Introduction to Clinical Trials

Narrated By: Billy Adeleke-Asalu

Source : EuropeAn AIDS Treatment GROUP.

What is a clinical trial?

Clinical trials are:

- experiments done on human participants
- designed to answer specific questions about biomedical or behavioral interventions;
- this may include new treatments and known interventions that warrant further study and comparison

What is a clinical trial?

- **Clinical trials** are research studies that explore whether a medical strategy, treatment, or device is safe and effective for humans, also may show which medical approaches work best for certain illnesses or groups of people
- Approaches can include:
  - new medicines or new combinations of medicines
  - new surgical procedures or devices
  - new ways to use an existing medicine or device

Hypotheses: The trial question

- Is the idea or theory that the trial aims to prove or disprove
- All trials or studies need to start with the question
  - Are red balloons more static than yellow balloons?
  - Do people with blue eyes better lovers than people with brown eyes?
  - Is one drug (A) better or equivalent to another drug (B)?

Primary endpoint

- This should be decided during the study design and before any patients are recruited
  - Once this primary endpoint is decided and ethics have approved the trial it cannot be changed without substantial effort
- The primary endpoint decides what level of evidence will be accepted to prove or disprove the hypothesis
  - The red balloon will pick up more pieces of paper than the yellow balloon over a 24 hour period
  - The blue eyes have it every time!
  - Drug A achieved a sustained viral response and lower LDL (low density lipoprotein) levels than drug B at week 48

Secondary endpoints

- These can ask additional questions such as
  - Did the yellow balloon burst more times than the red balloon (what was the pop rate)
  - Did drug A have increased side effects (these ideally should be listed and graded)
  - Did drug A have lower recorded toxicities (bilirubin urea creatinine etc)
  - Was drug A regime simplified (QD / BID)
- Cost effectives
- Costs of intervention
- Health effects produced (e.g. life-years gained)

Exploratory endpoints

Are usually not prospectively planned and are generally not rigorously evaluated like primary and secondary endpoints. These endpoints are used in treatment comparisons and also unplanned subgroup analysis with an exploratory (e.g., hypothesis generating) purpose:

- ✓ In certain situations, their results can be useful in designing future new trials. However, they are not useful for confirmatory purpose
- ✓ Win criteria are also called “clinical decision rules” for determining clinically meaningful treatment efficacy. They simply define how a positive clinical decision regarding the effectiveness of a test treatment in a trial is going to be reached
- ✓ The criteria are defined relative to one or more relevant clinical primary endpoints in the setting of comparing one or more doses of test and control treatments

What is an HIV/AIDS clinical trial?

HIV/AIDS

clinical trials help researchers find better ways to prevent, detect, or treat HIV/AIDS

Examples of HIV/AIDS clinical trials under way include:

- studies of new medicines to treat HIV
- studies of vaccines to prevent or treat HIV
- studies of medicines to treat infections related to HIV
- studies on how to better use HIV medicines

Trial design's

Randomised controlled trail	Experimental and Longitudinal

Case–control study	Observational and Longitudinal
Cross–sectional study	Carried out at a single time point
Cohort study	Observational and Longitudinal
Expert opinion	Observational and Longitudinal
Case series / case note review	Retrospective

