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Introduction to Clinical Trials

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SLOVACRIN

Introduction

- International legislation
- Good Clinical Practice (GCP)
- Investigator & the site
- Clinical Trials in numbers

Clinical Trials Legislation

- **International –** declarations, conventions, agreements
- **European –** directives, regulations
- **National –** laws, regulations, (CZE – RA (SÚKL) guidelines)
- **Local –** organization/hospital rules, quality standarts, …
- **Agreements –** protocol, contracts

International legislation – history

- **The Nurenberg Code (1947)**
  - voluntary consent is essential
  - for the good of society
  - based on results of animal experimentation and knowledge of natural history of the disease
  - protect the subjects from suffering and injury
  - degree of risk must never exceed the humanitarian importance
  - adequate preparation and facilities
  - scientifically qualified persons
  - subjects have the right to stop the experiment anytime, all must be conducted in good faith

International legislation – history

- **Declaration of Helsinki (first adopted in 1964, amended)**
  - General Principles
  - Risks, Burdens and Benefits
  - Vulnerable Groups and Individuals
  - Scientific Requirements and Research Protocols
  - Research Ethics Committees
  - Privacy and Confidentiality
  - Informed Consent
  - Use of Placebo
  - Post-Trial Provisions
  - Research Registration and Publication and Dissemination of Results
  - Unproven Interventions in Clinical Practice

International legislation – history

- **Council for International Organizations of Medical Science (CIOMS)**

– founded 1949 WHO a UNESCO

– 1982 International Ethical Guidelines for Health-related Research Involving Humans

– 21 original guidelines, revisions in 1993, 2002, 2009, 2016 → 25 guidelines

- **International Conference on Harmonisation ICH E6 - Efficacy Guideline – GCP**

– first in May 1995

– newest addendum from 1 Dec 2016, in effect from 14 Jun 2017

Guidline for good Clinical practice E6(R2)

- Freely available online – European Medicines Agency (EMA)
- 8 chapters

1. Glossary
2. The principles of ICH GCP
3. Institutional Review Board / Independent Ethics Committee (IRB/IEC)
4. Investigator
5. Sponsor
6. Clinical trial protocol and protocol amendment(s)
7. Investigator's brochure
8. Essential documents for the conduct of a clinical trial

The Principles of ICH GCP I

1. Clinical trials should be conducted in accordance with the **ethical principles** that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated **benefits justify the risks**.
3. The **rights, safety, and well-being of the trial subjects** are the most important considerations and should prevail over interests of science and society.
4. The **available nonclinical and clinical information** on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be **scientifically** sound, and described in a clear, detailed **protocol.**

The Principles of ICH GCP II

6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent **ethics committee** (IEC) approval/favourable opinion.
7. The **medical care** given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified **physician** or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given **informed consent** should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate **reporting, interpretation and verification**.

    (addendum - This principle applies to all records referenced in this guideline, irrespective of the type of media used.)

The Principles of ICH GCP III

11. The **confidentiality** of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. **Investigational products** should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the **quality** of every aspect of the trial should be implemented.

    (addendum - Aspects of the trial that are essential to ensure human subject protection and reliability of trial results should be the focus of such systems.)

New European legislative
Clinical Trials Information System – portal CTIS

- Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014
- Effective as of 31 Jan 2022
- Harmonises the procedures for the submission, assessment and monitoring of clinical drug trials

- 3 year transition period – previous Directive 2001/20/EC and regulation 536/2014 both in force
  - 1st year accepts all applications
  - During the 2nd and 3rd year all trials submitted and approved „the old way“ can be finished outside of the CTIS portal

CTIS I

- **Worspace for the sponsors**
- **Workspace for the regulatory/competent authorities**
- **Public website**
  limited access to information about submitted and approved clinical trials

CTIS II

- Harmonized rules for all EU countries
- Online communication between the sponsors and the regulatory authorities
- One electronic application for the trial for all countries
- Shortened and automatically set deadlines
- Safety reports (EudraVigilance database)

→ faster and more effective submission and approval process

Submission process of CTIS

➢Part I

– Same for all countries, CT documentation (protocol, IB, etc.) will be assessed by one member state = reporting member state

➢Part II

– Other concerned member states can raise requests for explanation or supplementation of the study documentation

– Ethical aspects, reimbursement for the trial subjects, data privacy (GDPR), informed consent, etc.

