Writing Clinical Research Protocols

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*What is a protocol?

- A detailed plan that sets for the study:
  - Objectives
  - Design
  - Methodology
  - Protocol- " …a complete written description of, and scientific rationale for, a research activity involving human subjects." (Protomechanics NIH)

- 3 general types of protocols:
  1. Retrospective review- usually with data
  2. Natural History study- may get tissue samples, DNA
  3. Interventional – Phase I/II, Phase III, Phase IV

*Who Reads Protocols?

- Keep the “audience” in mind:
  - Other physicians
  - Nurses/CRAs
  - IRB members
  - Scientific reviewers

- Why do we need a Protocol?
  - Scientific validity
  - Subject safety
  - Replicate the science if necessary
  - Regulatory requirements

*Parts of the Protocol

- Introduction/Abstract
- Objectives (including study schema)
- Background/Rationale
- Eligibility criteria
- Study design/methods (including drug/device info)
- Safety/adverse events
- Regulatory guidance
- Statistical section (including analysis and monitoring)
- Human subjects protection/informed consent

Adapted from:
Protomechanics: Chapter 1 (http://www.cc.nih.gov/ccc/protomechanics/),

CTEP Investigators' Handbook, 2002 (http://ctep.cancer.gov/forms/Hndbk.pdf)

*Parts of the Protocol

표 5.1. 신약 임상시험계획서에 수록되어야 할 내용

1. 임상시험의 명칭 및 단계
2. 임상시험의 실시기관명 및 주소
3. 임상시험의 책임자, 담당자 및 공동연구자의 성명 및 직명
4. 임상시험용 의약품등을 관리하는 약사의 성명 및 직명
5. 임상시험의 의뢰자명 및 주소
6. 임상시험의 목적 및 배경
7. 임상시험용 의약품등의 코드명이나 주성분의 일반명, 원료약품 및 그 분량, 제형 등
8. 대상질환
9. 피험자의 선정기준, 제외기준, 목표한 피험자의 수 및 그 근거

10. 임상시험의 기간
11. 임상시험의 방법 (투여 · 사용량, 투여 · 사용방법, 투여 · 사용기간, 병용요법 등)
12. 관찰항목 · 임상검사항목 및 관찰검사방법
13. 예측 부작용 및 사용상의 주의사항
14. 중지 · 탈락 기준
15. 효과 평가기준, 평가방법 및 해석방법(통계분석방법)
16. 부작용을 포함한 안전성의 평가기준, 평가방법 및 보고방법
17. 피험자동의서 양식
18. 피해자 보상에 대한 규약
19. 임상시험후 피험자의 진료 및 치료기준
20. 피험자의 안전보호에 관한 대책
21. 그 밖에 임상시험을 안전하고 과학적으로 실시하기 위하여 필요한 사항

임상시험 관련자를 위한 기본교재. 2006 Ministry of food and drug safety

*Title of a research project

- Accurate, short, concise
- Descriptive: should make the main objective clear, should mention the target population
- Key words: should contain key words for referencing
  - i.e.; TB in HIV – infected children

    -> Better: ‘Incidence of TB in HIV- infected children in North Uganda 2007-2008‘

Objectives/Background and Rationale

- Objectives should be stated clearly as hypotheses to be tested.
- Each objective should have a corresponding discussion in the statistical section.
- All protocols require a section detailing the scientific rationale for a protocol and the justification in medical and scientific literature for the hypothesis being proposed.
- Introductory section should be as succinct as possible and should be organized in a logical, sequential flow.

CTEP Investigators' Handbook, 2002 (http://ctep.cancer.gov/handbook/index.html)

*Writing Eligibility Criteria

- Eligibility criteria are the largest barrier to accrual to clinical trials
- Poorly written or poorly conceived criteria may undermine a trial's generalizability and scientific validity
- Eligibility criteria—stated as either exclusion or inclusion criteria—define and limit the kinds of patients that can participate in a clinical trial.
- Reasons for imposing eligibility criteria can include scientific rationales, safety concerns, regulatory issues, and practical considerations.

[1]*Fuks A, J Clin Epidemiol, 1998*
[2]*George SL, J Clin Oncol, 1996*

*Writing Eligibility Criteria

- Recommendations:
  - The number of eligibility criteria should be kept to a minimum.
  - Criteria should include only those absolutely necessary to ensure scientific validity and patient safety.
  - Eligibility criteria should be clearly defined and verifiable by an external auditor.