Literature review	Reports collective results from selected studies

Trial design's

Interventional trials

Randomised controlled study	Experimental and Longitudinal

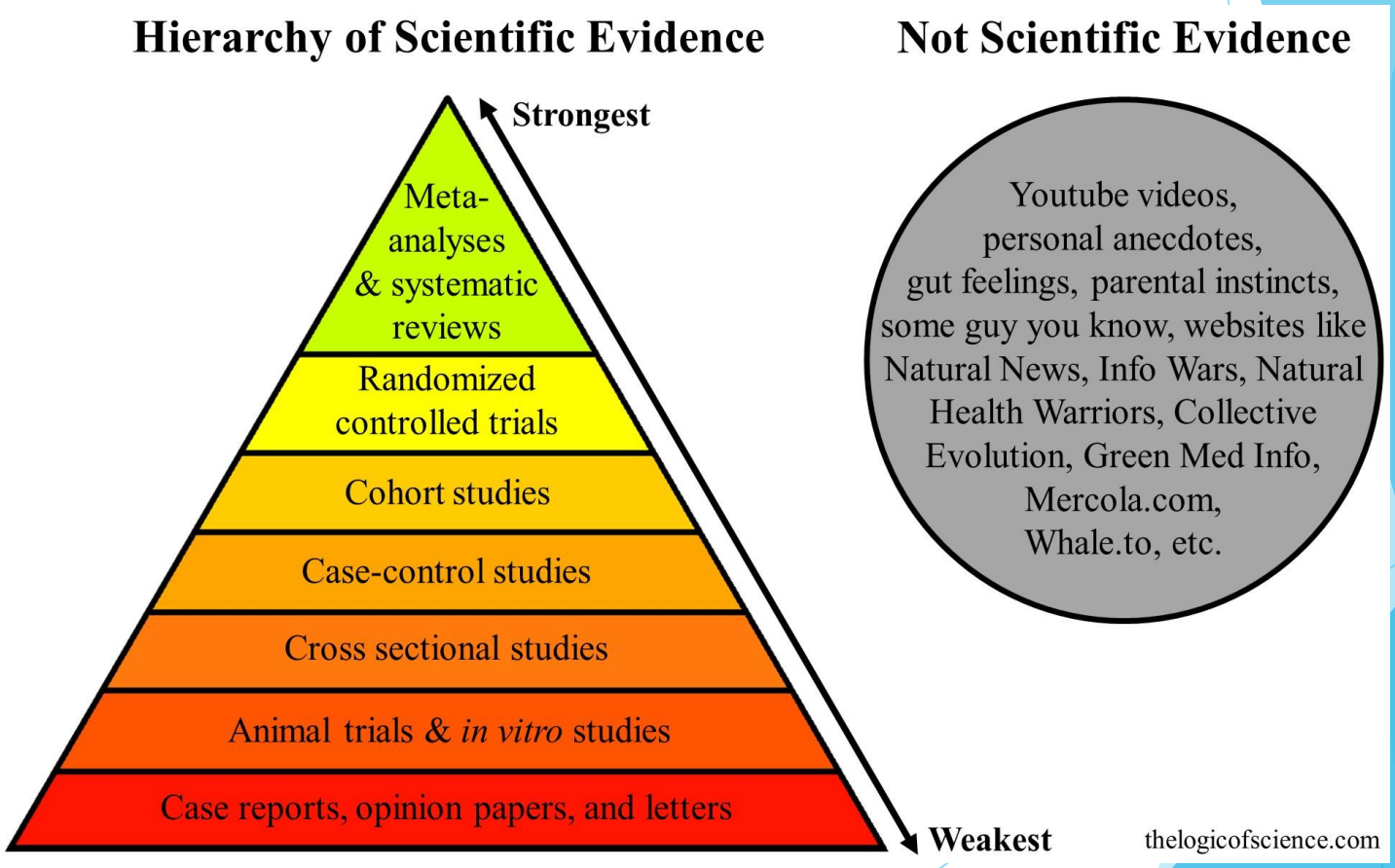
Observational trials

Case–control study	Observational and Longitudinal
Cross–sectional study	Carried out at a single time point
Cohort study	Observational and Longitudinal
Expert opinion	Observational and Longitudinal
Case series / case note review	Retrospective

Literature review

Reports collective results from selected studies

Trial designs and level of evidence

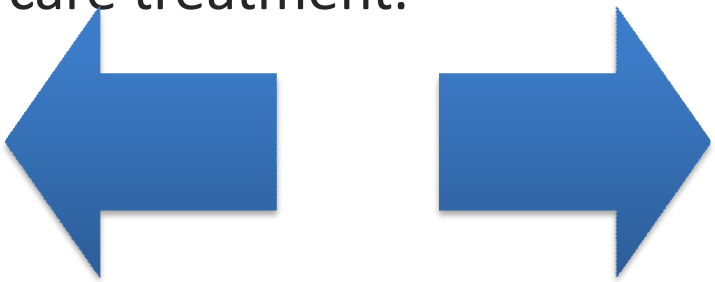


Interventional (Experimental)

- This is where something specific is done
- A drug (or other device) is given and the results of the intervention are recorded and analysed
  - Drug K causes diarrhea so switch drug K to drug J to see if the side effect lessens
  - Using a new drug OP1 to see if the drug OP1 can achieve a long term viral response at weeks 4 18 36 and 54

Observational

- This looks for evidence that something has happened
- Follows to see if anything does happen
- There is no interventions made other than the general standard of care treatment.



Observational (Epidemiologic)

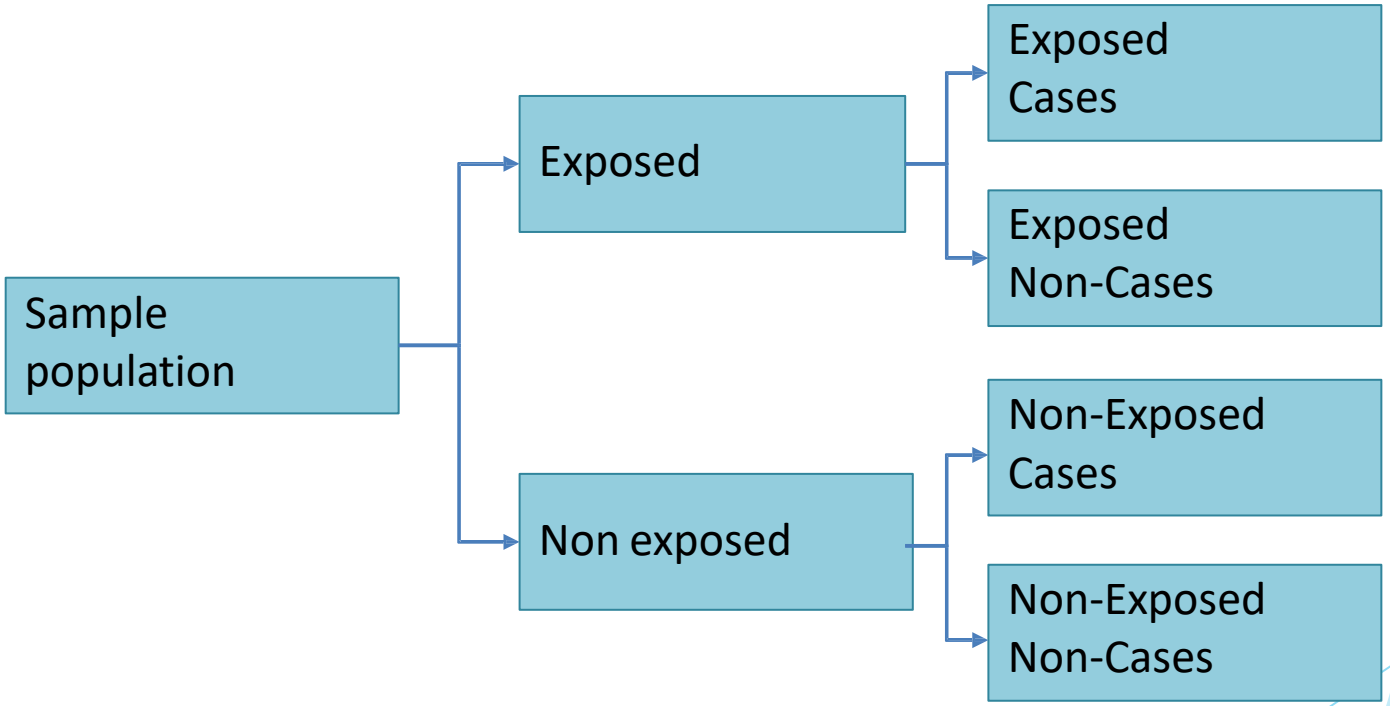
They can be differentiated based on "directionality" of study (data collection in time) into:

