# Understanding Clinical Trials

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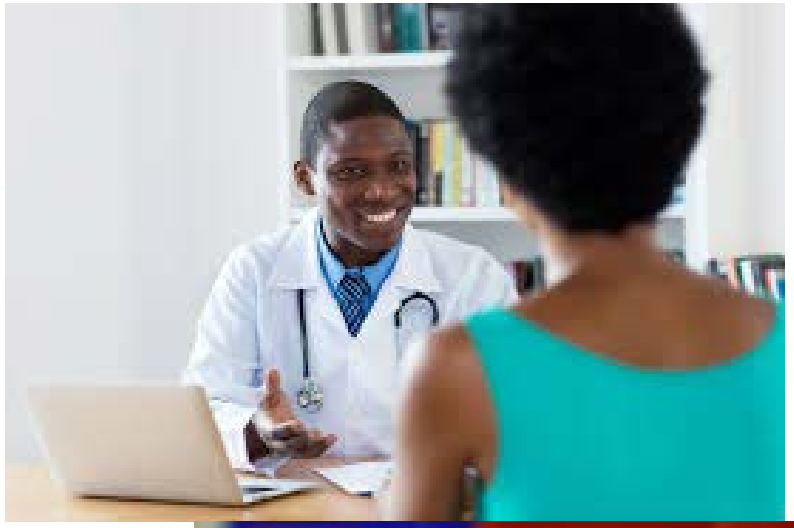
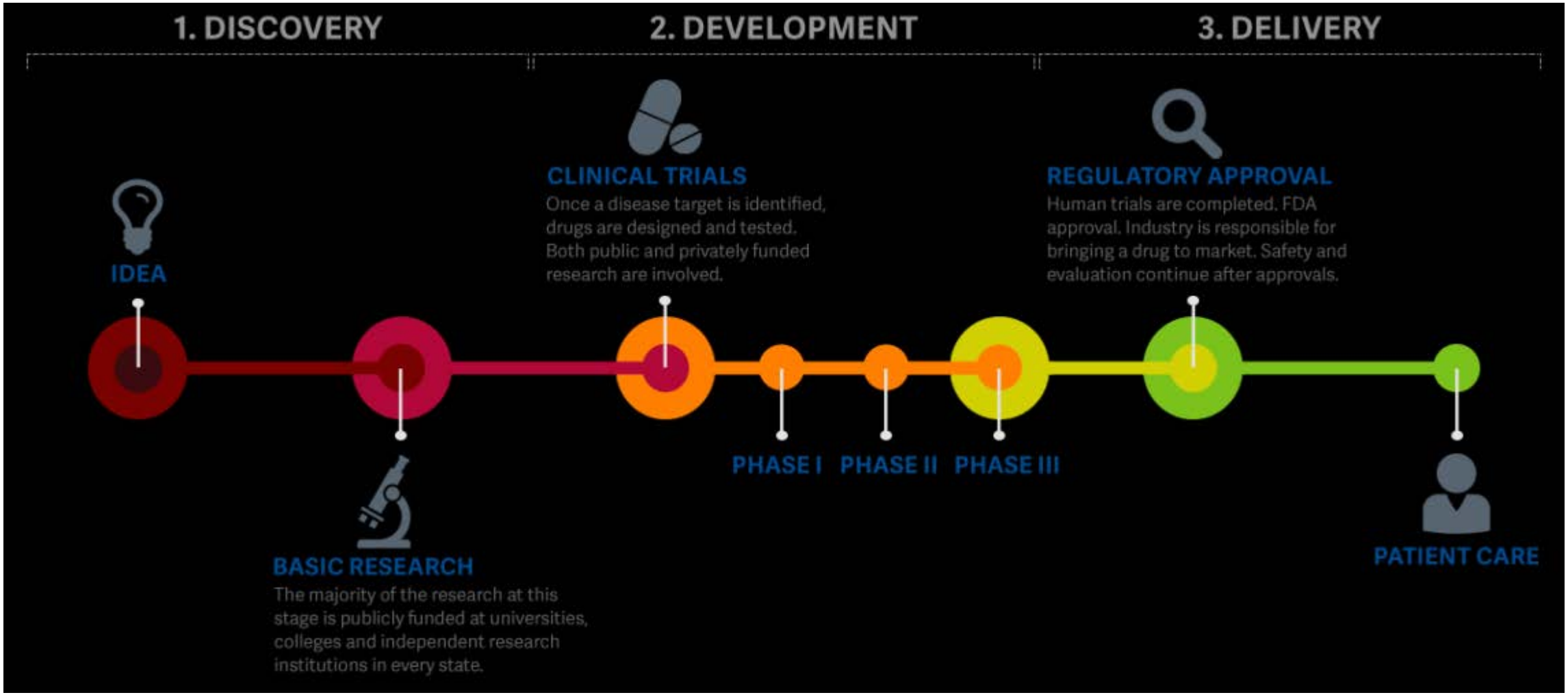
# Outline

