麻醉學 Anesthesiology
E	870	心臟血管醫學 Cardiovascular
F	872	牙科學 Dental
G	874	耳鼻喉科學 Ear, Nose, and Throat
H	876	胃腸病科學及泌尿科學 Gastroenterology and Urology
I	878	一般及整型外科手術 General and Plastic Surgery
J	880	一般醫院及個人使用裝置 General Hospital
K	882	神經科學 Neurology
L	884	婦產科學 Obstetrical and Gynecological
M	886	眼科學 Ophthalmic
N	888	骨科學 Orthopedic
O	890	物理醫學科學 Physical Medicine
P	892	放射學科學 Radiology

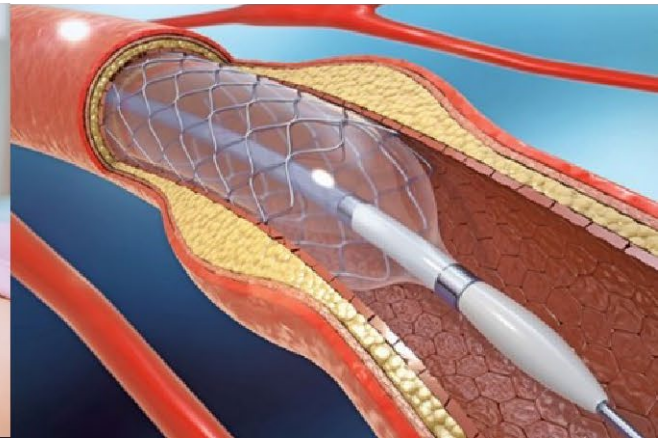
醫療器材依風險等級管理

Class 1 → 2 → 3 [TFDA, US FDA]

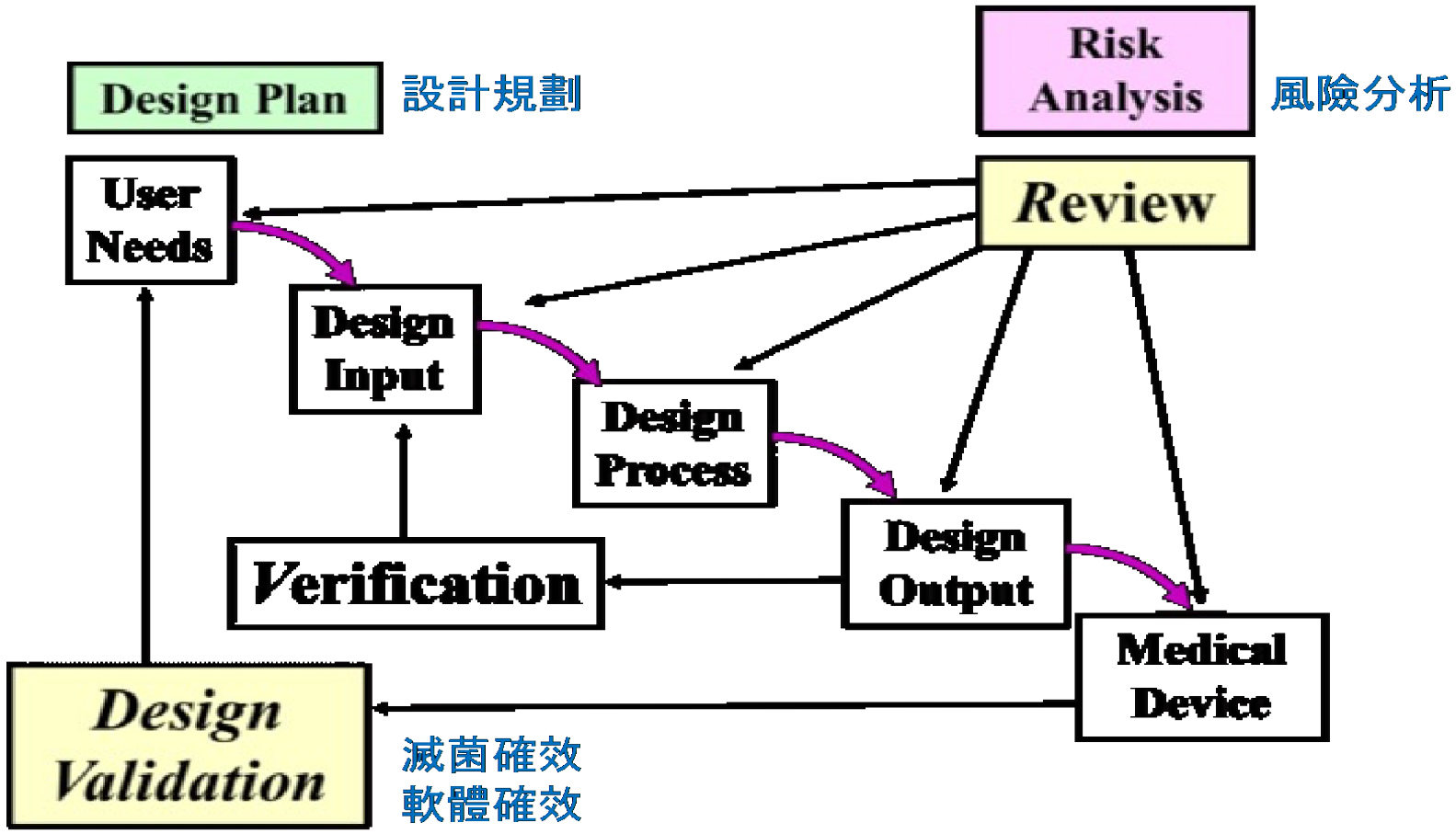
Class I → IIa、IIb → III [EU]