- non-directional: current disease and exposure status determined simultaneously (**cross-sectional**)
- start with disease classification and look back for history of exposure (**retrospective**)
- start with disease-free population and classify exposure status, follow into future for disease development (**prospective**)

Study Design	Past	Present	Future
Retrospective	Look for past exposure in cases and control	Select cases and controls	
Prospective		Select cohort; classify as to exposure to factor	Follow to assess frequency with which disease develops
Cross-Sectional		Select Sample and classify as to exposure to factor and disease status	

Cross – sectional

- Collects information at one time point



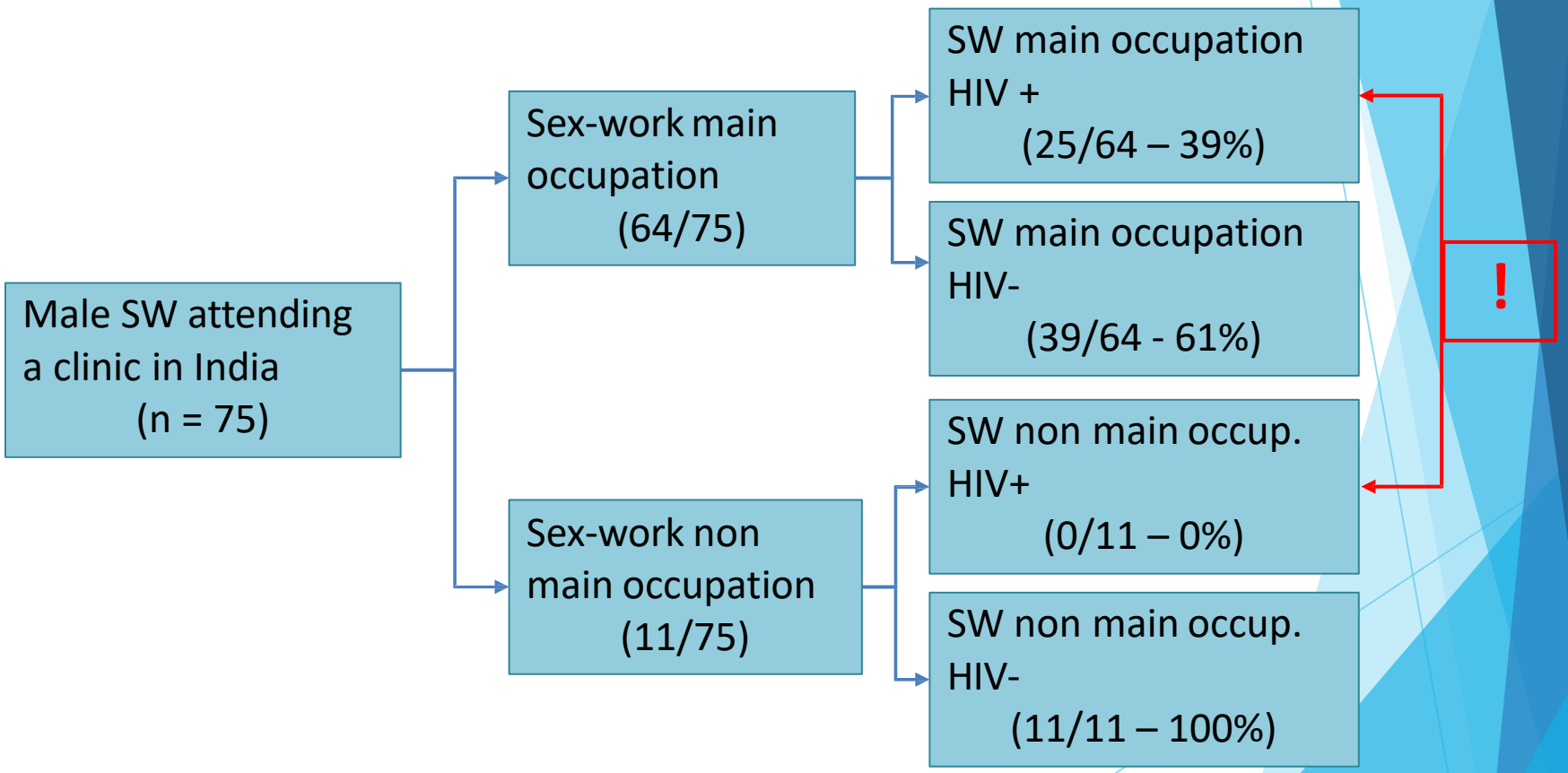
Example of Cross-sectional study in HIV

HIV and male sex workers (Shinde *et al*., 2009)

- Cross-sectional analysis to assess the prevalence of HIV and sociodemographic factors in male sex workers.
- The data were collected by interviewer-administered questionnaires (for sociodemographic and behavior data), clinical evaluation for sexually transmitted infections (STIs), and serological evaluation for STIs (including HIV).
- They found that HIV prevalence was higher among those in whom sex work was the **main occupation** compared with those in whom sex work was not the main occupation.

Example of Cross-sectional study in HIV

- **HIV and male sex workers (Shinde *et al*., 2009)**



Longitudinal

- Looks at individuals to see how things change
- This can follow both patients with no interventions and those with interventions

Retrospective

- Looks backwards in time
- Often looks through an established database
  - What percentage of patients failed their first combination
  - Were side effects recorded in other patients

Prospective

- Ask the question “what will be studied?”
- Then follows a cohort over a period of time
  - For example a new drug would follow those taking the new drug and those taking an existing drug over x amount of time
  - Is heart disease linked to HIV treatment?
    - If an increase in heart disease is seen then a secondary endpoint could be which class of drugs see’s the heart disease

So in describing a study…

- One of each (observational / experimental, cross-sectional / longitudinal, retrospective / prospective) should be included

- E.g.
  - An interventional longitudinal prospective study of the safety and efficacy of OP1 and ZTD

Randomisation

- This is designed to balance factors in each group (both known and unknown factors)
  - Sex age drinkers smokers genetics etc.
- Randomization stops bias
  - Prevents Dr's from only putting those most in need of treatment into the group that receives the active drug rather than a placebo drug
- Flip the coin

Randomised controlled trial (RCT)

- In HIV the comparison is between a new compound or novel approach to treatment vs an existing treatment
  - The existing treatment must now be the treatment that is believed to be the best current treatment
    - No new compound can be trailed against an old drug regime
- A RCT consists of 2 or more groups
  - One group is the control group (existing treatment option, or where no treatment a placebo)
  - One (or more) group(s) receives the new regime
- The control group proves / disproves if the new compound / intervention works better or worse, thus eliminating external factors

