BASIC PRINCIPLES OF CLINICAL RESEARCH

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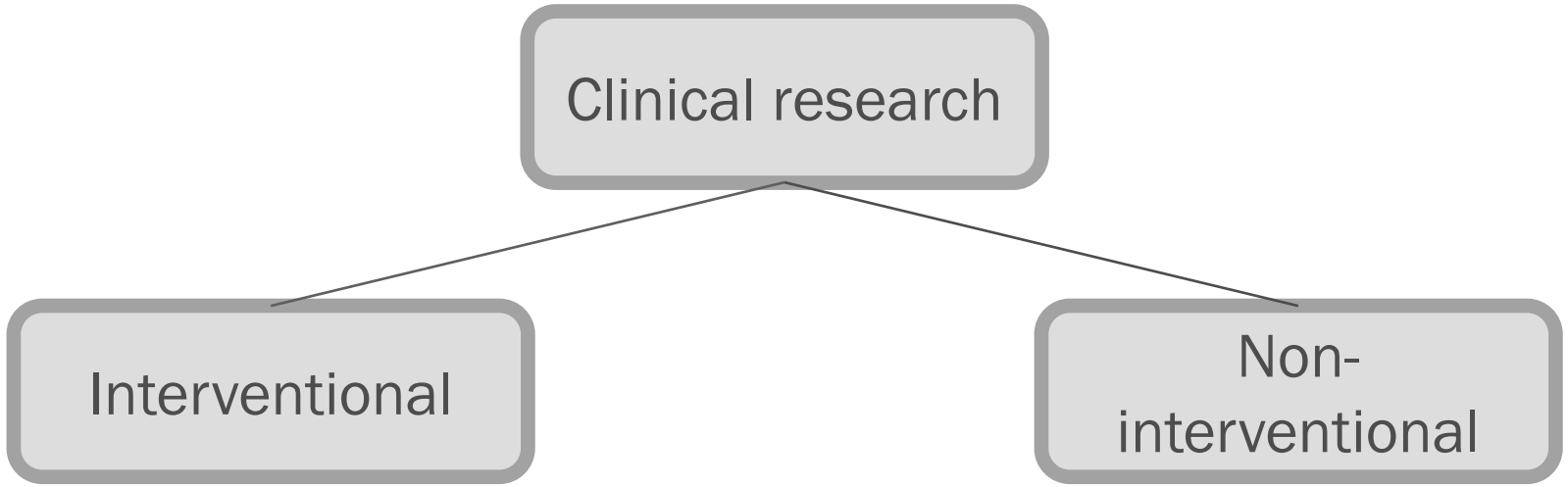
What is clinical research?

Any research regarding human health and disease that aims to add medical knowledge



Observational studies

Participants are observed to learn more about a specific intervention the participants are receiving

- The intervention is part of the routine medical care, patients are not assigned to specific interventions
- Patients may need to complete questionnaires
- No control group

What is a clinical trial?

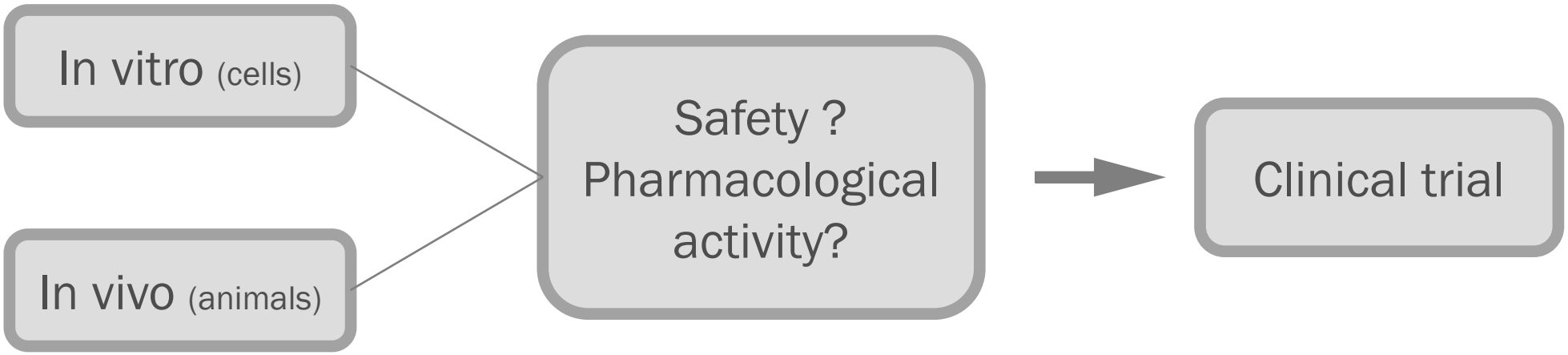
"Any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes"

- Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiological procedures, devices, etc …
- May be compared with a control group (receiving a placebo, another intervention or no intervention)

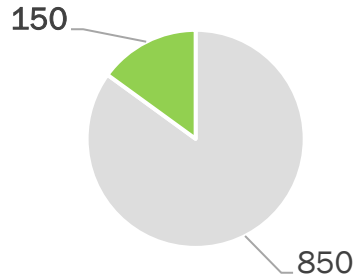
Clinical trial phases (drug development)

- Pre-clinical research
- Phase 1 - Safety
- Phase 2 - Efficacy
- Phase 3 - Safety and Efficacy
- Phase 4 - Post marketing surveillance

Pre-clinical research

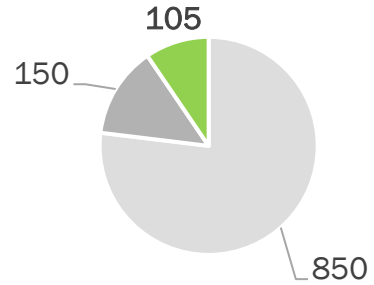


! 80 - 90% of drugs fail during pre-clinical research



Phase 1

- First-in-human studies
- 20 – 100 healthy volunteers or patients (in case of cancer therapies)
- Duration of several months
- Objectives:
  - ***Safety***
  - *Maximum tolerated dose (MTD)*
  - *Best way of administration*
  - *Pharmacokinetics*
  - *Pharmacodynamics*

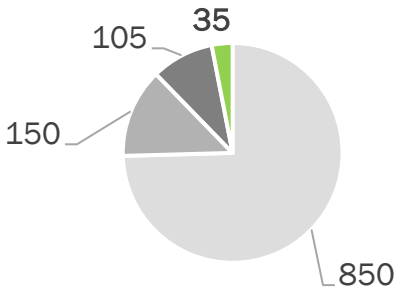


Approximately 70% of drugs move to the next phase

Phase 2

- First in target population studies
- 100 – 500 patients
- Duration of several months up to 2 years
- Objectives:
  - ***Efficacy***
  - *Side effects*
  - *Pharmacokinetics*
  - *Pharmacodynamics*

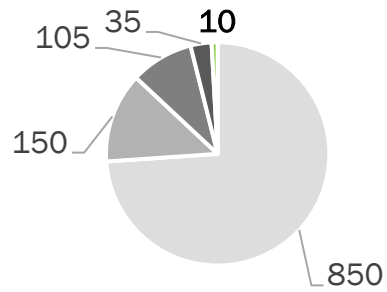
Approximately 33% of drugs move to the next phase



Phase 3

- Proof of efficacy studies
- Randomization (new treatment vs current treatment or placebo)
- 300 – 3000 patients
- Duration of 1 year up to several years
- Objectives:
  - ***Establish efficacy***
  - ***Safety*** *(long-term and rare side effects)*

Approximately 27,5% of drugs obtain marketing authorization



Phase 4

- Post-marketing studies
- Observational studies collecting real world data
- Thousands of patients
- Duration of several years
- Objectives:
  - *Safety (long-term and rare side effects)*
  - *Effectiveness*
  - *Quality of life*

Clinical research in practice

Guidelines and legislation

- Nuremberg code (since 1947)
- Declaration of Helsinki (since 1964)
- Good clinical practice (since 1996)
- European clinical trial regulation (since 2004, last renewed in 2022)

Aim: protect the rights and safety of participants, ensure credible results, harmonize clinical trial processes

Review

- Ethics committee (EC)
- Regulatory authorities (FAMHP)

Aim: ensure participant safety and compliance with good clinical practice

! Approval of both is required to start a clinical trial !