低風險 高風險

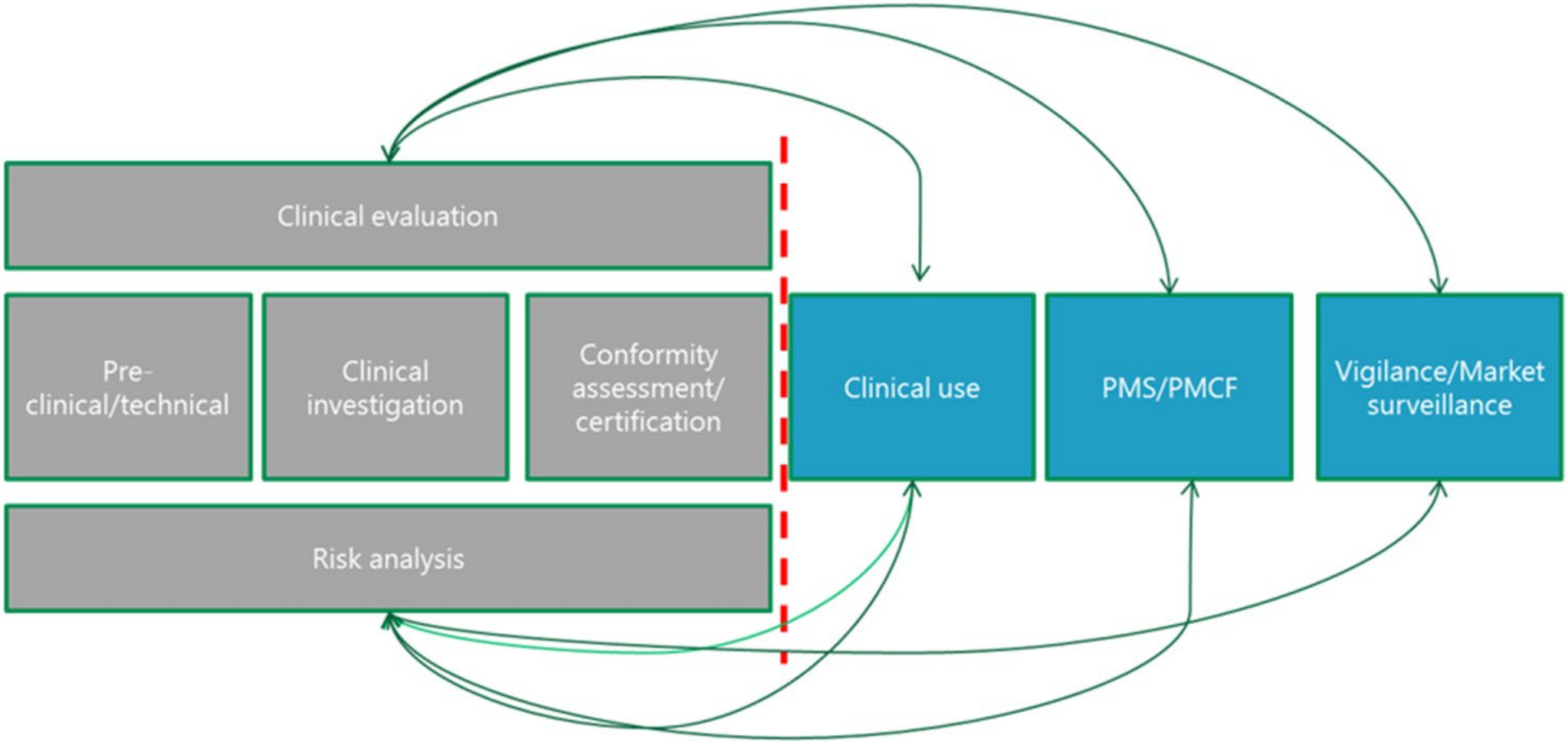




醫療器材設計開發程序

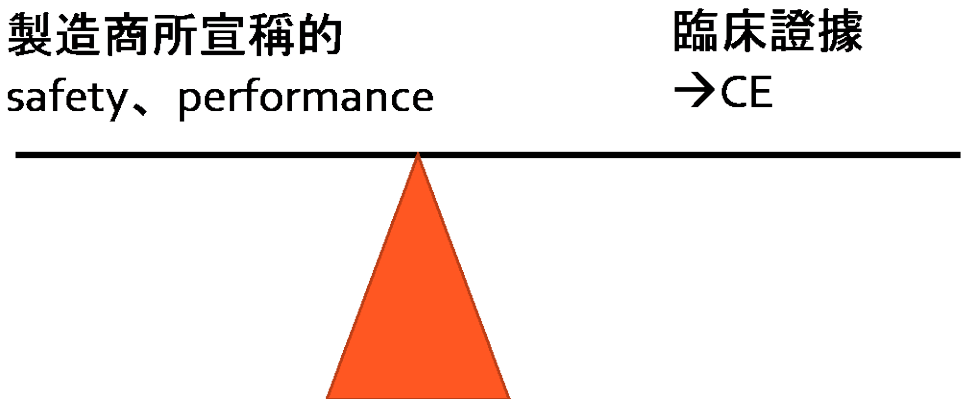

Design Plan
設計規劃
Risk Analysis
風險分析
User Needs
Review
Design Input
Design Process
Verification
Design Output
Medical Device
Design Validation
滅菌確效
軟體確效
臨床試驗
人因工程/可用性..

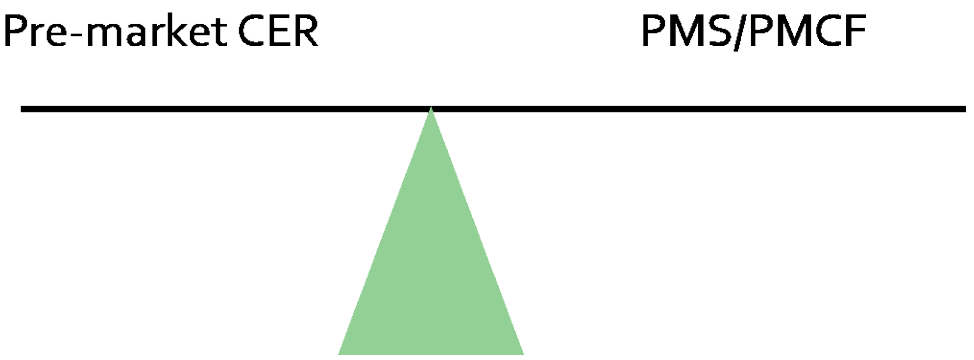
醫療器材生命週期管理概念



Ex. 歐盟的臨床要求文件

- 安全性及臨床效能摘要(Summary of Safety and Clinical Performance, SSCP)
- **臨床評估(Clinical Evaluation)**
- 上市後臨床追蹤(Post market Clinical Follow-up, PMCF)
- 臨床試驗(Clinical Investigations)