Clinical Study vs. Clinical Trial I

➢ **'Clinical study'** means any investigation in relation to humans intended:

a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products

b) to identify any adverse reactions to one or more medicinal products; or

c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products; with the objective of ascertaining the safety and/or efficacy of those medicinal products;

➢ **'Clinical trial'** means a clinical study which fulfils any of the following conditions:

a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned;

b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or

c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.

Taken from *REGULATION (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014*

Non-commercial (= academic) Clinical Trials

- **REGULATION (EU) No 536/2014**

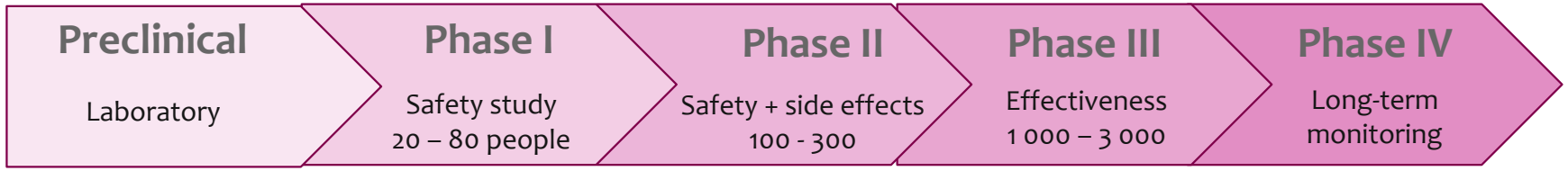
– Non-commercial sponsors frequently rely on funding which comes partly or entirely from public funds or charities.

– States may establish reduced fees for non-commercial clinical trials.

- Usually universities, hospitals, public scientific organisations, non-profit institutions, patient organisations or individual researchers
- Public funding (grants)

Clinical Trials – Introduction

- **Clinical trials vs. Medical Device Investigation**
- **Phases I-IV**



- **Subjects of CTs** – patients vs. healthy volunteers
- **Methodology – Golden Standart**
  - randomised, double-blinded, placebo controlled
- **Safety reporting**

CT Process - Glossary

CT	Clinical Trial
Sponsor	An individual, organisation or group responsible for initiating, managing, and financing a study
IMP	Investigational medicinal product
IB	Investigator´s Brochure – compilation of data on investigational products
CRF	Case Report Form – paper or electronic data/information on each CT subject
ICF	Informed Consent Form – the subject´s written approval of voluntary participation in study
EC	Ethics Commitee – multicentric (MEC) or local (LEC)
Site	Facility in which the study is conducted – hospital, private practice
CRA	Clinical Research Associate = study monitor
PI	Principal Investigator – main investigator at the site

CT Process

- Sponsor
- Investigator
- Study team
  - CGP, CV, responsibilities, qualification..
  - ICF for subjects
  - Protocol, Investigator´s Brochure
  - Safety reporting

CT Process – Roles I

- **Investigator**

– A person responsible for the conduct of the clinical trial at a trial site.

– If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.

ICH GCP 1.34

– Qualified by education, training, and experience

– Familiar with the Protocol, IB, and product information provided by the sponsor

– Be aware of and comply with GCP

ICH GCP section 4

CT Process – Roles II

- **Principle Investigator**

– The principal investigator may delegate (in writing only) tasks to team members but remain ultimately responsible for the proper conduct of the study

– Ultimate responsibility for the study team – CVs, education and other qualification, time and equipment

- **Resposibilities**

Before the start of the trial	Qualification of the study team, Resources, Agreements, Delegation of responsibilities
During and after the Trial	Informed consent, Compliance with the Protocol, Record keeping, Medical care, IMP distribution, Randomisation / Unblinding, Safety reporting, Archiving

