CT 01: 臨床試驗概論

Introduction to Clinical Trials

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Biostatisticians' Salary I

- Clinical Trials = Biostatisticians' Major Job
  - Design
  - Analysis

Biostatisticians' Salary II

- 2017 world: master biostatistics 55, 333—121,011
- US: Annual Income (US dollars):
  - Level I = $65,759-$84,332 (median = $75,367)
  - Level II = $90,098-$112,549 (median = $100,066)
  - Level III = $125,349-$151,050 (median = $135,862)

Biostatisticians' Salary III

- Hourly (US dollars):
  - Level I: $32-$41 (median = $36)
  - Level II: $43-$54 (median = $48)
  - Level III: $60-$73 (median = $65)

Statistics = Biostatistics = Data Science

- Tradition: focus on inference.
- Modern: design, collection, management visualization, exploration, analysis, report.

Textbook And References

- Textbook:
  - Friedman, Furberg & DeMets, (2015), Fundamentals of Clinical Trials, 5th ed.
- References:
  - Piantadosi (2017), Clinical Trials, 3rd ed.
  - Chow & Liu, (2014), Design and analysis of Clinical Trials, 3rd ed.
  - Cook & DeMets, (2009), Introduction to Clinical Trials.
  - Misc ...

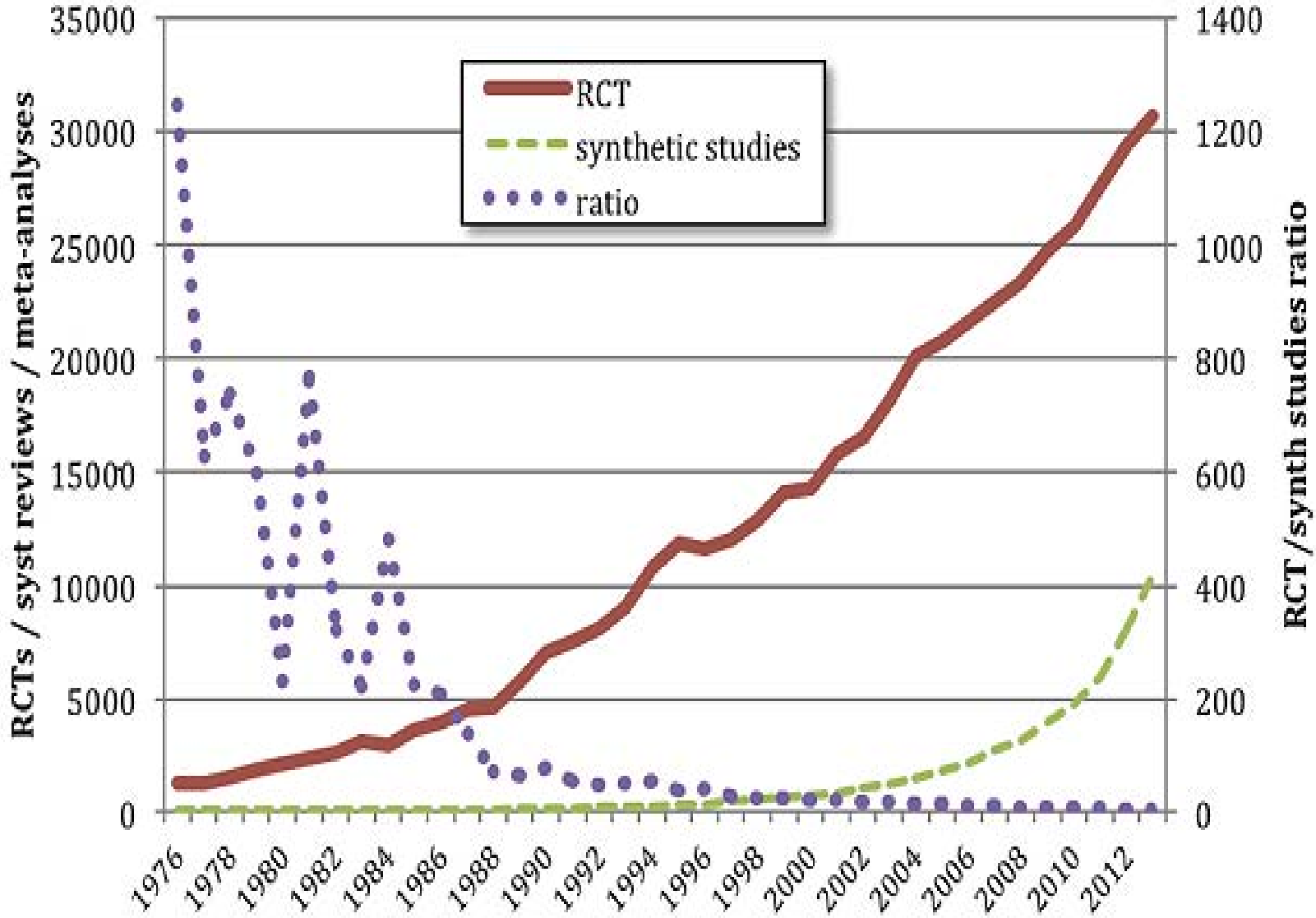

圖 1: 臨床試驗研究發表數量

Biostatisticians' Major Job = Clinical Trials I

- Communicate in English!
- Communicate in English!
- Communicate in English!

Biostatisticians' Major Job = Clinical Trials II