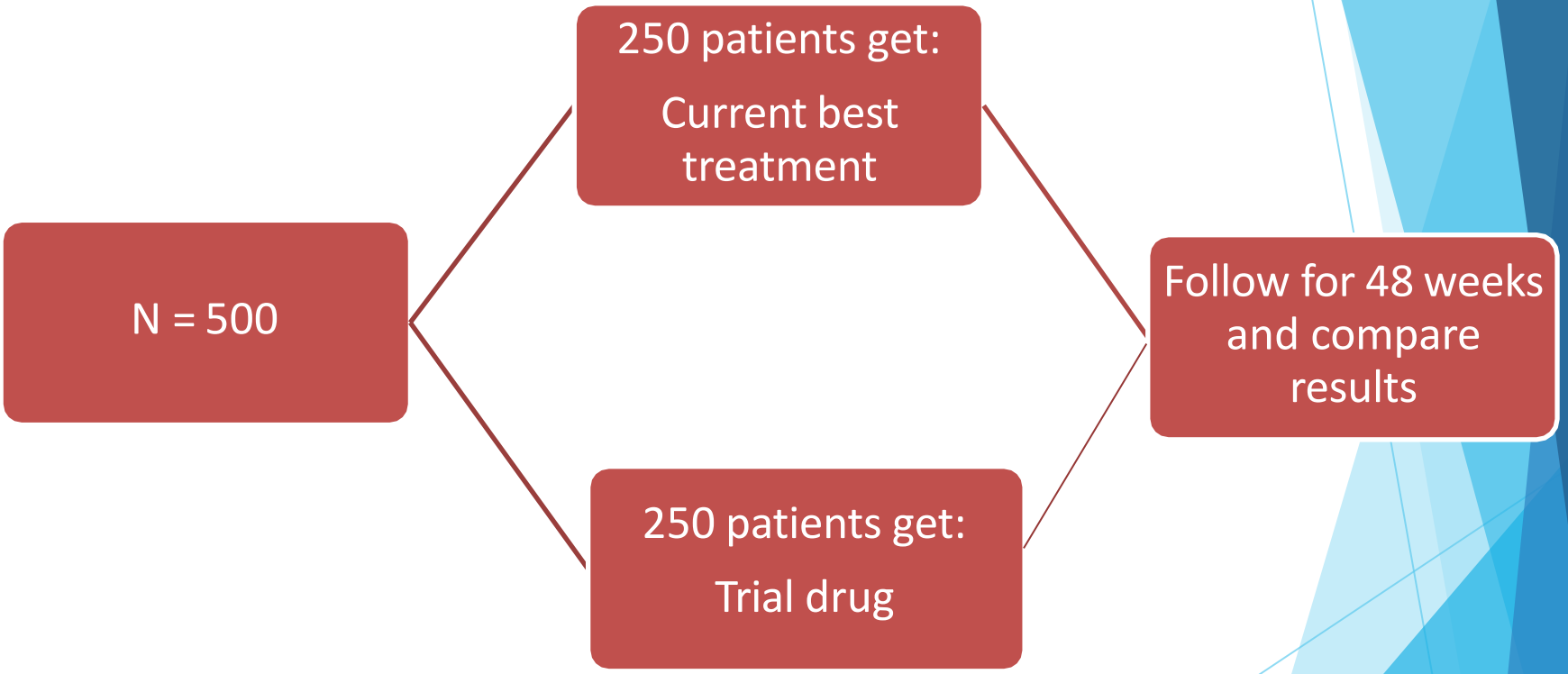
Blind and Double Blinded

- Blinding is the term used to describe a study participant, a researcher or a doctor not knowing which study group the participant has been assigned to.
- Blinded means the participant does not know which group they are in, but the doctor and researcher does
- A double blinded study means neither the participant or the doctor knows which group the participant is in
- Blinding prevents drug choice by Dr, personal beliefs of either and reporting (or not) of side effects

Placebo

- A dummy drug
  - Looks like, smells like and tastes like the new compound
    - But has no active ingredient!
- It has 2 uses
  - 1 to see if the active drug works
  - 2 to interpret side effects
    - 10% of people in the new compound group report headaches
    - 2% of people in the placebo / current treatment group report headaches
      - The new compound causes headaches
- It is a way to take into account the “placebo effect”