*Study Population

- Total number of subjects (including screen failures/subject withdrawals)
  - The number of eligibility criteria should be kept to a minimum
- Inclusion/Exclusion criteria
  - Age restrictions
  - Diagnostic methods (HGB $\geq$ 12) to determine eligibility
  - Pre-existing conditions
- Disallowed concomitant medications and/or treatment
- Inclusion of vulnerable populations (if applicable)
- Individual subject withdrawal criteria
  - Allowances for temporarily stopping drug/intervention
  - Dose Modifications
  - Non-compliance
- Eligibility criteria should be clearly defined and verifiable by an external auditor

*Sample Size

- The study is an experiment in people
- Need enough participants to answer the question
- Should not enroll more than needed to answer the question
- Sample size is an estimate, using guidelines and assumptions

*Study Design

- The study design section of the protocol should contain a stepwise description of all procedures required by the study.
- A good study design section includes sufficient information for the participating site to develop a comprehensive clinical pathway for study patients.

Study Design

- **Parts of the study design section may include:**
  - Initial evaluations
  - Screening tests
  - Required lab tests
  - Details of treatment and ancillary procedures
  - Agent information or device specifications
  - Dose scheduling and modification
  - Calendars

Adapted from: Protomechanics: Chapter 1 (http://www.cc.nih.gov/ccc/protomechanics/)

Drug/Device

- Drug preparation, administration, storage
- Dose modifications
- Device Implantation Procedures
- Required concomitant medications, if applicable
- Drug/Device accountability, retention, final disposition

*Endpoints

- **Identifiable change that shows the intervention did what it was supposed to do**
  - Primary Endpoint: measures the specific clinical effect the intervention is preventing/treating (i.e. survival, resolution of desease)
  - Surrogate endpoints: measures changes in symptom/biological indicator for the success of the intervention (i.e. T-cell count, radiographic imaging, etc.)
- **Should be Measurable**
- **Measures should be as objective as possible to avoid bias**
- **Should be feasible**