- Communicate in English!
- Communicate in Chinese!
- Communicate to Physicians/Researchers!

Clinical Trials

- Design
- Analysis

Scandal of Poor Medical Practice I

- Doctors use
  - wrong treatment,
  - right treatment wrongly, ...
- Unprofessional!
- Unethical!
- Unacceptable!

(Altman, BMJ, 1994.)

Scandal of Poor Medical Practice II

- Researchers (Biostatisticians) use
  - wrong techniques,
  - right techniques wrongly,
  - misinterpret results,
  - report results selectively,
  - cite literatures selectively,
  - draw unjustified conclusions, ...
- Unprofessional!
- Unethical!
- Unacceptable!

(Altman, BMJ, 1994.)

MOST IMPORTANT!

- Clinical Trials is Conducted by Law!

行政院衛福部法規 (多如牛毛) I

法規隨時在改變! (專業人士才有收入!)

- 醫療法
- 藥品優良臨床試驗規範
- 藥品查驗登記審查準則
- 醫療機構人體試驗委員會組織及作業準
- 體細胞治療人體申請與操作規範
- 藥物安全監視管理辦法
- 嚴重藥物不良反應通報辦法
- 藥物委託製造及檢驗作業準則
- 藥品生體可用率及生體相等性試驗基準
- 臨床試驗報告之格式及內容基準

行政院衛福部法規 (多如牛毛) II

- 新醫療技術 (含新醫療技術合併新醫 療器材) 人體試驗申請與審查作業程序
- 藥品臨床試驗申請須知
- 臨床試驗基準
- 藥品非臨床試驗安全性規範
- 藥品非臨床試驗優良操作規範
- 藥品查驗登記審查準則
- ...

醫療法: 第 8 條

- 本法所稱 人體試驗, 係指醫療機構依醫學理論於人體施行新醫療技術, 藥品 或 醫療器材 之試驗研究.

醫療法實施細則: 第 2 條 I

- 本法第八條所稱 新醫療技術, 指下列各款情形之一:
  1. 以藥品或醫療器材以外之物質, 植入或移植人體施行治療, 其安全或療效未經證實者.
  2. 以新程序或新方法施行者.
  3. 其他在國外已施行於人體, 中央主管機關認在國內有施行人體試驗之必要, 並經公告者.

醫療法實施細則: 第 2 條 II

- 本法第八條所稱 新藥品, 指下列各款情形之一:
  - 新成分, 新療效複方或新使用途徑之藥品.
  - 其他在生產國已核准使用於人體之藥品,
    中央主管機關認在國內有施行人體試驗之必要, 並經公告者.

