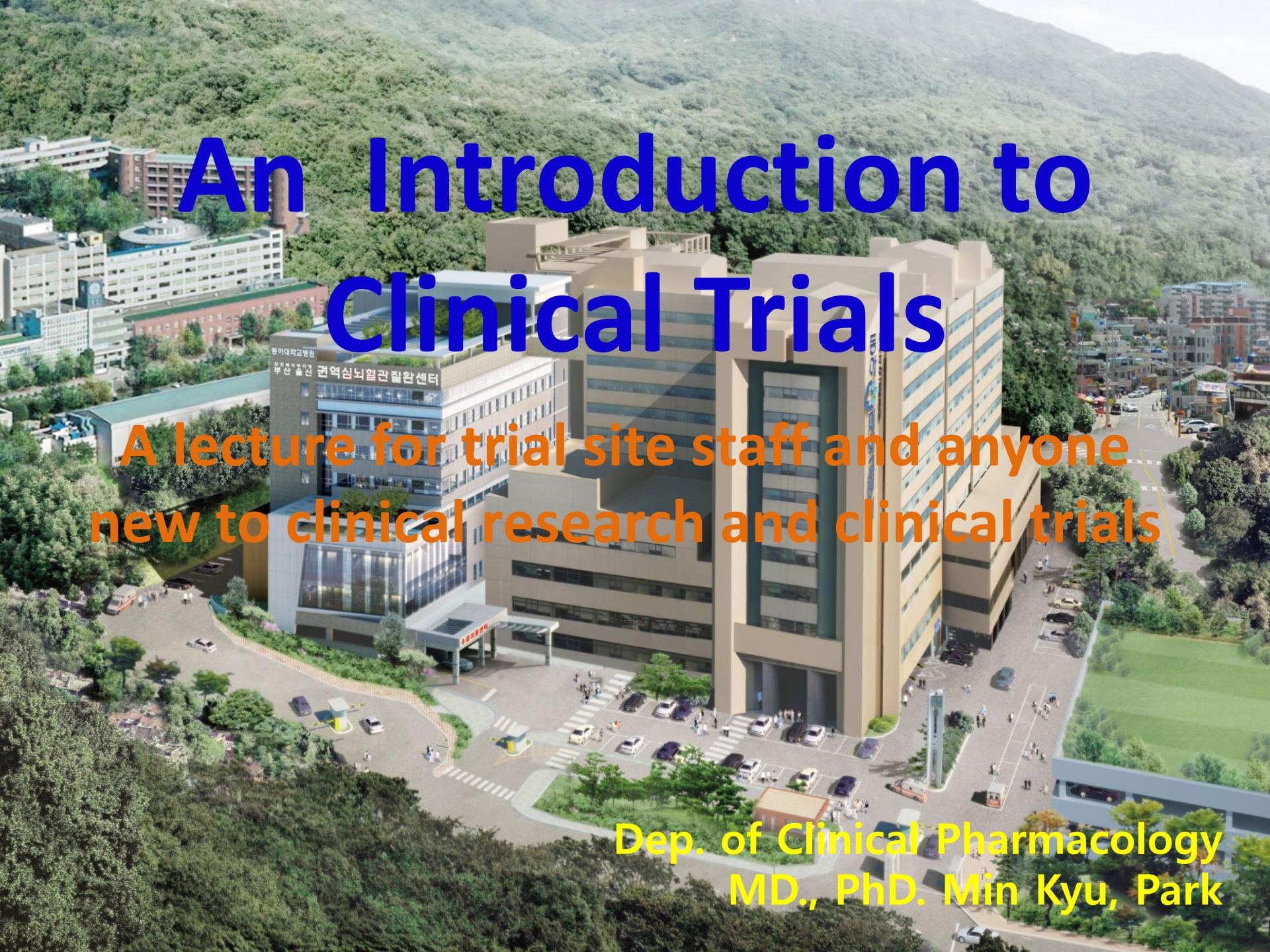

An Introduction to Clinical Trials

A lecture for trial site staff and anyone new to clinical research and clinical trials

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What is a Clinical Trial?

- A clinical trial is a tool for testing a drug, device, or technique

- Prospectively planned experiment for the purpose of evaluating potentially beneficial therapies or treatments

- In general, these studies are conducted under as many controlled conditions as possible so that they provide definitive answers to pre-determined, well-defined questions

Why do a clinical trial?