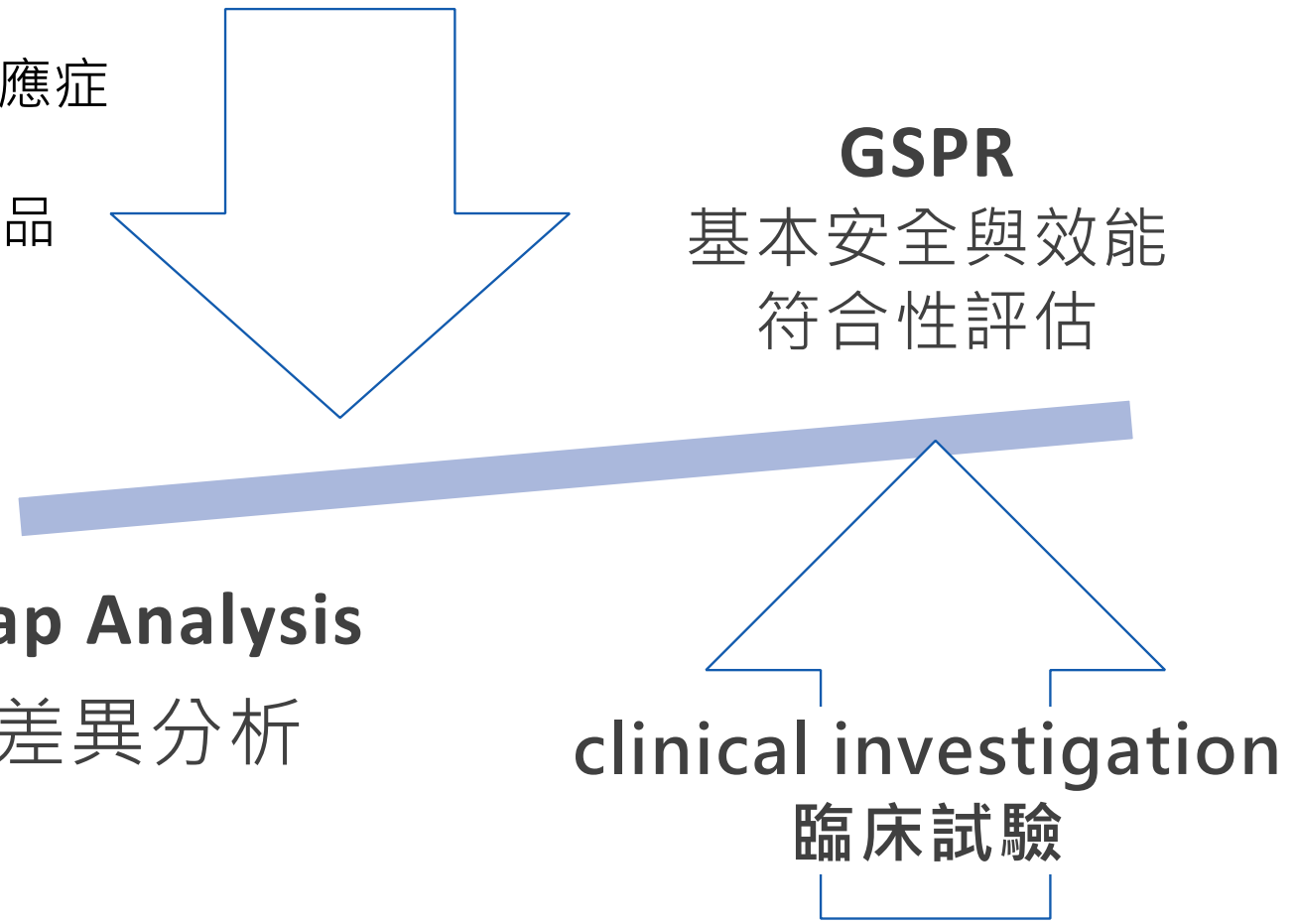




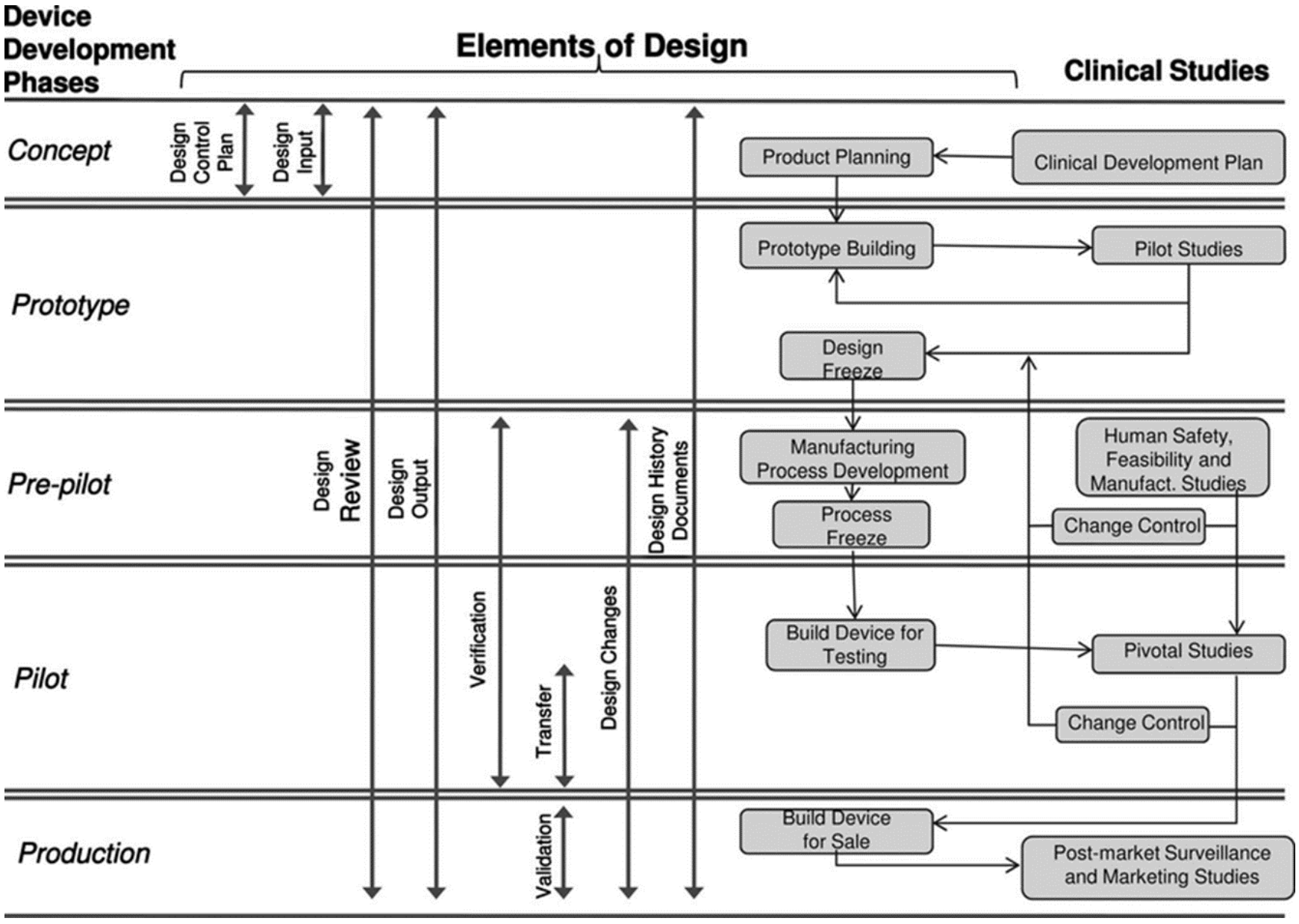

Clinical Evidence
· 臨床證據
· 具有代表性意義，可證明產品之臨床評估結果
Clinical Evaluation
· 臨床評估
· 運用臨床資料進行安全、有效及臨床效益之評估
Clinical Data
· 臨床數據
· 臨床試驗、科學文獻、上市後追蹤
可信度
眾多的研究結果彙總出一個總結
使用方法學、系統化、合理地持續收集評價、分析
彙整

何時該進行臨床試驗?