- What are clinical trials?
- Clinical trial pathway overview
- Phase I trials
- Assessing safety in clinical trials
- Blinding
- Phase II trials
- Phase III trials
  - Randomization
  - Large trial size
  - Interpreting results from phase III trials
- Regulatory approvals
- Phase IV trials

# What is a clinical trial?

A clinical trial is a research study in which study participants are given a medical treatment or other type of intervention to see the effect of that intervention on the person's health.




1. DISCOVERY
2. DEVELOPMENT
3. DELIVERY
IDEA
BASIC RESEARCH
The majority of the research at this stage is publicly funded at universities, colleges and independent research institutions in every state.
CLINICAL TRIALS
Once a disease target is identified, drugs are designed and tested. Both public and privately funded research are involved.
PHASE I
PHASE II
PHASE III
REGULATORY APPROVAL
Human trials are completed. FDA approval. Industry is responsible for bringing a drug to market. Safety and evaluation continue after approvals.
PATIENT CARE

## Phase 1

Tests drug on healthy individuals

Tests for safety, dosage and side effects

## Phase 2

Tests on larger group of effected individuals

Tests for efficacy and side effects

## Phase 3

Tests on new and wider demographic

Tests for long term effectiveness and comparisons with other medications

## FDA approval

Treatment determined effective and safe for public use

## Phase 4

Continues to test for effectiveness and safety

Can be taken off the market if necessary

# Before phase I trials begin

- Researchers test the drug, device or vaccine in laboratory studies first.
- They find out as much as they can about how the product works and what effects it has on human cells, tissues, or other laboratory reagents.
- If the product seems promising, they will then test the product in animals before starting a clinical study with human volunteers.

The animal studies are usually designed to measure:

- **Safety** (looking for any adverse effects)
- **Biological effects** in the animal model (for example, does the animal produce antibodies in response to a vaccine?)
- **Effectiveness**—whether the product works to produce the right outcome (for example, the vaccine protects the animals from disease when they are exposed)

# Getting ready for phase I trials

- Special production facilities are needed to make a very high quality version of the product that will be tested in human clinical trial.
- The product needs to be tested for purity and stability before it is ready to use in a clinical trial.
- The FDA has to approve the use of the product and the research plan before any new phase I study is started.

# Phase I trial: how does it work?

- The primary purpose of phase I trials is to find out if the product is safe.
- Often phase I trials will measure human biological responses to the product, such as antibody responses to a vaccine, or measuring how the body metabolizes a specific drug.
- All the participants in a phase I trial are monitored closely by the researchers to check for any safety issues.
- Phase I trials usually involve healthy volunteers (with some exceptions).
- Usually there is no expectation that the participants will get clinical benefit from the trial.

# Safety issues in clinical trials

- Any negative changes in the participants' health status, whether or not it is related to the study, is referred to as an Adverse Event.
- Each Adverse Event is evaluated to see if it might be related to the product being studied.

Adverse Events get classified in different ways:

- Serious Adverse Events versus non-serious
- Related, possibly related, or unrelated
- If there are Serious Adverse Events that are possibly or probably related to the study, often the study will be paused for further assessment of safety.


Hospital ID Code
Hospital Name
Patient Initials
Randomisation number
First
Last
Box
Pack
CRASH-3
TRIAL TITLE: Tranexamic acid for the treatment of significant traumatic brain injury:
an international randomised, double blind, placebo-controlled trial
ADVERSE EVENT REPORT FORM
Please report on this form any adverse event occurring up to 28 days after randomisation.
Please refer to the Protocol / Study file for events which need to be reported while the patient is in the hospital
After discharge and up to 28 days after randomisation ALL untoward events must be reported on this form.
1. Report type (circle)
Initial
Follow-up
2. Country
I. ADVERSE EVENT INFORMATION
3. Do you know date of birth
a) YES
b) NO – approximate
4. Sex
Please tick
Male
Female

# Adverse Events: examples

- In vaccine trials, participants might experience soreness, redness, or swelling at the vaccination site on their arm.
- These kinds of reactions are usually expected, related to the vaccine, and in most cases, not serious.