Control group



The Gold standard clinical trial Randomised double – blinded -controlled trial

RCT

Cohort study

Case-control study

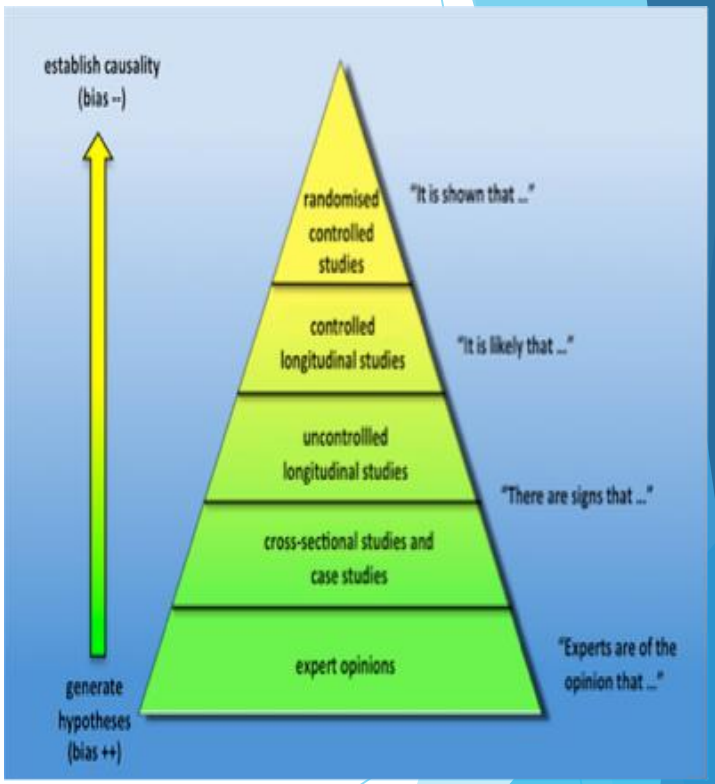
Cross-sectional study

Case series/case note review

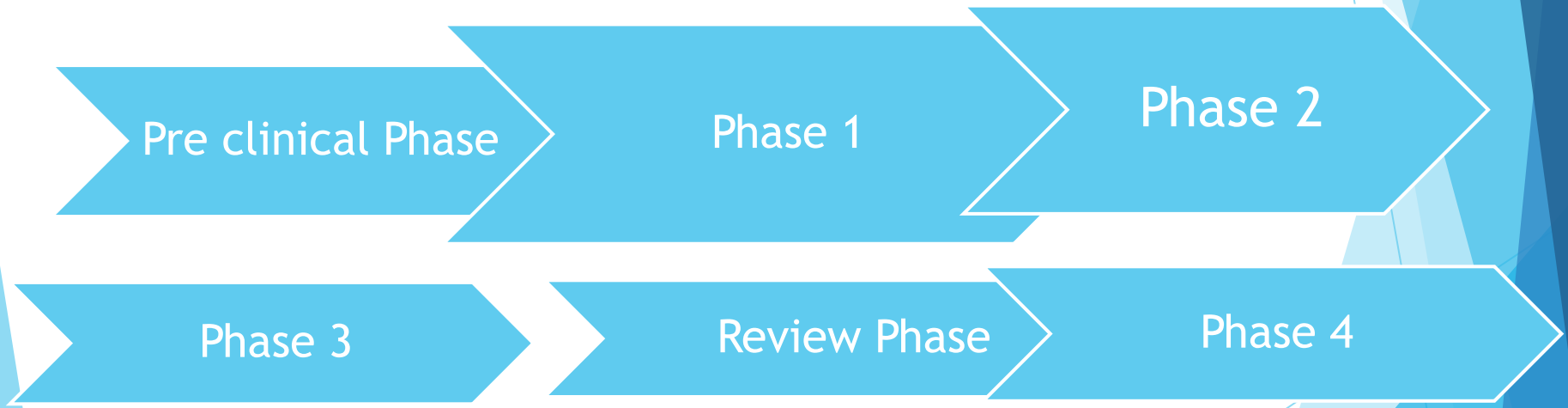
'Expert' opinion

BEST QUALITY EVIDENCE

WORST QUALITY EVIDENCE



Clinical trials are conducted in “phases”



Pre Clinical Phase

Testing of drug in non-human subjects, to gather efficacy, toxicity and pharmacokinetic information

1. Ethical approval
2. Regulatory approval

Phase 1

Researchers test a new drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects

1. Ethical approval
2. Regulatory approval
3. Patient screening
4. Investigator training

Phase 2

- The drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety

- 1.Clinical monitoring
- 2. Site audit

Phase 3

- The drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the drug or treatment to be used safely

Review Phase

- ALL recorded data is screened, monitored and evaluated by independent person's, prior to a full license being granted for market authorization

Phase IV

- Studies are done after the drug or treatment has been marketed to gather information on the drug's effect in various populations and any side effects associated with long-term use