- 新技術、無類似品
- 新臨床使用/宣稱適應症
- 臨床資料不足
- 植入式、高風險產品
- 利益/風險評估

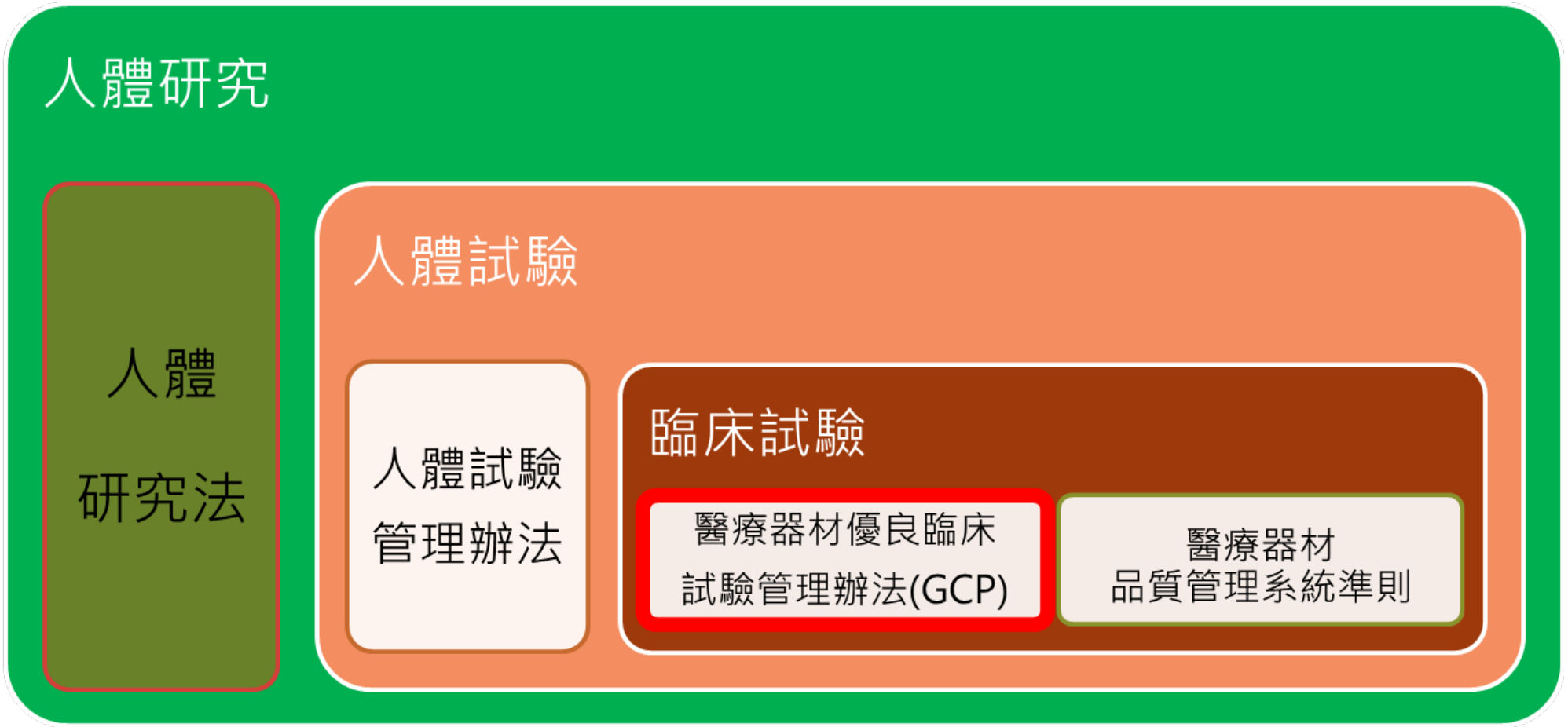


Clinical Development Plan



醫療器材臨床試驗法規

醫療器材臨床試驗相關法規



醫療器材管理法

第四章【醫療器材臨床試驗之管理】

第37條

- 臨床試驗機構或試驗委託者發起醫療器材臨床試驗，應申請中央主管機關核准後，始得為之。但無顯著風險經中央主管機關公告者，不在此限。
- 臨床試驗機構執行前項試驗，應善盡醫療上必要之注意，除情況緊急者外，應先取得受試者之同意。
- 前二項醫療器材臨床試驗之管理範圍、作業規範、申請程序、審查基準、利益迴避、資訊揭露、監督管理、查核、受試者同意書應記載內容及其他應遵行事項之辦法，由中央主管機關定之。⇨ GCP