- To answer a clinical problem
- To gain new knowledge about a new or established treatment
- To support a “claim”
  - for gaining government regulatory approval
  - for marketing a drug, device, or technique

What makes Clinical Trial different from 'Standard of Care'

- Involves human subjects
- Test an 'intervention' – be it a product, procedure or health care sytem….in order to improve standard of care!
- Measures effects over a period of time
- Most have a comparison CONTROL group
- Must have method to measure intervention
- Focuses on unknowns: effect of intervention
- Must be done before medication is part of standard of care
- Standard of Care all about clinicial judgment decision/flexibility – trials need all to stick with the protocol, no deviation – within your clinical judgment

What is an investigational product?

'a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form'

<u>Placebo</u>

Used as a control treatment

1. **An inert substance made up to physically resemble a treatment being investigated**
2. **Best standard of care if "placebo" unethical**
3. **"Sham control"**

So are trials a good thing, have they improved healthcare?

Formal record of clinical trials dates back to the time of the *"Trialists":*

- Dr. Van Helmont's proposal for a therapeutic trial of bloodletting for fevers [1628]
- Dr. Lind's, a ship surgeon, trial of oranges & limes for scurvy [1747]

Historical Highlights of Drug Trials

1909: Paul Ehrlich - Arsphenamine
1929: Alexander Fleming - Penicillin
1935: Gerhard Domagk - Sulfonamide
1944: Schatz/Bugie/Waksman – Streptomycin

So where do I start?

Basic Concepts

The protocol. Establishes the question – ideally has just one and this is the **primary end point**. Common failing is too many end points. The best designed trials keep it simple as this make a clear answer more likely and easier to acheive

Secondary objectives; a few related, appropriate secondary questions are normal as long as they do not distract from the primary. Some might be exploratory.

Trial is then designed around these. The protocol sets out how the question will be answered

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

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

Informed Consent Form

- As it says … a form by which you gain ‘informed consent’
- Few key requirements which must be included. Very difficult balance … examples of 17 page forms. Still ‘informed’ consent?
- In Swahili ‘research’ also means ‘explorative test’ therefore difficult to explain difference between standard of care and research – this is a key principle of giving consent.
- Special circumstances – children and emergency. What about this setting? Really so different? When do you need a witness?
- Whole point of GCP is to protect the rights of the subject

The Case Record Form

- Turns the protocol into your data capture system
- Should only collect data listed in the protocol and nothing else… i.e unless you will use ‘weight’ and have set out to do so, no need to record. Often far too long and collects data that is not used.
- Differs from the source data - patient notes and lab reports. This is a central concept in GCP that data is always verifiable
- Data taken from here and entered into a database and then exported to statistical package. Important to keep CRFs to allow you to go back and resolve data queries

Database and Statistics

- Likely to need stats advice right at the start to help you decide on the all important ‘n’…. How will you randomise, maybe you don’t need 1:1. Keeping the numbers down is helpful. Time, cost and ethics – but you still need to answer the question

- Protocol needs to explain statistical objectives of your trial but it is the report and analysis plan that sets out how you will analysis the data.

