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A basic Introduction to Clinical Trials and Good Clinical Practice (GCP) …

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EORTC
European Organization for Research and Treatment of Cancer

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What is a Clinical Trial?

A properly planned and executed clinical trial is a powerful experimental technique for assessing the effectiveness of an intervention!

What is an Investigational Product (IP)?

"… 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"

What makes a Clinical Trial different from “Standard of Care”

- Involves human subjects
- Tests an intervention (product, procedure, etc.)
- The aim is to improve standard of care
- Measures effects over a period of time
- Most trials have a comparison CONTROL group
- Must have a method to measure intervention (protocol)
- Focuses on unknowns: effect of the intervention
- Must be done before medication is part of “Standard of Care”

Why Do Research Studies?

- To collect data on events, conditions and populations
- To test hypotheses formulated from observations and / or intuition
- Ultimately, to better understand and improve health outcomes

Types of Medical Research Studies?

- Non-directed Data Capture
  - *Vital Statistics*
- Directed Data Capture & Hypothesis Testing
  - *Cohort Studies, Case Control Studies*
- **Clinical Trials**
  - ***Investigation of Treatments / Conditions***
  - ***Drug Trials***

So are trials a good thing? Have they improved healthcare?

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

- Dr. James Lind's, a ship surgeon, trial of oranges & limes for scurvy [1753]

Der britische Arzt
Dr. James Lind

Die erste mehrarmige Studie

Die vermutlich erste mehrarmige Studie der Geschichte (sogar gleich eine sechsarmige!) führte 1753 der britische Arzt Dr. James Lind durch. Er wollte etwas finden, was die Seeleute vor dem gefürchteten Skorbut bewahrt. Diese Krankheit trat oft auf langen Seereisen auf und ging mit Entzündungen im Mund, Blutungen und Schwäche einher, oft mit tödlichem Ausgang. Dr. Lind teilte zwölf erkrankte Matrosen in Gruppen à zwei Personen ein, die als Nahrungsergänzung Apfelwein, stark verdünnte Schwefelsäure, Essig, Meerwasser, eine Spüllösung für den Gaumen oder Zitrusfrüchte erhielten. Das Ergebnis: Nur die Matrosen der letzten Gruppe zeigten baldige Genesung, die anderen nicht. Heute weiß man, warum: Skorbut ist nichts anderes als ein massiver Mangel an Vitamin C, und Zitrus-früchte enthalten viel davon.

So where do I start? - Basic Concepts

The Protocol - Establishes the question - ideally has just one question which is the **Primary Endpoint**. Common failing is too many endpoints. The best designed trials **keep it simple** as this makes a clear answer more likely and easier to achieve.

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

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

The Protocol ... all in the Title

Single centre, placebo controlled, etc. etc. etc.

Who is conducting the trial? Who is sponsoring it? Where is it to be conducted and on whom will you be conducting the research?

What are you testing? Is it safe, have the tests been validated? Why is this research needed?

What are the risks? What are the procedures? How will data be collected? How did you calculate how many patients you will need?

Informed Consent Form

As it says … a form by which you gain "**Informed Consent**" from your patients or trial participants!

Few key requirements which must be included. Very difficult balance … examples of 20+ page forms. Still "informed" consent?

Sometimes difficult to explain the 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 patients!

Database and Statistics

Likely to need **statistical advice** right at the start to help you decide on the all important "**n**" ... How will you randomize? 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 analyse the data. Must be finalized before database close to avoid risk of manipulating the data.

Database should be secure and have an audit trial. Currently difficult in non-commercial trials.