臨床試驗重要考量

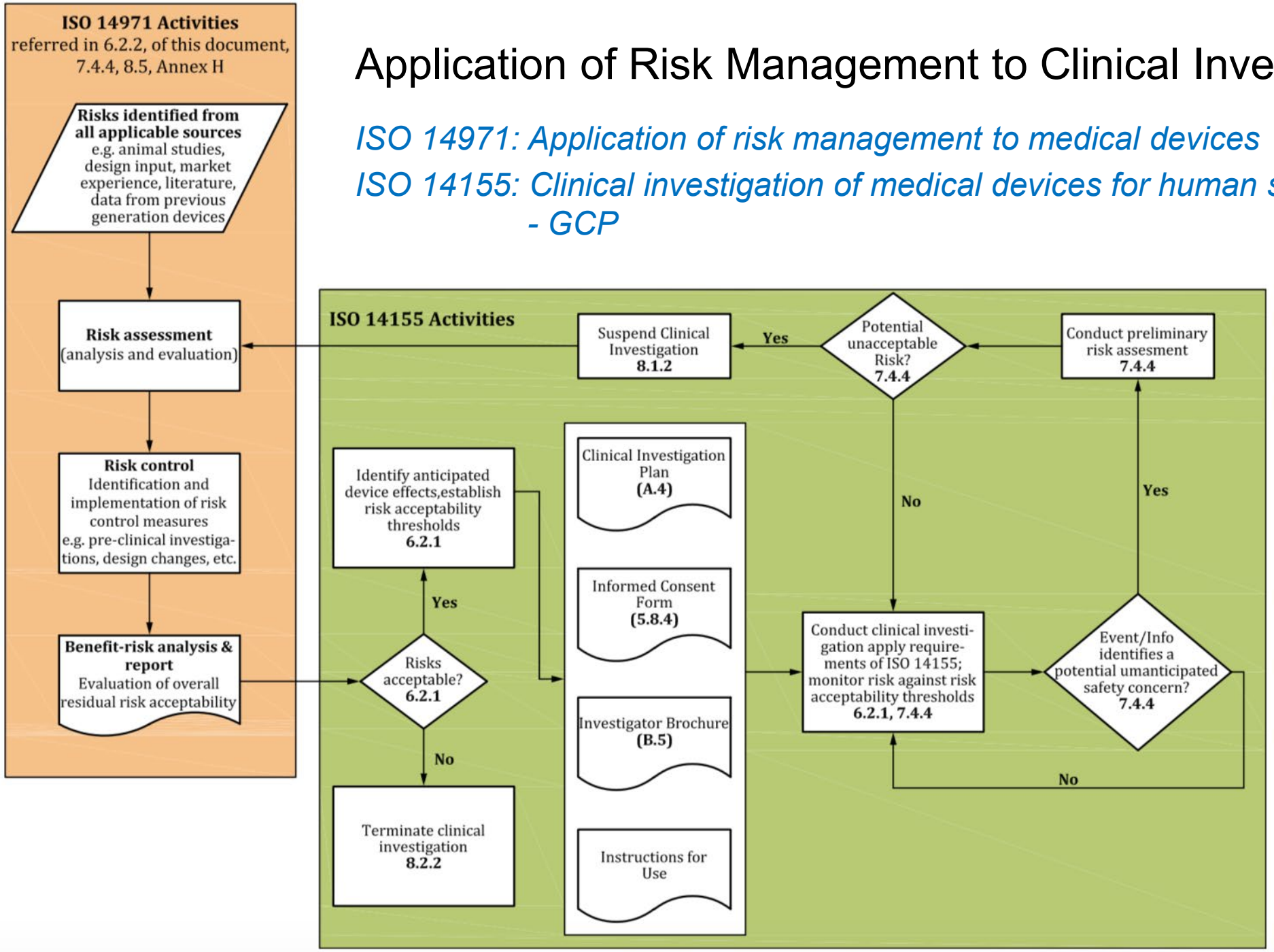
臨床試驗規劃-專案管理

- Specific for Medical Device
- Regulation & harmonized standards:
  - ISO 14155:2020、ICH E6、Domestic regulation (ex.醫療器材優良臨床試驗管理辦法)
- Covering the whole stages of clinical trial
- Ethical Principles – Declaration of Helsinki
- Risk Analysis & Evaluation
- Concept of Quality Management