- In drug trials, participants might have a change in the results of standard blood tests, for example, tests that measure how well the liver is functioning.
- Depending on how much change there is, this could be not serious, or serious.
- Changes could be related or unrelated to the drug.

# Adverse events: how to tell if they are related to the product?

- Investigators and medical monitors are checking every adverse event closely.
- To determine whether an adverse event is related, they use many sources of information:
  - Prior evidence from similar products or trials
  - Individual medical history
  - Biological rationale for relatedness
  - Timing in relation to when the participant received the product
- Because of the importance of safety for all participants, there are independent monitors assessing the adverse events:
  - A safety committee will assess all serious adverse events.
  - Serious adverse events that might be related to the product must be promptly reported to the IRB and the FDA.
  - A special committee called a Data and Safety Monitoring Board looks at all the unblinded clinical trial data periodically.

# Blinding in clinical trials

- Many phase I and II trials that use control groups or placebos, and almost all phase III trials, are *blinded.*
- Blinding means that participants and study staff do not know which participants have received the active product and which have received placebo.
- Often the investigators are also blinded—in which case the trial is called “double blind.”

- The reason for blinding is to avoid having participants, staff or investigators change their behavior or their assessment of the outcomes based on knowing whether an individual received active product or placebo.
- Statisticians sum this up by saying this reduces bias.

# Moving from phase I to phase II trials

- If a product has been tested in phase I trials and no serious safety issues are identified, it may move to phase II trials.
- Many products in phase I trials do NOT move on to phase II for one or more of the following reasons:
  - Product might have too many side effects
  - Might not produce the right biological response
  - Product might not be feasible to use in the population that needs it
- If investigators plan to move from phase I to phase II, they must first get approval from the FDA.
- All the data obtained from the phase I trial must be reviewed.

# Phase II trials

- Phase II trials involve a larger study population and gather more safety data, as well as, preliminary evidence about efficacy—does the product work.
- Some kinds of adverse events might be more uncommon and might be missed in a phase I trial.
- Phase II trials usually have some endpoints (data collected) about whether the product works.
- In vaccine trials, researchers often look for presence of antibodies or other immune responses, and some signs that people are protected from the disease.
- The same safety oversight procedures apply to phase II trials (checking all adverse events, etc).

# Phase III trials

- Phase III trials are large trials designed to test whether the product works—referred to as efficacy trials.
- For a treatment trial, the new treatment will be compared to either a placebo, or an existing treatment, if there is one approved for that disease or condition.
- In a vaccine trial, a new vaccine will be compared to a placebo, or to an existing vaccine, if there is one for the disease in question.
- Large numbers of participants are needed.
- Again, the same safety reporting procedures are used for all participants