Note: Both EC and FAHMP need to provide feedback within 28 days (15 days for phase 1 trials) after the submission file has been declared complete, but it can take up to several months before an advice is given

Review – Ethics committee

- Relevance
- Benefit-risk assessment
- Protocol
- Capability of study staff
- Suitability of site facilities
- Informed consent form
- Insurance
- Participant compensation

Review – Regulatory authority

- Compliance with GCP and legislation
- Safety, quality and efficacy of medical intervention
- Risk-benefit assessment

During clinical trial:

› Inspections

After clinical trial:

› Marketing authorization

Key players

- Sponsor
- Investigator and study team
- Participant

Sponsor

= a person, company, institution, organization or group that is responsible for the initiation, management and (arranging) financing of a clinical trial

- Protocol writing
- Selection of qualified investigators
- Informing investigators
- Data management
- Quality control
- Reporting of safety findings to the authorities
- Submitting amendments of study documents to the ethics committee
- …

Sponsor - CRO

May delegate its tasks to a Clinical Research Organization (CRO), but the ultimate responsibility of the trial remains with the sponsor

Most common CRO tasks:

- Quality control
- Data management
- Reporting of safety findings
- Submitting amendments of study documents

Sponsor – Quality control

Important part of conducting a clinical trial is data collection

↳ Collected data entered in electronic Case Report Form (eCRF)

↳ Reviewed by CRA for accuracy (= source data verification)

Hospital admission - discharge details Document-No. 6584 - 1

Admission Date 25.08.2020 dd.mm.yyyy **Discharge Date** * 24.09.2020 dd.mm.yyyy ☐ Not discharged * — Comment Query

* If the patient was not discharged until next cycle is started (patient not leaving hospital between two chemotherapy cycles), please enter the last day before the next cycle initiation as the discharge date and then check "Not discharged".

Chemotherapy regimen ◉ 1st induction ○ 2nd induction ○ Consolidation ○ Salvage ○ Autologous transplant ○ Other — Comment Query

Regimen name Cytarabine 200 mg/m2 D1-7, Idarubicine 12 mg/m2 D1-3 — Comment Query

Start date 29.08.2020 dd.mm.yyyy **Stop date** 05.09.2020 dd.mm.yyyy — Comment Query

Other concomitant treatment for LMA/MDSit during this chemotherapy cycle? ◉ Yes ○ No — Comment Query

Midostaurin ○ Yes ◉ No **Azacitidin (e.g.Vidaza®)** ○ Yes ◉ No **Venetoclax (e.g.Venclyxto®)** ○ Yes ◉ No — Comment Query

Decitabin (e.g. Dacogen®) ○ Yes ◉ No **Other** ◉ Yes ○ No Gemtuzumab — Comment Query

Neutropenia 1st day 31.08.2020 dd.mm.yyyy **Neutropenia last day** * 24.09.2020 dd.mm.yyyy **Neutropenia not resolved** * ☐ **Total days of neutropenia** Score **25 days** — Comment Query

* If neutropenia did not resolve during this cycle (patient still neutropenic at discharge or if patient remained hospitalized until next chemotherapy cycle), please use the date of discharge or last day before next chemotherapy cycle as "Neutropenia last day" and check "Neutropenia not resolved".

