European AIDS Treatment Group

European African Treatment Advocates Network

# Introduction to Research and Development and Clinical Trials

Damian Kelly
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- Development stage
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- Clinical trials

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# Introduction to Research and Development

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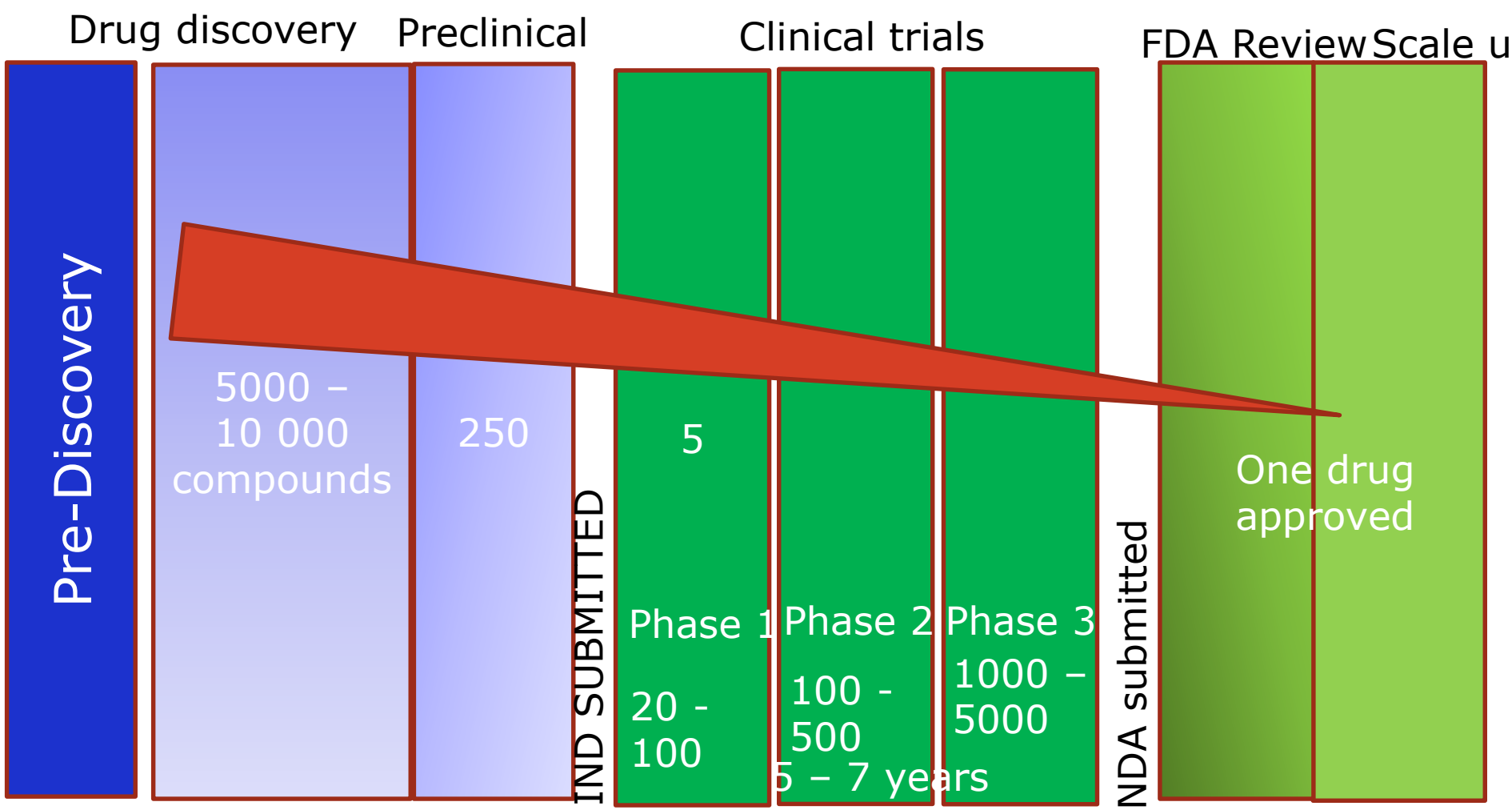