醫療法實施細則: 第 2 條 III

- 本法第八條所稱 新醫療器材, 指下列各款情形之一:
  - 新原理, 新結構, 新效能或新材料之醫療器材.
  - 其他在生產國已核准使用於人體,
    中央主管機關認在國內有施行人體試驗之必要, 並經公告者.

藥品優良臨床試驗規範: 第一二條

- 臨床試驗/研究 (Clinical Trial/Study):

  任何在人身上執行的研究, 用來發現或證明

  - 研究用藥品在臨床, 藥理與/或其他藥效學作用;
  - 與/或確認研究用藥品的不良反應;
  - 與/或探討研究用藥品的吸收, 分佈, 代謝, 與排泄,
  - 以確認其安全性與/或療效.

  臨床試驗與臨床研究為同義字.

Overview Clinical Studies

- Observational (prospective, retrospective, cross-sectional)
- Experimental

What is a Clinical Trial?

A clinical trial is defined as a prospective study comparing the effect and value of intervention(s) against a control in human beings.

Clinical Trials I

- Prospective (not retrospective)
  - therapeutic
  - preventive
  - diagnostic
  - . . .

Clinical Trials II

- Intervention/Equipment
  - drug
  - exercise
  - education
  - behavior
  - device
  - diagnostic procedure
  - . . .

Clinical Trials III

- Control: Similar Baseline
  - no intervention control
  - historical control
  - placebo control
  - active control (current standard treatment)

▶ Early phase studies may be controlled or uncontrolled.

Clinical Trials IV

Humans (not Animals) as Experiment Unit

- ethics
- informed consent

Clinical Trials V

- Evaluation of the effect
  - efficacy (explanatory)
  - effectiveness (pragmatic)
  - safety
  - quality of life
  - cost-effectiveness