Response to chemotherapy ◉ Complete ○ Partial ○ No response ○ PBM not done — Comment Query

Sponsor – CRA

Clinical research associate (CRA) is the first point of contact for the investigator and study team

- Monitoring
- Support
- Training

Investigator and study team

Investigator = physician (usually)

Study team = sub-investigators, study nurses, study coordinators, pharmacists

- Conduct the study
- Recruit participants by obtaining informed consent (IC)
- Protect the rights, safety and welfare of participants
- Maintain adequate and accurate records
- Ensure delegates are qualified for their tasks
- Supervise the proper handling and use of the investigational product(s)
- Reporting of safety findings to the sponsor
- …

Investigator and study team - IC

Informed consent = written, dated and signed approval of a person to voluntarily participate in a clinical trial, after being fully informed about the aim, significance and risks of that trial

- For children the parents or legal representative need to give informed consent
  - ↳ *Assent may be requested from children*
- For persons that are not capable of giving informed consent a legal representative needs to give informed consent
- For illiterates an impartial witness needs to attend the informed consent discussion and needs to approve in writing that the participant understands the study and voluntarily agreed to participate

Participant

- Understand the study and its possible risks
- Comply with study requirements
  - *Adhere to medication regimen*
  - *Show up at study visits*
- Provide truthful answers
- Report side effects

Question 1

Ann set up a multicenter trial to investigate the quality of life in CLL patients receiving Acalabrutinib by using questionnaires. AstraZeneca provides financing for the trial, but didn't contribute to the protocol. Which statement is true?

- This is a phase 4 clinical trial, Ann is the sponsor and AstraZeneca is the investigator
- This is an observational trial, Ann is the investigator and AstraZeneca is the sponsor
- This is a phase 4 clinical trial, Ann is the investigator and AstraZeneca is the sponsor
- This is an observational trial, Ann is the sponsor and AstraZeneca is the investigator
- This is both an observational and phase 4 clinical trial and Ann is both the sponsor and investigator

Question 2

Louis, 80 years old, has multiple myeloma and already received several lines of therapy. His treating physician noticed that he has progressive disease and wants to propose participation in a clinical trial as there are no other treatment options. However, Louis never learned to read. How can Louis give informed consent?

- He has to appoint a legal representative who can give informed consent instead of him
- An impartial witness has to attend the informed consent discussion and approve in writing that Louis understands the study and voluntarily agreed to participate
- Oral consent for participation in a clinical trial is sufficient if this is well documented in the patient file
- The treating physician can give informed consent instead of Louis because he took the Hippocratic Oath and may therefore only do what is best for the patient

Question 3

Pfizer has been testing a new drug for AML for several years and finally finished the phase 3 clinical trial. The results of this trial were positive and the new drug seems to have a higher efficacy and safety than the currently available therapies. Therefore Pfizer wants to obtain marketing authorization to make the drug commercially available. What should Pfizer do to obtain this marketing authorization?

- They have to submit a request to the ethics committees were the phase 3 trial was conducted and each ethics committee has to approve the request
- They don’t have to do anything. Pfizer will automatically receive marketing authorization if the results of the trial were positive
- They need to collect confirmation of all investigators that conducted the phase 3 trial that the drug would be an added value for the target patient population and send these confirmations to the minister of public health
- They have to submit a request to the regulatory authorities containing all relevant scientific data that was collected during every trial with the new drug in the target patient population

Question 4

Which tasks regarding a clinical trial are the responsibility of the sponsor? (Select all that apply)

- Writing the protocol
- Recruiting participants
- Reporting safety findings to the regulatory authorities
- Ensure delegates are qualified for their tasks
- Maintain adequate and accurate records
- All of the above
- None of the above

Question 5

Which task is no responsibility of the ethics committee in a clinical trial? (Select all that apply)

- Evaluate the safety, quality and efficacy of the medical intervention
- Assessing the benefits versus the risks
- Reviewing study documents
- Evaluate the capability of the study team
- Perform inspections
- All of the above
- None of the above

THANK YOU !

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References:
www.ema.europa.eu
www.fda.gov
www.famhp.be
www.cancer.org