Investigational New Drug
New Drug Application

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# Research process

**Goal**

**Pre-Discovery** – but of what?

Basic research: understand the disease and find potential agents or molecule to target the disease

**How**

Academic, governments, pharmaceutical companies, other for profit companies (bio-tech)

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# Discovery stage

Goal

find a drug candidate – beyond the molecule

How

develop the molecule to optimize it

change its structure

make it stable

# Development stage

6 -8 years Still no human trials

## Investigational new drug application (ING)

Goal

To obtain FDA approval to test the new drug in humans

How

All preclinical data is reviewed by the FDA and the trail plans are looked at to see if the drug is safe to move into human trials.

# Preclinical stage

6 – 8 years

Goal

Is the drug safe?

Extensive testing (before giving to humans)

Is the drug effective?

Does it do what is expected or something else

How

Tests are carried out in the laboratory and on animal models – no human experimental stage

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# Clinical trials

6 – 8 years

## Goal

To test in “healthy” volunteers to see if the drug is safe

Then moves to test if the drug is effective

Rarely is the new drug given to a patient needing the treatment in early trials

## How

Starting with a phase 1 clinical trial the new drug is given to a small number of “healthy "people (circa 50)

Then moves to phase 2 and then phase 3 clinical trials which include patients

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# Review

0 – 2 years post trial start date

## Goal

The FDA reviews all results and outcomes to determine if the drug can be approved for the use in patients

## How

Reviews ALL clinical and preclinical findings, manufacturing plans, proposed labeling and any relevant papers

Independent advisory committee views sourced

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# Clinical Trials.

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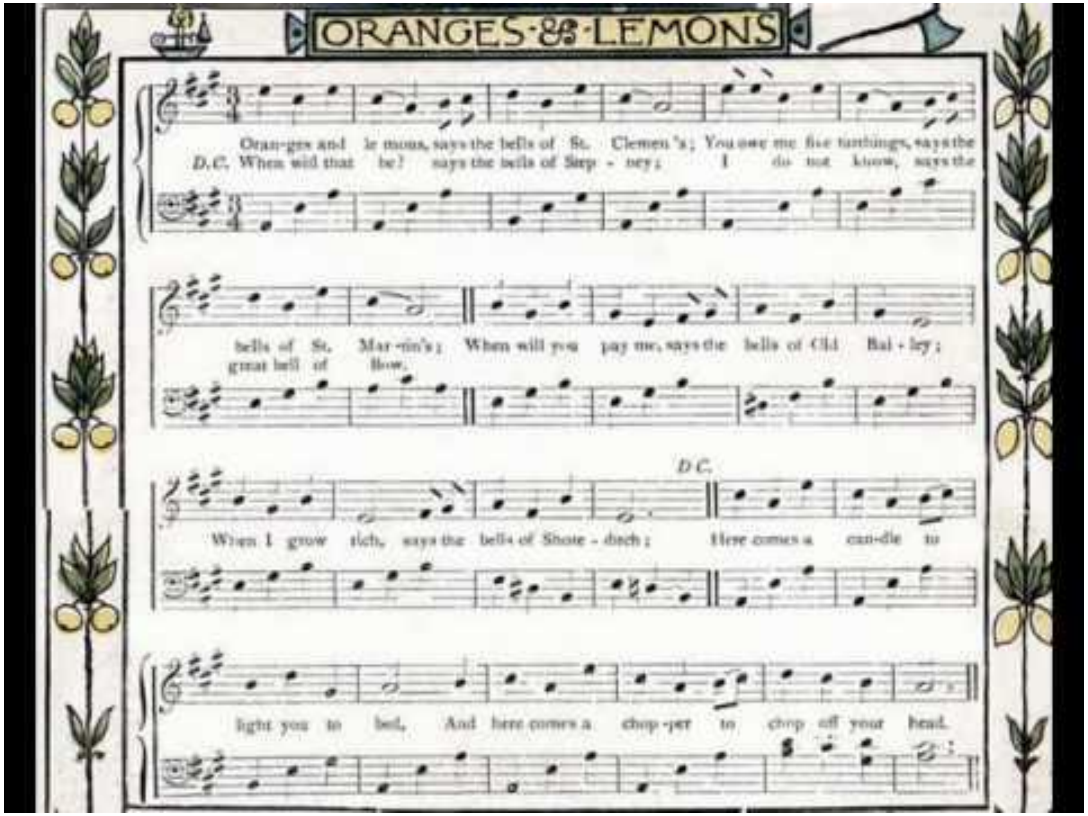
# What is a clinical trial?