Keys to follow the Protocol … Case Record Forms, Source Data and SOPs

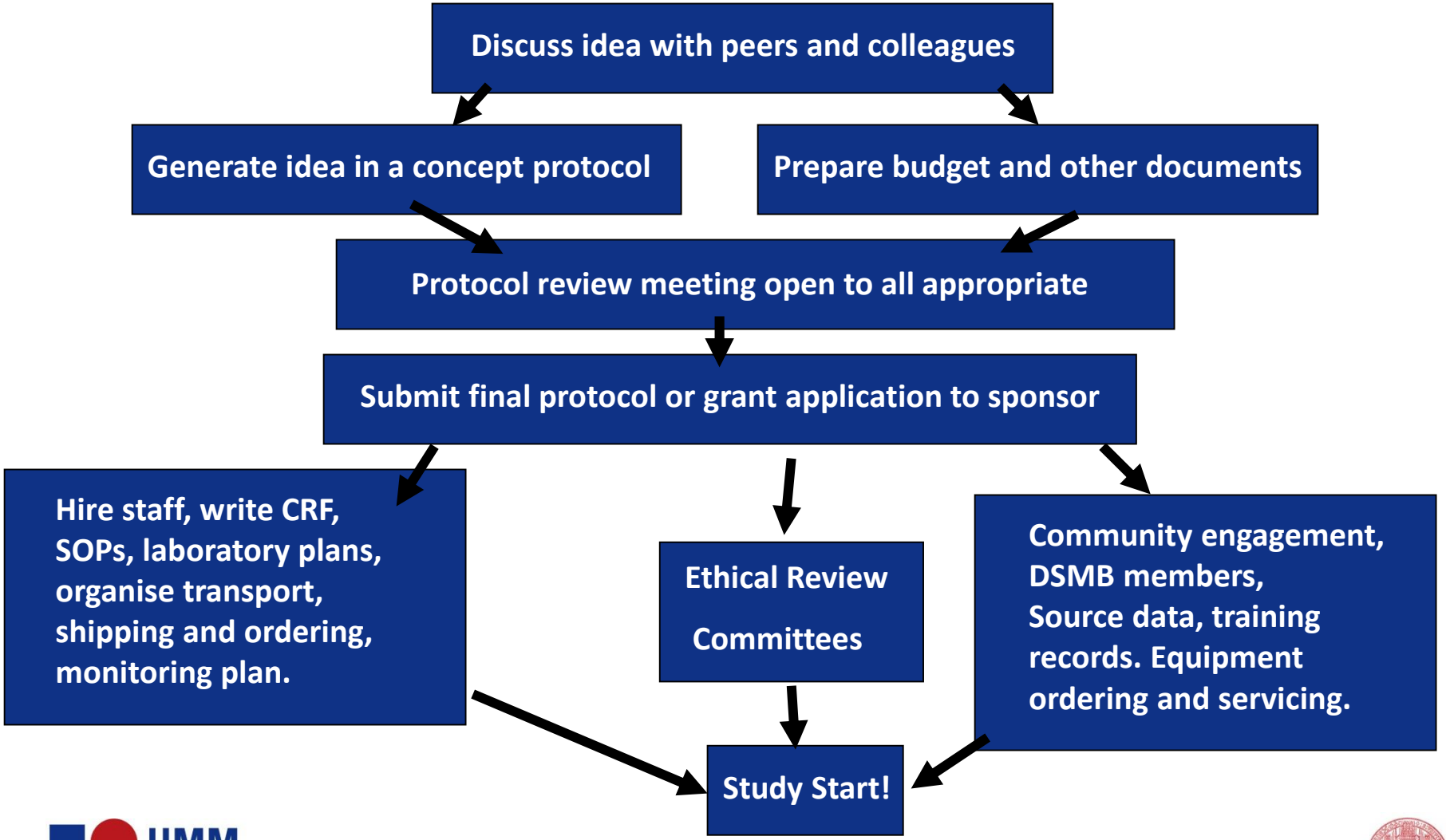
- The Case Record Form (**CRF**) turns the protocol into a data capture system.
- Should only collect data listed in the protocol and nothing else … often far too long and collects data that is not used.
- Differs from the **Source Data** - patient notes and lab reports. This is a central concept in GCP that the data is always verifiable.
- Data taken from here and entered into a database and then exported to statistical package. Important to keep CRFs and source data to allow you to go back and resolve data queries.
- Operation manuals or **SOPs** translate the protocol to the practical and operational steps appropriate to your site.

Who is involved?

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

And possibly …

How a trial is started ...?



Why did we need recognised international guidelines for conducting trials?

- Following 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 trials 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 patients are protected and by all those given a drug or intervention in the future based upon that data.

Definition of ICH-GCP

"a **standard** for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are **protected**."

Definition of ICH-GCP

- **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 *versus* benefits
2. Obtain IRB/IEC approvals
3. Protect the subjects
    - Obtain Informed Consent
    - Ensure safety, rights & confidentiality
4. Use a qualified study team
5. Handle investigational products appropriately
6. Implement quality systems
7. Record and analyze information appropriately
8. Follow the protocol and trial SOPs

Other things to think about

- Clinical trial insurance
- Safety reporting
- Ethics committee safety and annual updates
- Clinical trial registries
- Sponsor reports
- Publication planning
- Logistics, transport, budgeting
- Drug storage and sample transportation, export, storage
- Data archiving
- SOPs, training records and equipment service contracts
- …

Too daunting, are you put off completely?

Don’t be!

Excellent way to learn about research!

More money than ever going into capacity building for clinical trials in resource limited settings.

Many opportunities for training and further qualifications.

Great field of research - whatever your training!

- **Getting an answer to a trial could influence the way patients are managed or make a new drug available.**
- **Offers the possibility for improving health outcomes for thousands rather than one patient in front of you.**

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Discussion and Questions

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