- Database should be secure and have an audit trail

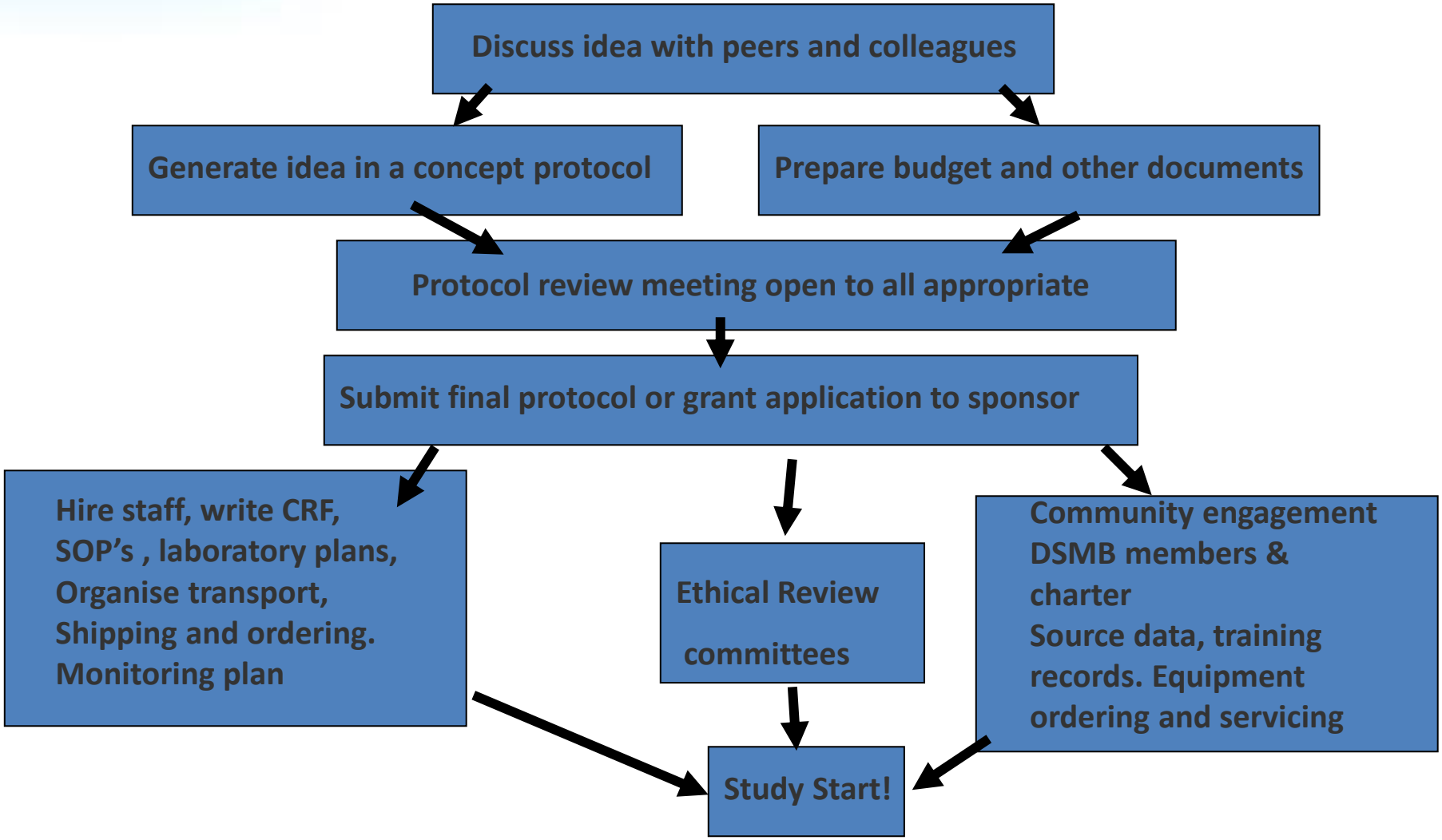
Who is involved?

- Investigators
- Coordinators / Project managers
- Nurses, clinical officers, fieldworkers
- Pharmacists
- Data manager and entry clerks
- Monitor / QA
- Laboratory staff

And possibly….

- Data safety and monitoring board
  ex) IDMC (Independent Data Monitoring Committee)

How a trial is started…?



Why did we need recognised international guidelines for conducting trials?

- Following famous cases such as the Nazis in WWII and black American men in syphilis studies (1932 –1972) there followed the declaration of Helsinki
- Agreement between countries that there needed to be a global standard by which all trial are conducted
- This is ***Good Clinical Practice*** – protects those in a trial, but also those who's treatment will depend on the data
- Essentially ensures that the rights of the patient are protected and by all those given a drug or intervention in the future based upon that data

Definition

- **Quality Data + Ethics = GCP**
- **Data and Reported Results are Credible, and Accurate = quality data**
- **Rights, Integrity, and Confidentiality of Trial Subjects are Protected = ethics**

The basics on how to comply with GCP

1. Write a good protocol -Weigh risks vs. benefits
2. Obtain IRB/IEC approvals
3. Protect the subjects –
   - Obtain Informed Consent,
   - Ensure safety, rights & confidentiality
4. Use qualified study team
5. Handle investigational products appropriately
6. Implement quality systems
7. Record and analyze information appropriately
8. Follow the protocol and trial SOP's!!!!

Other things to think about

- Clinical trial insurance / Non-negligent harm cover
- Safety reporting
- Ethics committee safety and annual updates
- Clinical trial registries
- Sponsor reports
- Publication planning
- Logistics, transport, budgeting
- Drug/vaccine storage
- Sample transportation, export, storage
- Data archiving
- SOP’s, training records and equipment service contracts

Thank You