Clinical trials are experiments done in clinical research on human participants are designed to answer specific questions about biomedical or behavioral interventions, including 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

# History - 1747



# 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 make 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 ever 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 (eg 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

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# What is an HIV/AIDS clinical trial?

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# 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:

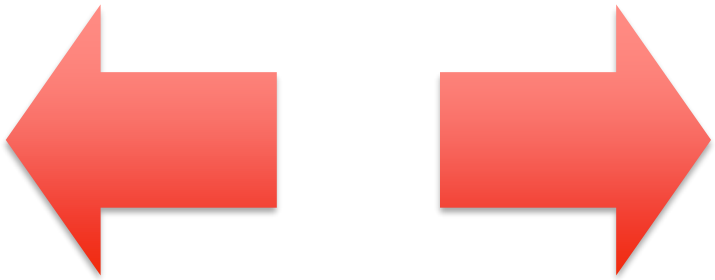
- studies of new medicines to treat HIV
- studies of vaccines to prevent or treat HIV
- studies of medicines to treat infections related to HIV

# Trial design's

| | |
|---|---|
| Randomized control 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 |

# 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.



# 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 analyzed
  - 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

# Cross – sectional

- Collects information at one time point

# Longitudinal

- Follows 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

# Randomization

- 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

# Randomized 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 or not, thus eliminating external factors

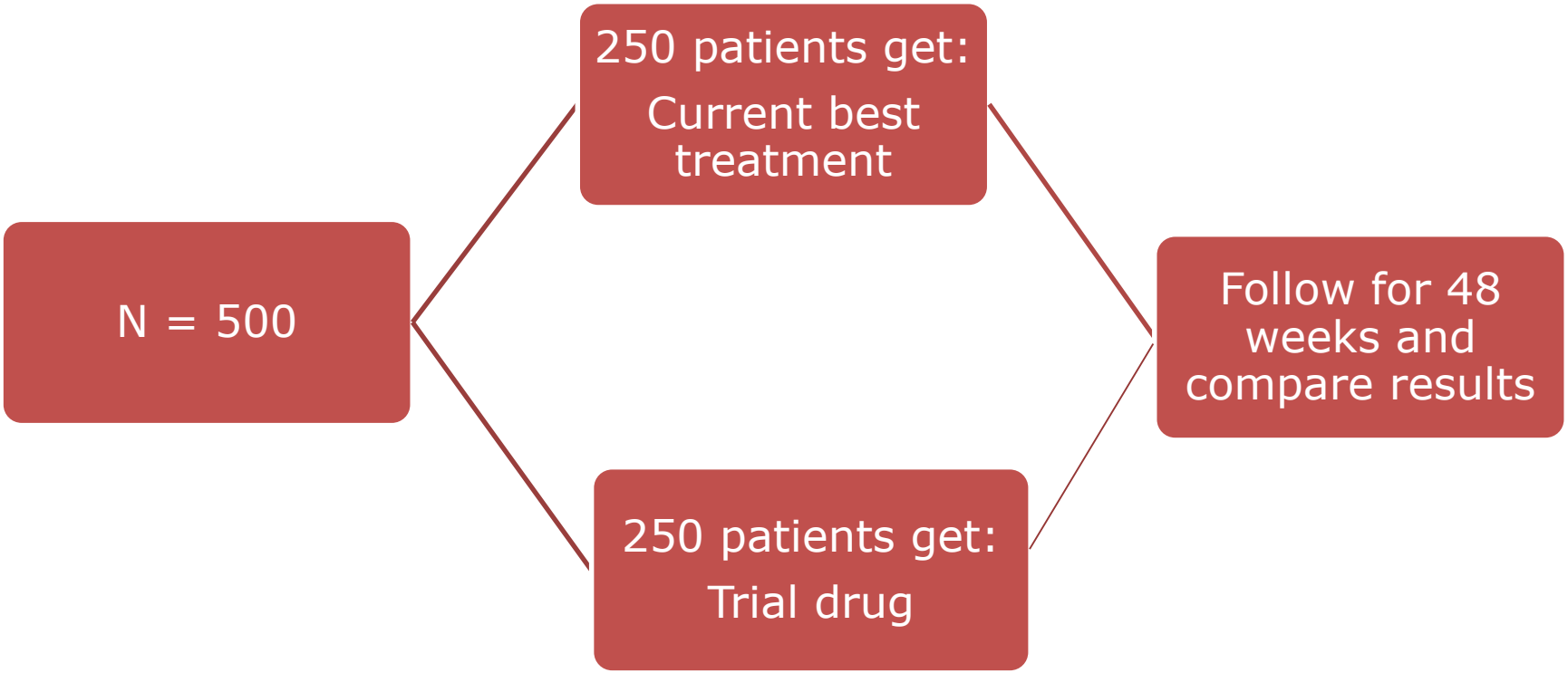
# Blind and Double Blinded

- Blinding is the term used to describe a patient, a researcher or a doctor not knowing which study group the patient has been assigned to.
- Blinded means the patient does not know which group they are in, but the doctor and researcher does