Application of Risk Management to Clinical Investigations

ISO 14971: Application of risk management to medical devices

ISO 14155: Clinical investigation of medical devices for human subjects - GCP



【醫療器材優良臨床試驗管理辦法】

第一章　總則

第1條

本辦法依醫療器材管理法（以下簡稱本法）第三十七條第三項規定訂定之。

第2條

本辦法用詞，定義如下：

一、受試者：指參與臨床試驗而接受試驗用醫療器材或作為試驗對照之個人。

二、易受傷害群體：指因年齡、智能或身體（生理）狀況缺乏充分決定能力，或因所處環境、身分或社會經濟狀況而容易遭受不當影響、脅迫或無法以自由意願作決定者。

三、試驗主持人：指臨床試驗機構執行臨床試驗之負責人。

四、試驗委託者：指臨床試驗之發起及管理者。

五、受託研究機構：指接受試驗委託者委託，執行試驗委託者有關臨床試驗之全部或一部業務。

六、試驗偏離：指未依臨床試驗計畫書規範執行之偏差情形。

七、不良事件：指受試者參加臨床試驗所發生，與試驗用醫療器材間不以具有因果關係為必要之不良情事。

八、醫療器材不良反應：指與試驗用醫療器材有關之不良事件。

九、嚴重不良事件：指受試者發生下列情事之一：

（一）死亡。

（二）危及生命。

（三）暫時或永久性失能。

（四）受試者之胎兒或嬰兒先天性畸形。

（五）需住院或延長住院。

（六）其他可能導致永久性傷害之併發症。

十、嚴重醫療器材不良反應：指與試驗用醫療器材有關之嚴重不良事件。

第3條

執行臨床試驗，應遵行下列規定：

一、符合赫爾辛基宣言之倫理原則。

二、符合科學原則。

三、符合風險最小化原則，對受試者侵害最小，並確保風險與利益相平衡。

四、經臨床試驗倫理審查委員會（以下簡稱審查會）核准。

五、徵求受試者同意。

六、保障受試者之自主權及隱私權。

第4條

試驗委託者應擬訂臨床試驗計畫，經審查會及中央主管機關核准後，始得執行。

試驗主持人及臨床試驗機構應依前項核准之計畫，執行臨床試驗。

第二章　試驗委託者

第5條

試驗委託者應訂定、執行及管理臨床試驗工作，並確保資料之完整性及受試者之權利、安全與福祉。

第6條

試驗委託者應完成試驗用醫療器材之下列臨床前研究，並以臨床前數據及臨床評估之結果，證明試驗設計之合理性：

一、產品設計。

二、安全性及功能性測試。

三、風險分析。

四、其他必要之臨床前研究。

第7條

試驗委託者應於中央主管機關公告指定之網頁，依第四條第一項核准後三十日內，登錄下列臨床試驗相關資料：

一、臨床試驗機構名稱。

二、試驗委託者名稱。

三、試驗主持人姓名。

四、臨床試驗名稱。

五、臨床試驗核准文號。

六、臨床試驗核准日期。

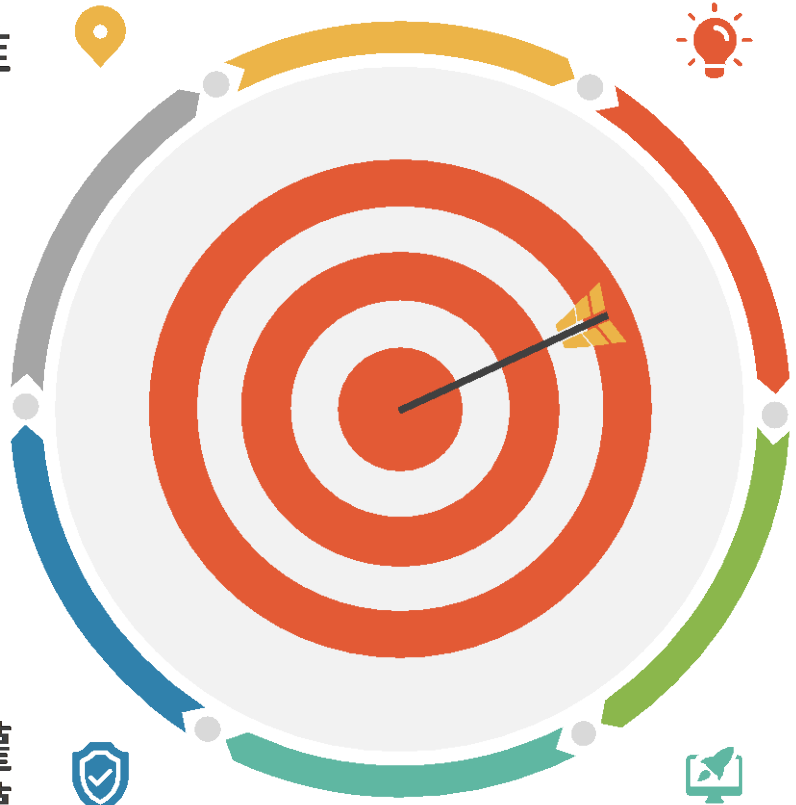
七、臨床試驗目的。

八、受試者納入、排除條件。

九、受試者人數。

十、試驗用醫療器材名稱。

臨床試驗原則



經IRB核准

赫爾辛基宣言之倫理原則

徵求受試者同意

符合科學原則

保障受試者自主權和隱私權

風險最小化，確保風險與利益平衡

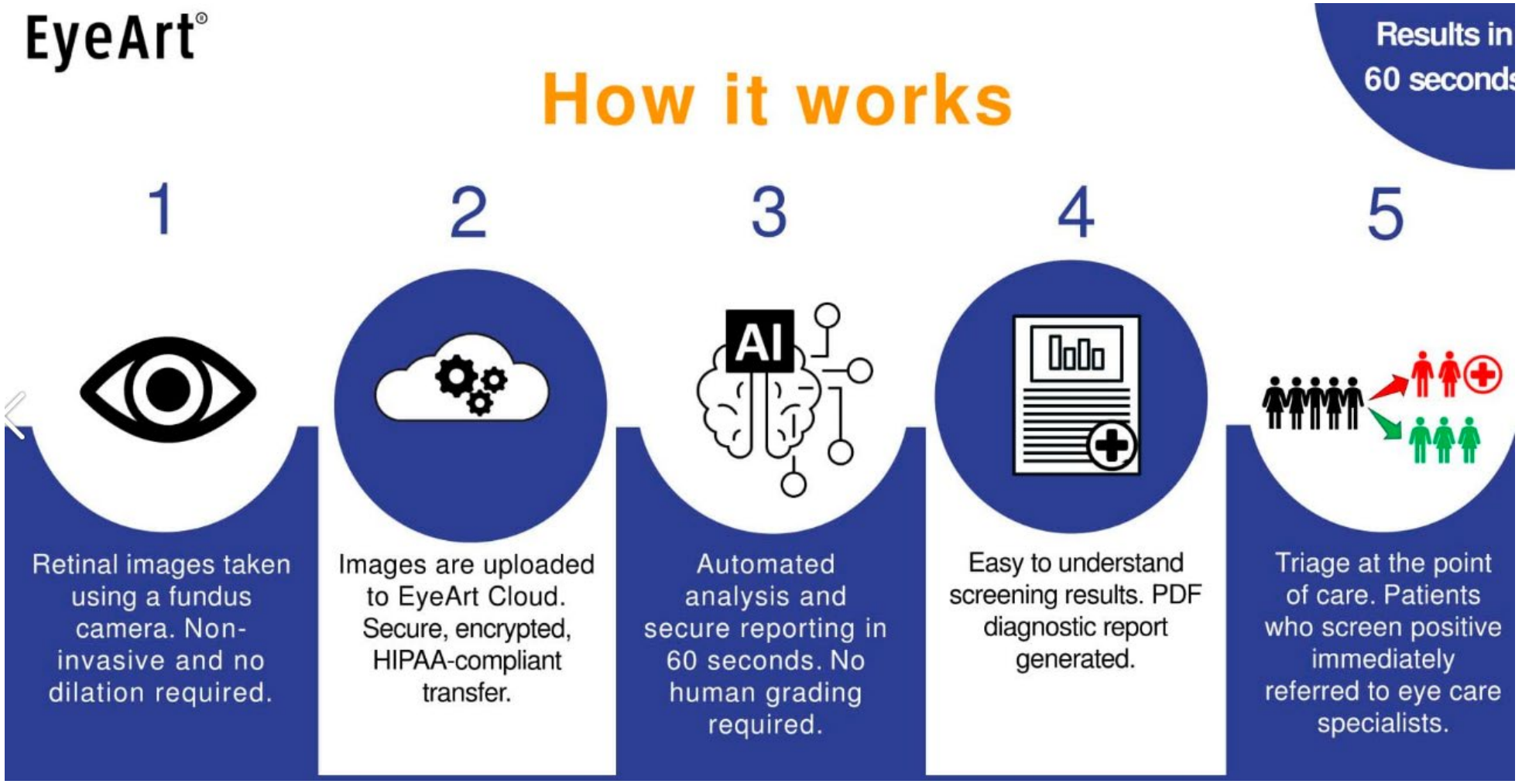
【醫療器材優良臨床試驗管理辦法 第三條】

試驗設計- 共通的考量原則

執行流程-遵循GCP


Approved Protocol
Investigator Selection
Approval Process
Statistical Analysis
Data Entered and Reviewed
Patient Recruitment and Participation
Presentation and Publication of report
Data Filed and Registration Obtained

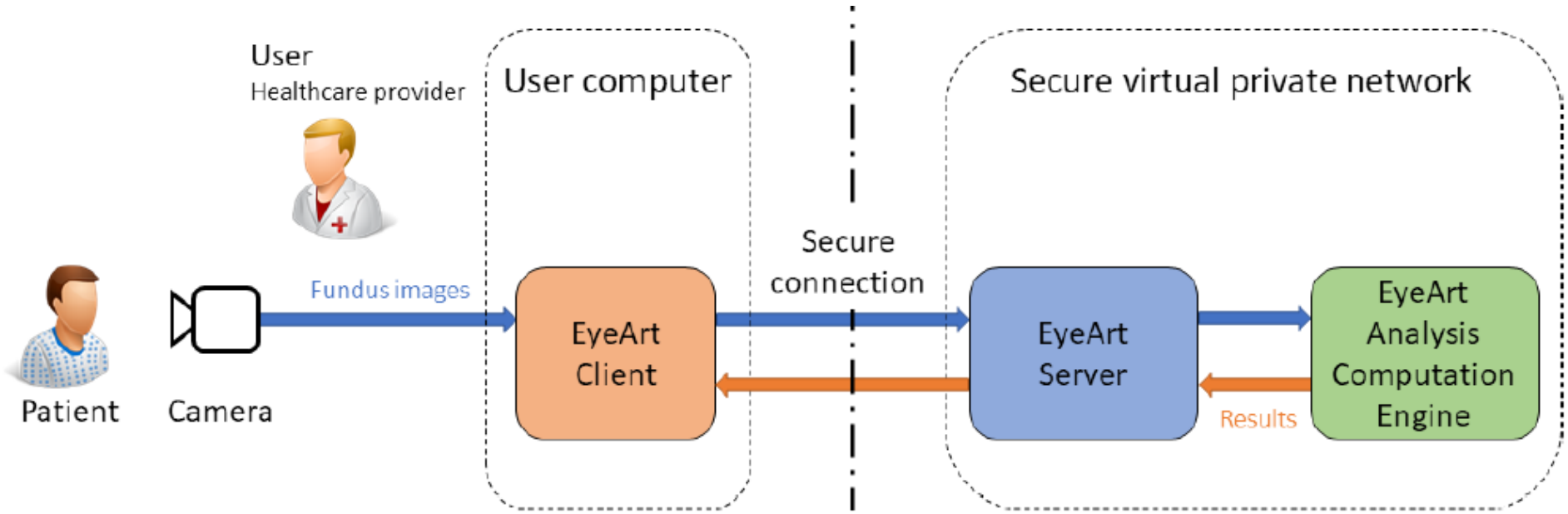
Case Study



Source: https://pdf.medicalexpo.com/pdf/eyenuk-inc/eyeart-presentation/122102-194313.html