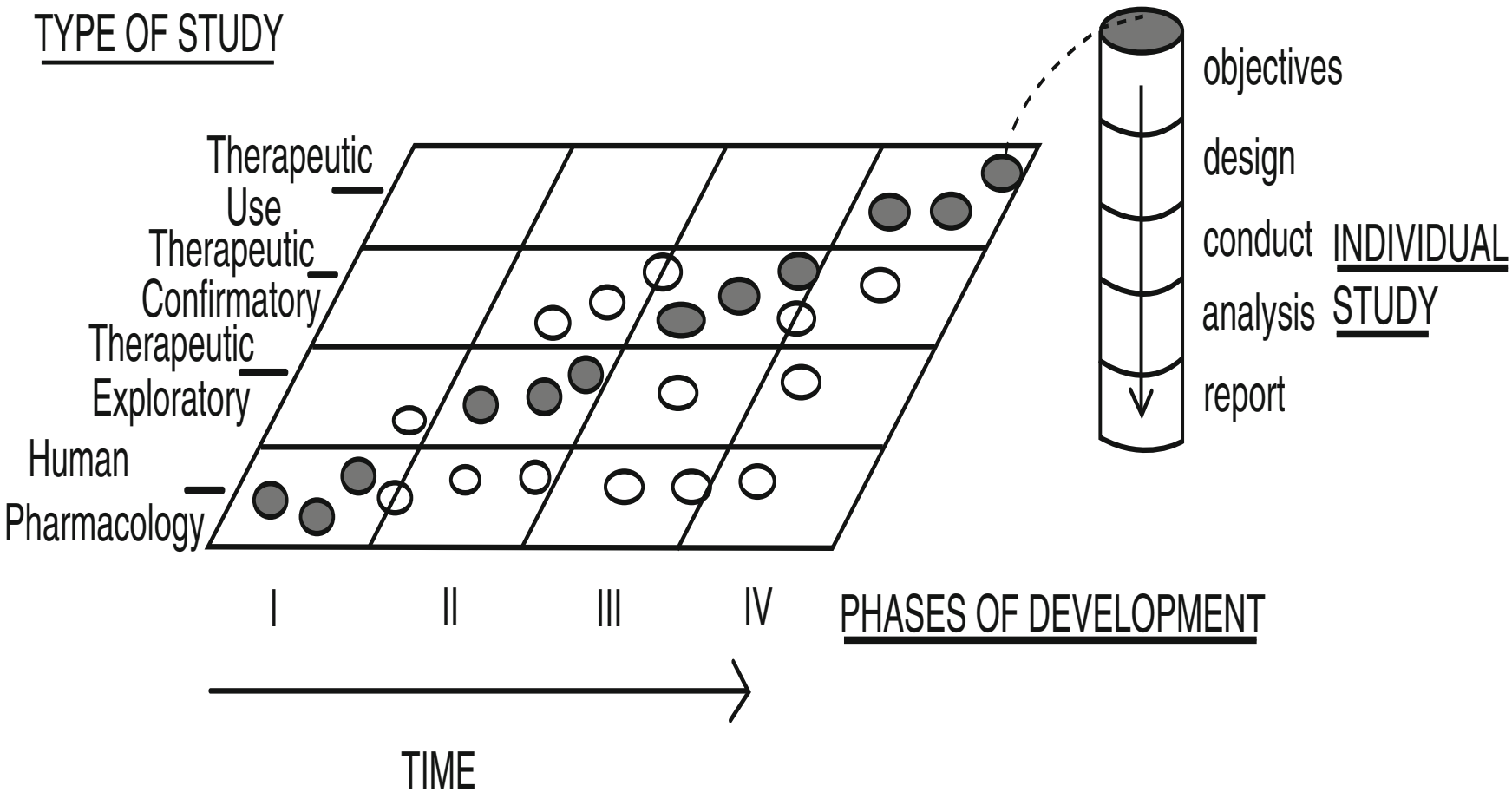

圖 2: Clinical Trials: Traditional Classification

Clinical Trials: Traditional Classification

- Phase I
- Phase II
- Phase III
- Phase IV

Phase I = Dose Finding (DF)

- Determine safe dosage range & identify AE
- Dose-finding: maximum tolerated dose (MTD)
- First time in human
- Small group = 30 subjects
- Normal volunteers, patients failed by the existing therapeutics
- Pharmacokinetics = body affects a drug
- Pharmacodynamics = drug affects a body
- Clinical Pharmacology and Toxicity
- Dose-Escalation & Evaluate Safety
- Several months

Phase II Trials: Safety and Efficacy Studies (SE)

- Estimate of the probability of success in phase III.
- Success depends on a variety of factors:
  - estimate/confirm treatment beneficial and adverse effects
  - determine feasibility
  - estimate event rates of the target population
- Further evaluate safety + AE (adverse effects)
- intermediate group = 25-300 patients with disease
- Not comparative (II, IIa) vs. comparative (IIb)
- Several months to 2 years
- No adequate power to evaluate primary outcome(s)

Phase III Trials: Comparative Treatment

- Confirmatory Trials
- Randomized Controlled Trials (RCT)
- Large group = patients with disease
- Compare effectiveness and safety +AE
- Estimate treatment effects
- 1 to 10 years

Phase IV Trials: Expanded Safety (ES)

- Post-marketing studies
- Surveillance trial
- Estimate the frequency of long-term (uncommon) adverse events, toxicity, or drugs interactions.
- Device: implanted for the whole life
- COX-2 (arthritis): increase cardiovascular events
- Thiazolidinediones (DM): increase heart failure

Mixed/Hybrid Types of Trials

- Phase o Trials
- Phase I/II Trials
- Phase IIa/IIb Trials
- Phase II/III Trials
- Phase IIIb Trials