So we now have a trial hypothesis and trial design:

now what?

- Sponsor needed
- Trial management board
- Protocol
- Patient information sheet (PILs)
- Site selection
- Ethical approval
- Regulatory approval
- Patient screening
- Investigator training
- Clinical monitoring
- Site audit
- Data management
- Study close
- Data interpretation
- Publish results

Protocol

Sponsorship

PROTOCOL

- Title SU2016, a phase 2b randomized open label study of….
- Compound number SU20161423
- Development phase IIB
- Effective date xx APR 2016
- Subject SU20161423 HIV1 myocardinal infextion
- Author(s)
- Sponsor signatory
- Sponsor information page
- Clinical study identifier (SU201621423)
- Sponsor legal address and contact address
- SAE contact information

The role of the community engagement during C -T

Community Engagement 1

Defining **"Community" -** Communities are not homogeneous and may have competing interests and priorities; they may not always fit a single definition

The community may be segmented into adults, women, adolescents, and children, depending on the nature of the research

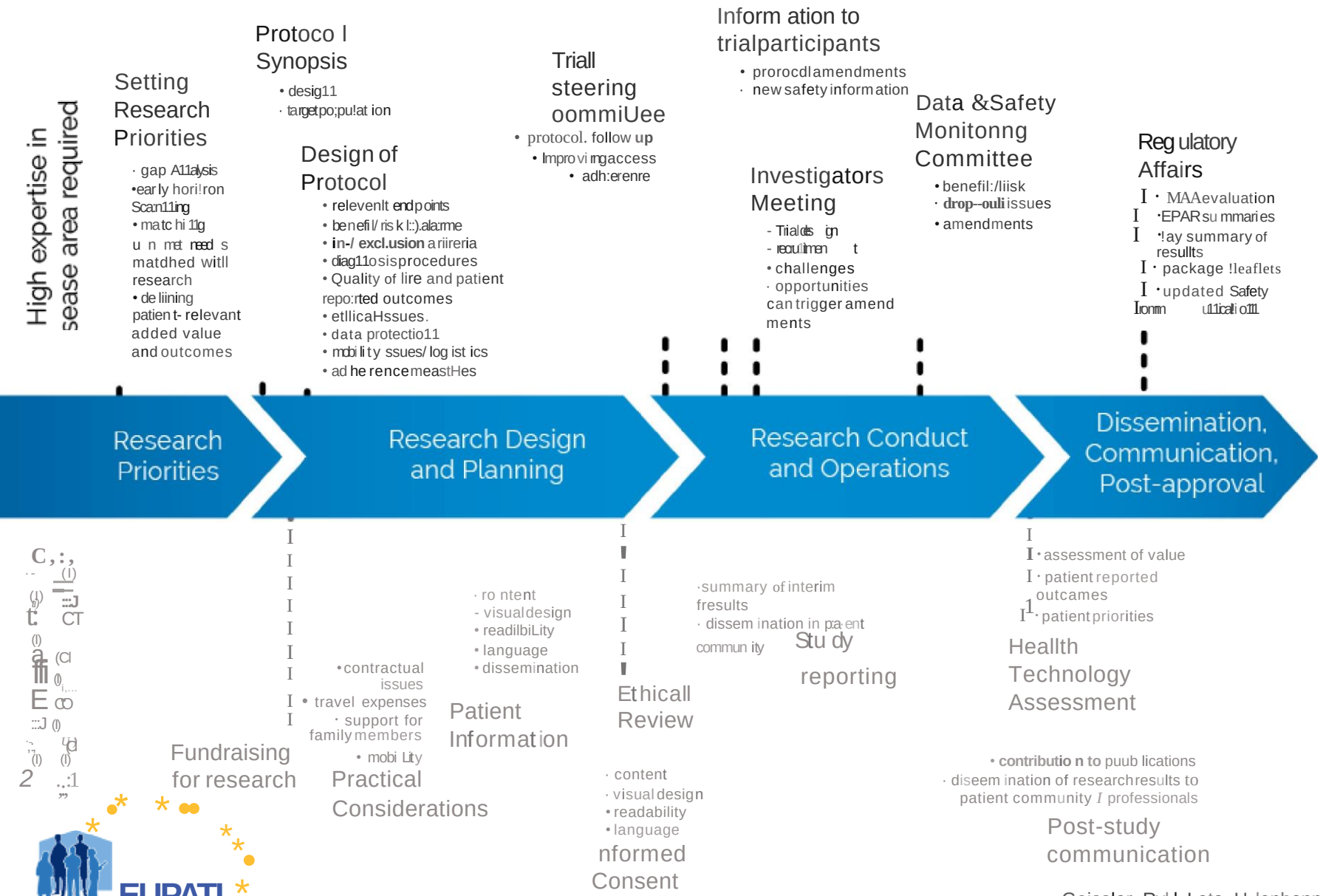
people with co-infections, such as tuberculosis or hepatitis C