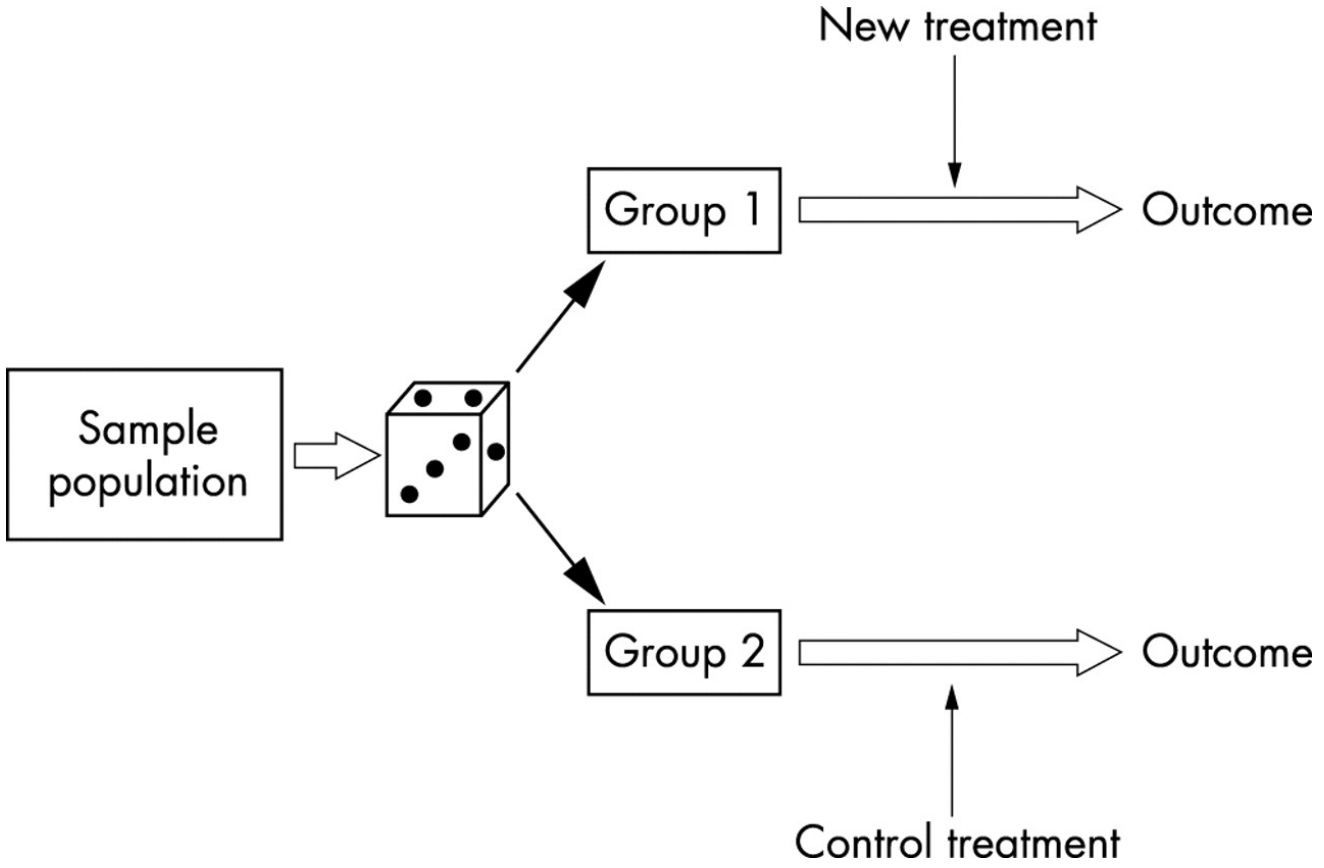
# Large randomized controlled trials

- **Randomization** is needed to make sure both groups (treatment group and placebo/control group) have the same characteristics.
- In other words, researchers don’t want treatment assignment be biased towards certain subgroups in the population.
- **Large trials** are needed to make sure the researchers can reliably see differences between the two (or more) groups.
- For example in vaccine trials, researchers will compare the number of people who get the disease in the vaccine group compared to the placebo/control group.

# Randomization

Example: a clinical trial with two groups, new treatment versus placebo

Study participants are assigned at random (like rolling dice or flipping a coin) to group 1 or group 2