Clinical Trials Classification I

- Exploratory vs. Confirmatory
- Explanatory vs. Pragmatic
- Single Center vs. Multi-Center
- Small vs. Large
- Superiority vs. Noninferiority/Equivalence
- Screening vs. Diagnostic
- Therapeutic vs. Preventive
- Single Dose vs. Multiple Doses
- Institutional vs. Community

Clinical Trials Classification II

- Single Drug vs. Add-on
- Single Drug vs. Combination Drugs
- Standard vs. Adaptive/Sequential
- Standard vs. Clustered
- Medical vs. Surgical
- Population vs. Personalized/Individualized
- Efficacy vs. Toxicity/Safety
- Vaccine, Gene Therapy
- Dose Response, Finding, Comparison

Disadvantages of RCTs

- Expensive
- Time consuming
- Can only answer a single question

So, why bother?

Reasons for doing RCTs

- 統計人員要求與堅持 (統計人員才有工作與高收入!)
- Required by FDA (and others) for new drugs and some devices
- Only study design that can prove causation
- Most influential to clinical practice

Equipoise

- Question important and not answered
- Evidence of benefit, not conclusive

What's Special about RCTs?

- Randomization - equipoise
- Intervention - relatively safe
- Placebo - acceptable clinical option
- Measurements - safe and tolerable
- Interim monitoring - careful and timely

Retrolental Fibroplasia Lesson I

- Premature newborns, lung dysplasia, need High dose O_2
- What is the exact high dose? 100% or lower?
- Search for a cause in 1953:
  - High dose O_2: 479 infants benefit
  - High dose O_2: 147 infants blind with retrolental fibroplasia
- 1953 NIH Conference - Two opinions
  1. Need O_2 controlled study
  2. No need, already convicted

Retrolental Fibroplasia Lesson II

- 1953 RCT began, planned 1,000 infants
- 800 infants

O_2 Concentration	Blindiness
Standard 100%:	23%
Reduced 50%:	7%

- 1954 published, high O_2 practice stopped.
- Epidemic subsided.
- However, 10,000 infants had been blinded.

(Silverman, 1977, Scientific American)

Corticosteroid and Traumatic Brain Injury

- Small trials: inclusive
- Meta-analysis: no differences
- One large trial:
  - 14-day mortality: steroid 18% higher
  - 6-month mortality: 15% higher

β-Carotene and Cancer

- β-carotene would prevent cancer?
  1. Epidemiological studies strongly suggested.
  2. High β-carotene in fruits and vegetables lower cancer risk
  3. Pathophysiology
- Clinical trials needed to establish cause and effect

RCT: Vitamin E and β-carotene I

- The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study

RQ:	Do vitamin E and beta-carotene prevent lung cancer in smokers?
Design:	RCT, factorial, 6.1 years
Subjects:	29,133 smokers, Finnish men aged 50-69
Intervention:	1. α-tocopherol, 50 mg/day vs. placebo
(factorial)	2. β-carotene, 20 mg/day vs. placebo
Outcome:	Lung cancer incidence

RCT: Vitamin E and β-carotene II

- Incidence Rate (per 10,000 person years)
- Relative Risk: β-carotene vs. control

	Incidence Rate		
Outcome	β-Carotene	Control	RR
Lung Cancer Cases	56.3	47.5	1.19
Lung Cancer Deaths	35.6	30.8	1.16

RCT: Vitamin A and β-carotene I

- The Beta-Carotene and Retinol Efficacy Trial (CARET)

RQ:	Do vitamin A and beta-carotene prevent lung cancer in smokers?
Design:	RCT, factorial, 4.0 years
Subjects:	18,314 men, smokers or asbestos workers
Intervention:	1. Retinol (25,000 IU) vs. placebo
(factorial)	2. β-carotene (15 mg) vs. placebo
Outcome:	Lung cancer incidence

RCT: Vitamin A and β-carotene II

- Relative Risk (95% CI), treatment vs. placebo

	Lung Cancer	Death (all causes)
All Subjects	1.28 (1.04-1.57)	1.17 (1.03-1.33)
Asbestos-exposed	1.40 (0.95-2.07)	1.25 (1.01-1.56)
Smokers	1.23 (0.96-1.56)	1.13 (0.96-1.32)

圖 3: Today's Random Medical News

Protocol: Guidance/Regulation References

- Good Clinical Practice: Consolidated Guidance (ICH-E6)
  - Section 6, Clinical Trial Protocol and Protocol Amendment(s)
  - Section 4.5, Compliance with Protocol

GCP Definition (GCP 1.44)

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial.