People with co- and multi-morbidities (ageing populations)

The role of the community engagement

- provide the most direct opportunity
- invest themselves in the research
- better penetration of communities
- raising awareness within the community
- can help build trust between
- must meet the needs of the populations
- to become knowledgeable about the social and cultural context
- community collaboration requires an ongoing, long-term commitment

Patient involvement in medicines R&D



EUPATI
European Patients' Ac.a.demy on 1'1111:rapeutic In novatfon
www.eupat i. eu

Geissler, Ryl l, Leto, U lenhopp EPALCO/EUPATI (2015,, unpublished)

Patient involvement in clinical development

Patient advocates can provide input into:

- **Study design**:
  - Studies should take into account the needs of the patients. This means the research priorities and research outcomes being measured should be important to and provide value for the users of the medicine.
- **Study literature and informed consent**:
  - Study literature and informed consent forms (and the informed consent process) should be clearly understandable to all study participants.
- **Study logistics** (such as travel, time spent):
  - The study should be planned so that it is convenient for study participants and takes their needs into account, especially those resulting from their indication/disease.
- **Recruitment and retention**:
  - Raising awareness of studies within the community of interested patients. Patient organisations should also be informed about relevant studies and be able to provide information to patients.
- **Dissemination**:
  - The results of research should be widely available

Source: eupati.eu

Patient involvement in clinical development

Patient advocates can have roles as:

- **Driving force**:
  - Lobbying for the development of clinical trials for the condition(s) they/their organisations represent.
  - (Co-)financing a clinical trial.
  - Developing the clinical research protocol.
  - Getting a research team together for a clinical trial.
- **Co-research**:
  - Leading a focus group or discussion session for research.
  - (Co-)writing a scientific article on the research results of the clinical trial.
- **Reviewer**:
  - Review patient information that is to be used in a clinical trial.
- **Advisor**:
  - Giving advice to, or being an advisory member of, a national or European regulatory authority committee, an ethics committee, or a clinical research programme committee.
- **Information provider**:
  - Supplying disease, demographic, and/or other characteristic information on the members represented.
  - Supplying information to patients on the possibilities of taking part in a clinical trial.
- **Research participant**: Source: eupati.eu
  - As a participant in a clinical trial testing the effects of a new treatment or medicine.

Patient information leaflet (PILs)

- This should be written using the following:
- Font size 12
- Short sentences
- No long paragraphs
- Pictures should be used
- Timelines should be used
- Non medical language should be used

- REMEMBER THE AVERAGE READING AGE OF THE PUBLIC IS 12 YEARS OLD

Trail management board

- These are groups made up from
  - researchers,
  - scientists,
  - statisticians,
  - doctors,
  - community members,
  - Data Safety Monitoring Boards (DSMB),
  - academia
  - advisors
- And this is where you could also be as a community representative

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?

‘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 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
  – this is captured in the protocol and this must be stuck to meticulously if the question is to be answered!!
- Focuses on unknowns: effect of intervention
- Must be done before medication is part of standard of care
- Standard of Care all about clinical judgement decision/flexibility – trials need all to stick with the protocol, no deviation – within your clinical judgement

Why Do Research Studies?

To collect data on usual and unusual events, conditions, & population groups

To test hypotheses formulated from observations and/or intuition

Ultimately, to understand better – improve health outcomes with change

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 Treatment/Condition***
- ***Drug Trials***

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

– this is captured in the protocol and this must be stuck to meticulously if the question is to be answered!!

- 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

Some Examples of Trials....

They could be small investigator-led fellowship type studies that are addressing a disease management question, through to large multi-centre programmes within collaborations or with product development sponsors assessing new products for licensure

They might be ward based….

Improving disease management in very sick children such as severe malaria, malnutrition and management of seizures and in-patient trials for product development such as PK studies

Or Community Based…

Phase II and III regulatory trials in drug and vaccines for malaria and HIV. Academic proof of concept trails. Large phase IV surveillance studies.