Example-EyeArt (K200667)

EyeArt is indicated for use by healthcare providers to automatically detect more than mild diabetic retinopathy and vision-threatening diabetic retinopathy (severe non-proliferative diabetic retinopathy or proliferative diabetic retinopathy and/or diabetic macular edema) in eyes of adults diagnosed with diabetes who have not been previously diagnosed with more than mild diabetic retinopathy. EyeArt is indicated for use with Canon CR-2 AF and Canon CR-2 Plus AF cameras in both primary care and eye care settings.



Source: https://www.accessdata.fda.gov/cdrh_docs/pdf20/K200667.pdf

C. Non-clinical Testing

EyeArt (software version v2.1.0) was identified as having a major level of concern as defined in the FDA guidance document "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices."

Verification and validation activities at unit, integration, and system level were performed. In all instances, EyeArt functioned as intended and results observed were as expected (i.e. all specifications were met).

Comprehensive risk analysis has been conducted for EyeArt with identification and detailed characterization of the hazards including their causes and severity. Adequate risk control measures have been designed and implemented to mitigate all identified hazards to acceptable levels.

EyeArt also implements comprehensive cybersecurity measures for data confidentiality, data integrity, and data and service availability. Designed to meet industry standard cybersecurity best practices, EyeArt ensures that data remains secure (with encryption during transit and at rest) and private (with authentication and authorization protocols enabling access).

EyeArt has been designed to provide results that are aligned with the clinical practice recommendations for the ophthalmic care of patients with diabetes and has been developed in a clinically aligned framework.

A change protocol was also submitted, to allow for updates and improvements to EyeArt while ensuring that the changes do not introduce risks that adversely affect the safety and effectiveness of the device for its intended use.

D. Clinical Testing

1. Overview

EyeArt was validated in a prospective, multi-center pivotal clinical trial (ClinicalTrials.gov ID NCT03112005). A total of 942 subjects were consented of which 915 subjects met study eligibility criteria. The study was designed to support a *De Novo* submission since a predicate device did not exist when the EyeArt clinical trial was launched. To better align the analysis population with the proposed intended use population, analyses were presented on 655 participants after excluding subjects who did not meet certain additional prespecified criteria (e.g., subjects 21 years old or younger). The 655 participants were enrolled in the study at 11 US study sites that included primary care centers and general ophthalmology centers. The participants were further divided into two cohorts: one for subjects enrolled during a period of sequential enrollment only (235 subjects, with 45 enrolled at primary care sites and 190 enrolled at ophthalmology sites) and the second enrolled during a period when procedures allowed sequential as well as enriched enrollment (420 subjects, with 335 enrolled at primary care sites and 85 enrolled at ophthalmology sites). The performance of EyeArt was evaluated against a reference standard determined by experienced and certified graders at the Fundus Photography Reading Center (FPRC) per the Early Treatment for Diabetic Retinopathy Study severity (ETDRS) scale on dilated 4-wide field stereo fundus imaging by FPRC certified photographers.

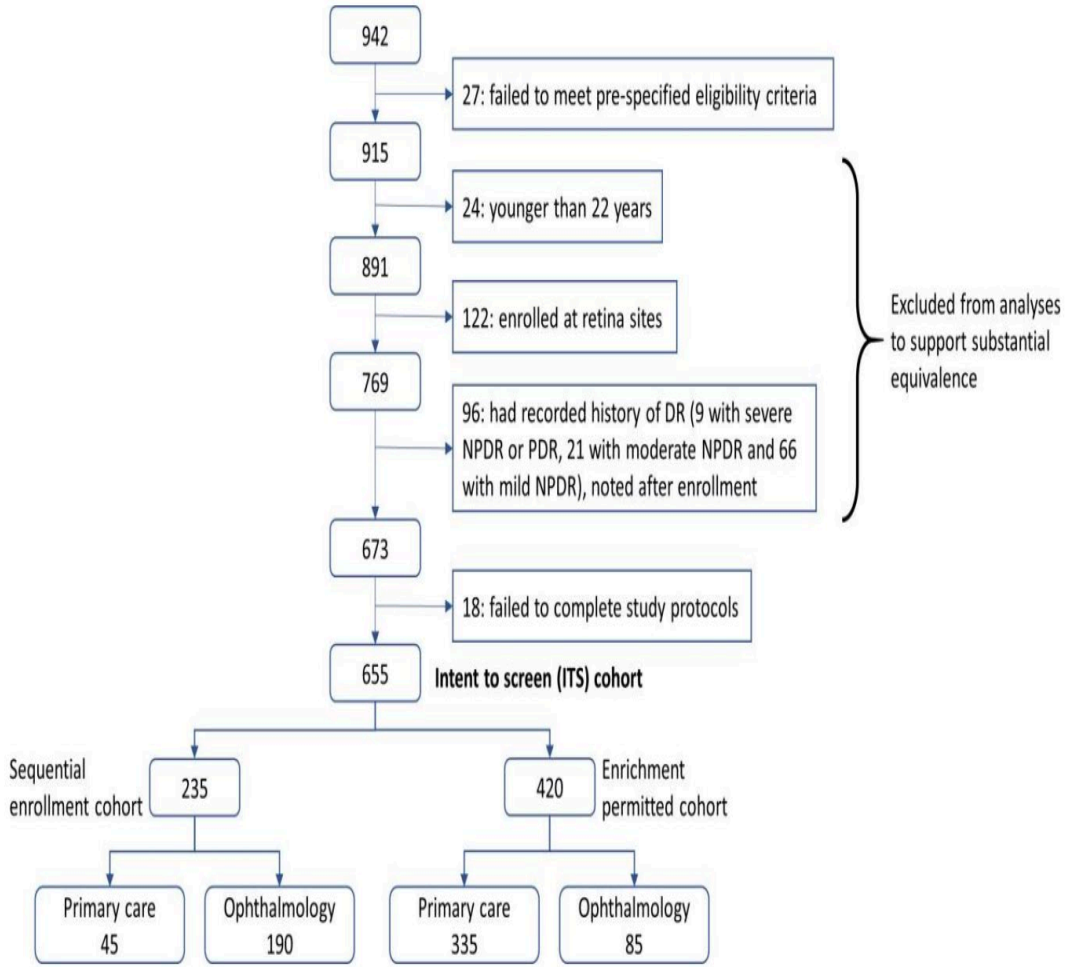
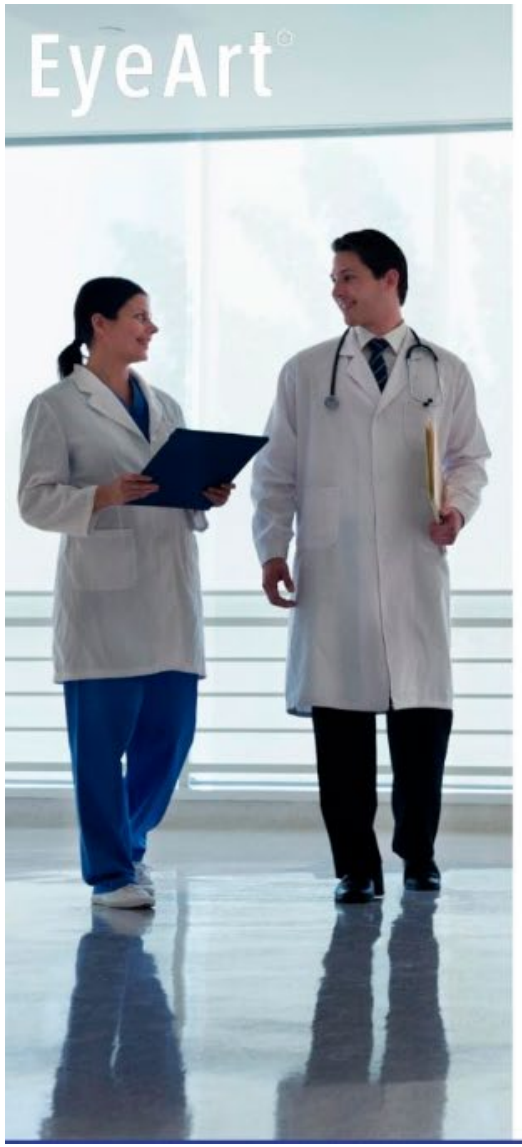