- A double blinded study means neither the patient or the doctor knows which group the patient 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
- Placebo drugs prevent patients from being put at risk

# Control group



# The Gold standard clinical trial
# Randomized double – blinded placebo-controlled trial

RCT

Cohort study

Case-control study

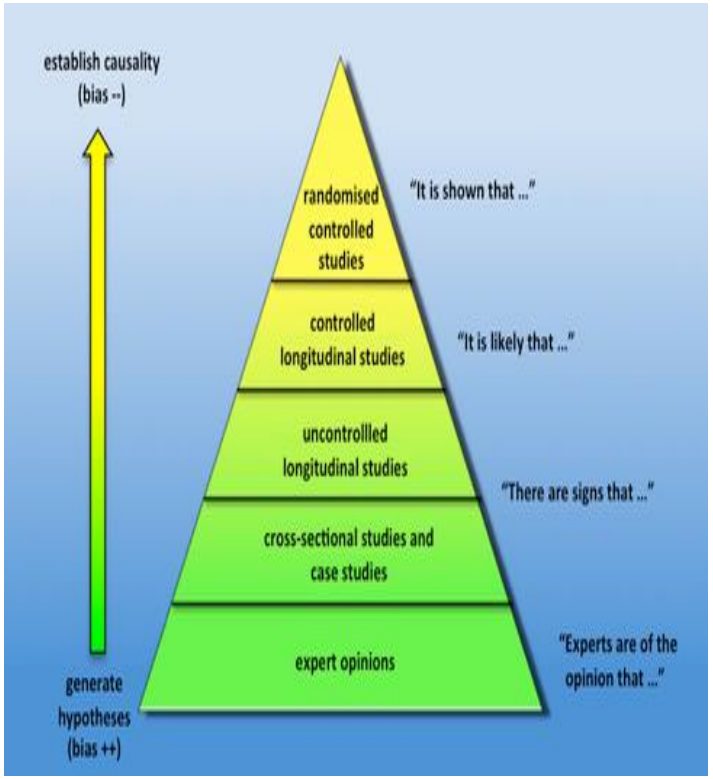
Cross-sectional study

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...
2...
3...
4...

# 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

1...
2....
3....

# Review Phase

- Ethical approval
- …
- …

# 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

1...
2...
3....
4....

# 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 oinformation

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# The role of the community engagement during CT

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# 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 communities of adults, adolescents, and children, depending on the nature of the research, or people with co-infections, such as tuberculosis or hepatitis C virus, or other stakeholders

- provide the most direct opportunity
- invest themselves in the research
- better penetration of communities with more acceptable
- raising awareness about within the community
- can help build trust
- 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 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 people made up from researchers, scientists, statisticians doctors community members DSM Boards, academia advisors

- And this is where you could also be as a community representative

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# Resources:

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

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