*Blinding

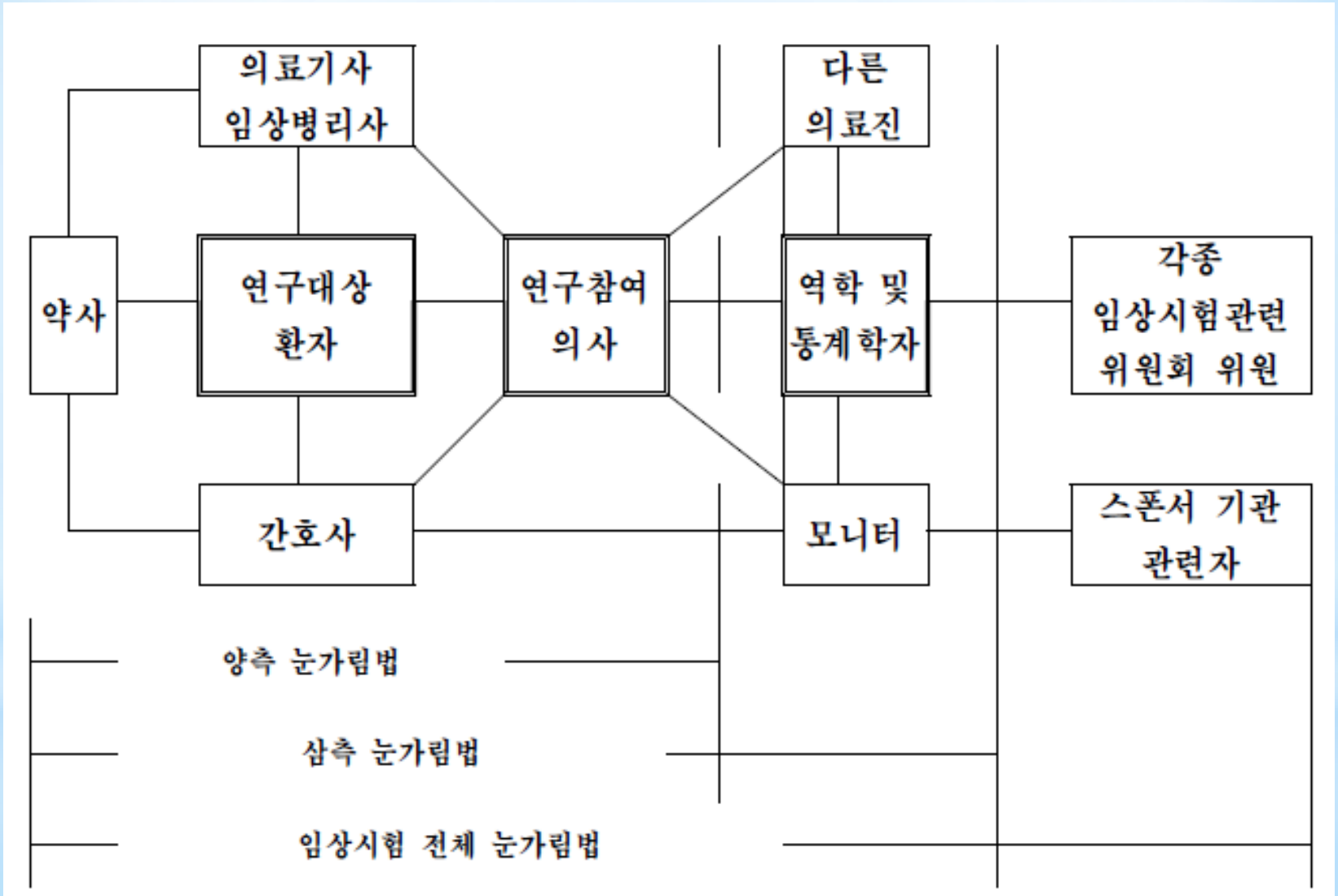
- **Single Blind**

  – subject doesn't know what treatment group they have been assigned

- Double Blind

  – subject and investigator don't know treatment assignments

*비교임상시험에서 눈가림법의 개념.



Randomization

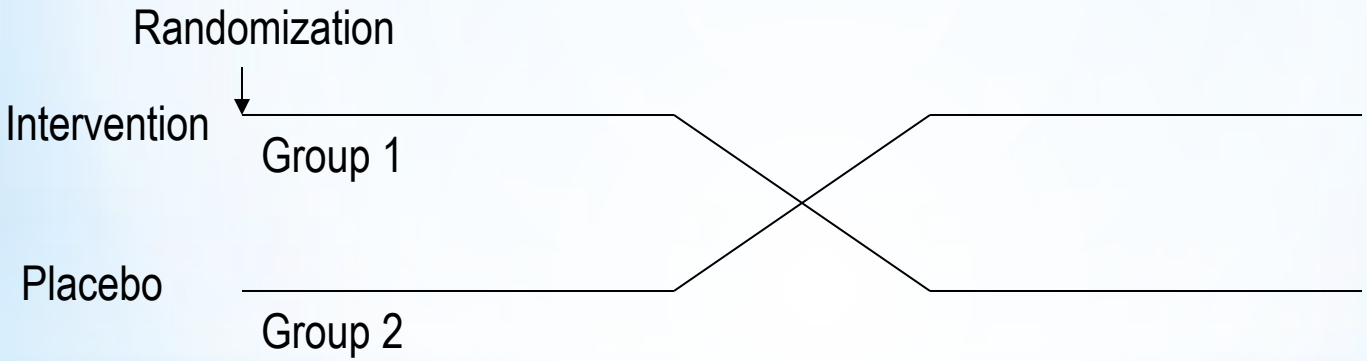
- Selection of treatment/control group by chance
- Purpose – Minimize Bias
- Several methods
  - Fixed Allocation Randomization
    - Simple (flipping a coin)
    - Blocked
    - Stratified
  - Adaptive randomization

Parallel Design

- Subjects are assigned to study arms/groups and stay in that group for the duration of their study participation

Cross-over Design

* One group is assigned to treatment and one to a control group, at some point in the study they switch assignments



Open Label Extension Study

* Investigators and subjects know what intervention they receive

Group 1 ——————————————————————

Observational Study

- No Intervention
- Draw inferences about the effect of a treatment on subjects, where the assignment of subjects into a treated group versus a control group is outside the control of the investigator
  - Used when it may be unethical or impractical to conduct a randomized trial
  - Used for studying public health effects
- May involve clinical procedures
- May be long term

*Safety

- **The Safety (or Adverse Events) section should include:**
  - Detailed information for reporting adverse events, including reporting to the FDA and/or the sponsor
  - Unblinding processes (if applicable)
  - Lists of expected adverse events

The Statistical Section

- Make sure that study objectives and study design elements in the statistical section mirror those in described in the Objectives section!
- If the study involves stopping rules, make sure that descriptions and definitions of toxicities in the statistical section match those in the Safety/AE section.

Human Subjects Protection

- **This section includes discussion of:**
  - Subject selection and exclusion
  - Proposed methods of patient recruitment
  - Recruitment (or exclusion) of special subjects, including vulnerable subjects
  - Lists of potential risks and benefits, including justification for risks

*Informed Consent Form

- ***NIH*** recommends the following be included:
  - Statement that the study involves research
  - Purpose of the research and the length of the study
  - Description of risks and benefits
  - Discussion of alternative therapies
  - Confidentiality policy
  - Compensation for injury
  - Contact for further questions/information
  - Statement of voluntary participation

Q & A