Figure 2: Subject disposition and cohorts used for analyses to support substantial equivalence.



Unparalleled clinical evidence

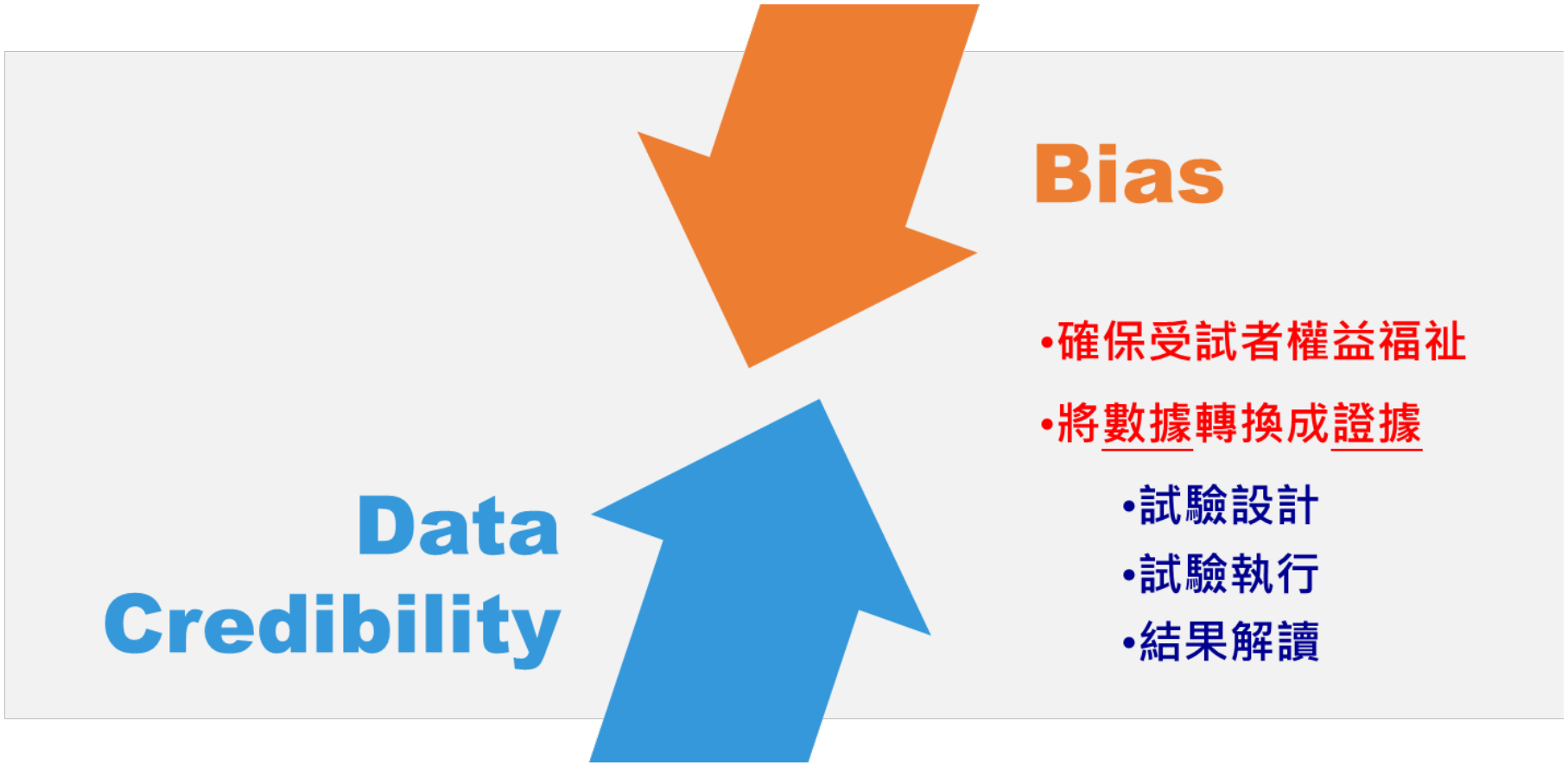
Technology proven in very large studies

101,710	20,258	91%
PATIENT VISITS	PATIENT VISITS	SENSITIVITY AND SPECIFICITY
USA STUDY	NHS UK STUDY	100K+ PATIENTS

- 91% sensitivity and 91% specificity in over 100K patient visits
- Results comparable to human graders in a fraction of the time and cost
- Compliant with internationally recognized clinical standards
- Available 24/7: can process exams in large batches

Source: https://pdf.medicalexpo.com/pdf/eyenuk-inc/eyeart-presentation/122102-194313.html

[結論] 臨床試驗重要考量



謝謝您的聆聽!