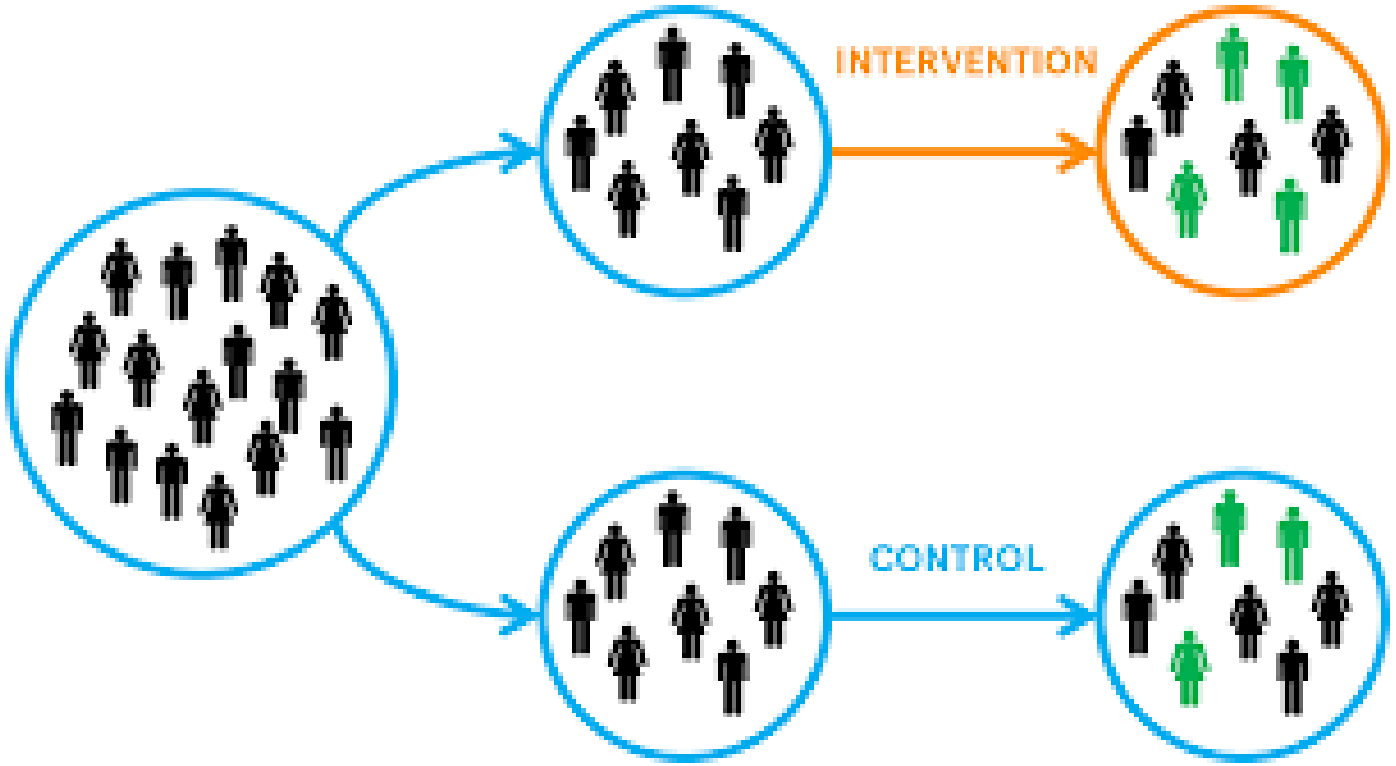


# Measuring endpoints

In a phase III trial, the researchers compare the numbers of people who have the outcome of interest in the two groups.

For example, the first group (intervention) might get a new vaccine, and the second group (control) might get a placebo.

The researchers assess how many people were protected from disease in the vaccine group compared to the placebo group



# Interpreting results from phase III trials

Clinical trials might show that a product:

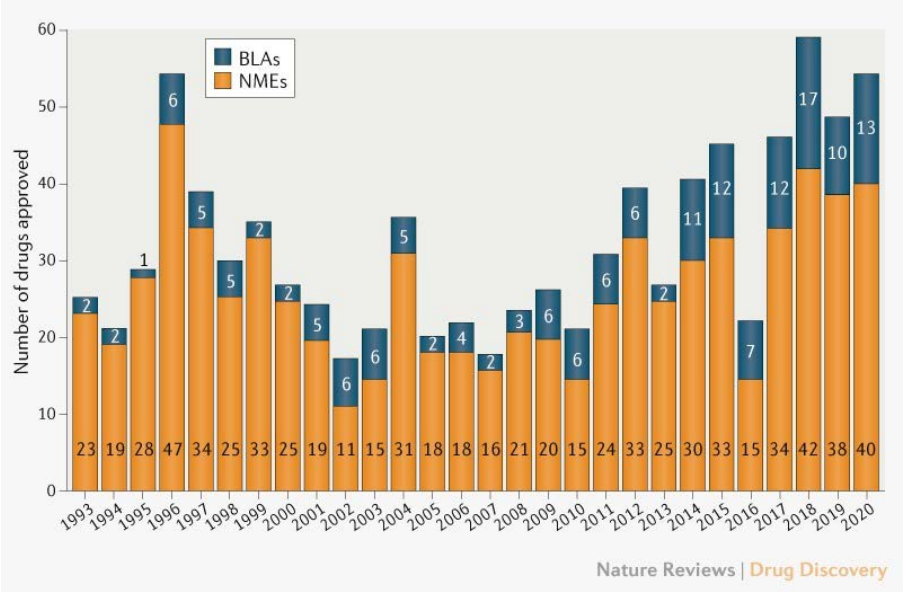
- **Is effective** (better outcomes in intervention group compared to placebo or control group)
- **Has no effect** (no difference between intervention group and placebo or control group)
- **Has negative effects** (intervention group has worse outcomes than placebo or control group)

Clinical trialists use statistical tests to help interpret trial results

- Statistical tests help determine if the results are reliable.
- Statistical tests help distinguish between results that reflect real efficacy versus results that could happen by chance.

# FDA approval

- A new product such as a drug or vaccine cannot be marketed in the US without FDA approval.
- FDA reviews all the data from clinical trials (phases I, II and III) and determines whether the data show that the product is safe and effective enough be authorized for use by the public.

# Phase IV trials

- After a product is approved by the FDA and used by the public, more data may be needed to determine how well it works in different populations and whether any very rare side effects might come up.
- Phase IV studies, also called post-marketing studies, gather data from the product being used on a broad population level.
- Information from these studies can help provide guidance to patients and health care providers about who should use the product, about additional safety information, or other relevant information.

# Questions?

# Some additional resources on clinical trials

- *[I will fill these in]*