- The protocol should be
  - developed before the beginning of participant enrollment;
  - remain essentially unchanged except perhaps for minor updates.

Protocol 試驗計畫書

- 新醫療技術 (含新醫療技術合併新醫 療器材)
  人體試驗申請與審查作業程序
- 藥品優良臨床試驗規範 (準則)
- 醫療機構人體試驗委員會組織及作業準
- 臨床試驗報告之格式及內容基準
- . . .

藥品優良臨床試驗規範

第四四條, 試驗計畫書 (Protocol):

- 描述臨床試驗的目的, 設計, 方法, 統計考量, 與編制的文件.
  通常試驗計畫書亦提供試驗的相關背景與理論,
  也可能由其他參考資料提供.
  試驗計畫書這個名詞包括試驗計畫書變更.

藥品優良臨床試驗準則 第陸章: 臨床試驗計畫書 I

法規隨時在改變! (專業人士才有收入!)

- 一: 一般資訊 protocol cover sheet
- 二: 背景資訊 background/justification
- 三: 試驗目的 objectives
- 四: 試驗設計 study design and methods
- 五: 受試者的納入及退出 inclusion/exclusion/withdraw
- 六: 給藥及處置方式 study drugs
- 七: 療效評估 measurements and observations
- 八: 安全性評估 monitoring and management

藥品優良臨床試驗準則 第陸章: 臨床試驗計畫書 II

- 九: 統計方法 statistical methods
- 十: 原始資料的直接檢視
- 十一: 品質管制 quality control
- 十二: 倫理考量 ethic consideration
- 十三: 資料處理及保存 data management and storage
- 十四: 財務及保險 finance and insurance
- 十五: 發表著作原則 publication principle
- 十六: 附錄 appendix

Protocol I

▶ Standard Protocol Items:

Recommendations for Interventional Trials (SPIRIT 2013 Statement)

- A. Background of the study
- B. Objectives
  - 1. Primary question and response variable
  - 2. Secondary questions and response variables
  - 3. Subgroup hypotheses
  - 4. Adverse effects

Protocol II

- C. Design of the study
  - 1. Study population
    - (a) Inclusion criteria
    - (b) Exclusion criteria
  - 2. Sample size assumptions and estimates
  - 3. Enrollment of participants
    - (a) Informed consent
    - (b) Assessment of eligibility
    - (c) Baseline examination
    - (d) Intervention allocation (e.g., randomization method)
  - 4. Intervention(s)
    - (a) Description and schedule
    - (b) Measures of compliance
  - 5. Follow-up visit description and schedule
  - 6. Ascertainment of response variables

Protocol III

- (a) Training
- (b) Data collection
- (c) Quality control

- 7. Assessment of Adverse Events
  - (a) Type and frequency
  - (b) Instruments
  - (c) Reporting
- 8. Data analysis
  - (a) Interim monitoring, including data monitoring committee role
  - (b) Final analysis
- 9. Termination policy

Protocol IV

- D. Organization
  - 1. Participating investigators
    - (a) Statistical unit or data coordinating center
    - (b) Laboratories and other special units
    - (c) Clinical center(s)
  - 2. Study administration
    - (a) Steering committees and subcommittees
    - (b) Monitoring committee
    - (c) Funding organization

Protocol V

- Appendices
  - Definitions of eligibility criteria
  - Definitions of response variables
  - Informed Consent Form

Protocol: English Edition

- Update Laws, Regulations, Codes and Rules!
- See Textbooks!

Thanks!