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]

Data safety and monitoring board

Clinical trial steering committee

Historical Highlights of Drug Trials

- 1909: Paul Ehrlich - Arsphenamine
- 1929: Alexander Fleming - Penicillin
- 1935: Gerhard Domagk - Sulfonamide
- 1944: Schatz/Bugie/Waksman – Streptomycin
- By 1950, the British Medical Res. Council developed a systematic methodology for studying & evaluating therapeutic interventions

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

The protocol….all in the title

- Single centre, placebo controlled 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’
- 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. 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 following the Protocol….The Case Record Form, Source Data and SOP's.

- Data safety and monitoring board
- Clinical trial steering committee
- The Case Record form turns the protocol into a 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 and source data to allow you to go back and resolve data queries
- Operations manuals or 'SOP's translate the protocol to the practical and operational steps appropriate to your site

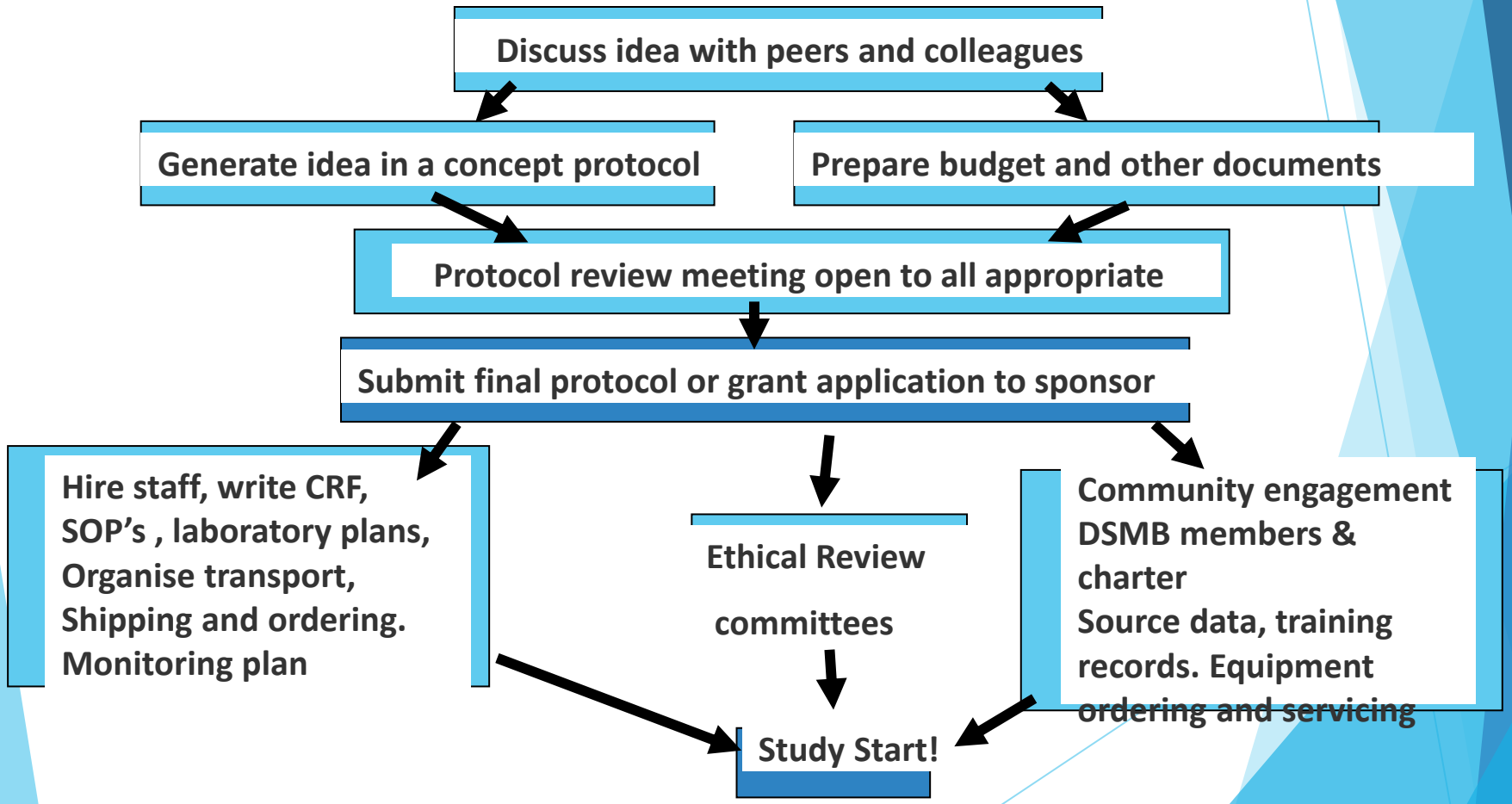
Who is involved?

- 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
- Clinical trial steering committee

How a trial is started...?



Why did we need recognized 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 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.”

(ICH GCP)

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

Too daunting, are you put off completely?

- Don’t be!
- Excellent way to learn about research – plenty of help… and plenty of funding out there
- 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/vaccine available. The possibility for improving health outcomes for thousands rather than one patient in front of you

Resources:

https://www.clinicaltrialsregister.eu
https://clinicaltrials.gov/
http://aidsresearch.org/about/
http://www.ncbi.nlm.nih.gov/
http://www.eupati.eu
Globalhealthtrial.org