Qualifications & Agreements

- **All study staff should be qualified by education, training & experience** (provide CV / other documentation)
- Everyone must be familiar with the protocol, Investigator brochure, GCP & regulations
- A list of tasks appropriately delegated to qualified personnel is required
- **The investigator - responsibilities:**
  - Follow the protocol
  - Follow the principles in the Declaration of Helsinki, ICH GCP and appropriate national laws
  - Permit monitoring & auditing by sponsor and inspection by regulatory agencies
  - Other items detailed in the contract that relate to the conduct of the trial

Resources

- **Demonstrate potential for recruiting required subjects**
- Have time, staff & facilities to conduct the trial
- Ensure that all staff are adequately informed about protocol, investigational product, & trial duties
- Investigator is responsible for supervising individual or party to whom the investigator delegates trial-related duties and functions
- If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual or party is qualified

ICH GCP 4.2

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ICH GCP 4.2

Informed Consent

- A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form

- Ethical obligation to inform the trial subject (Declaration of Helsinki)
- Every subject must be consented **before any trial-related procedure**
- Any written information & the consent form must be approved by the ethics committee before being used
- Permission for concerned persons (monitors, auditors, …) to access the subjects' medical and study files

ICH GCP 4.8

Informed Consent

- Each subject must understand exactly what is involved by being in the trial:
- The language used must be understandable to the subject
- Full verbal explanation must be given and any questions answered
- Subject must have ample time to consider their decision
- Subject cannot be influenced
- Subject should sign and personally date the consent form
- The person conducting the consent discussion should sign and personally date the consent form
- Subject must receive a copy of the signed & dated written consent form
- Special procedures for minors, emergency situations & people who cannot legally consent for themselves

Medical Care

- A qualified physician should be responsible for all trial-related medical decisions
- Adequate medical care must be provided to subjects for any adverse events
- Subject's primary physician should be informed about their participation

Protocol Compliance

- Trial must be conducted according to the protocol
- Protocol must be approved by EC & regulatory authority (CTR – national authority)
- Deviations or changes must be approved by sponsor first (unless safety-related)
- Any deviations must be documented & explained

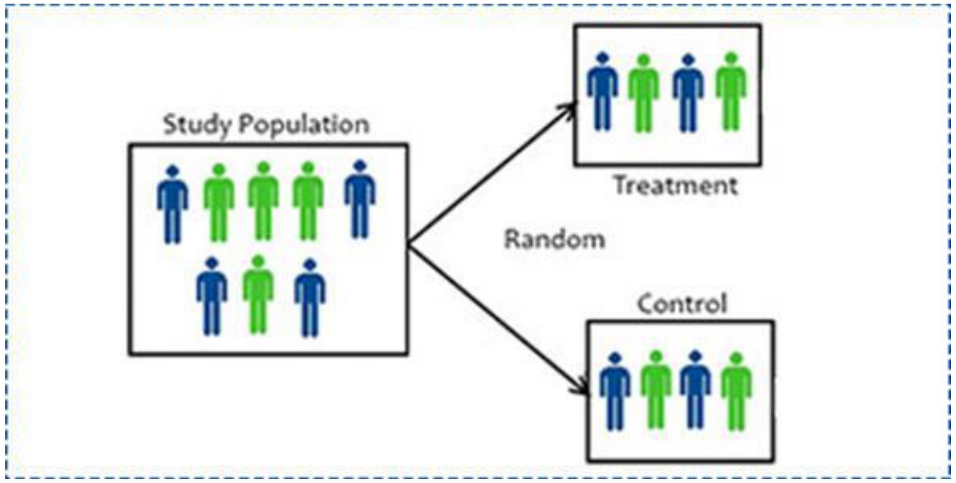
ICH GCP 4.5

Safety Reporting

- Adverse events (AEs) and/or laboratory abnormalities should be reported to sponsor according to requirements
- Serious Adverse Events (SAEs):
  - Death
  - Life-threatening
  - Inpatient hospitalisation or prolongation of hospitalisation
  - Persistent or significant disability/incapacity
  - Congenital anomaly/birth defect
- There may also be protocol-specific categories)
- All SAEs should be reported to sponsor immediately (within 24 hrs)
- Additional requested information should be provided to sponsor / EC

ICH GCP 4.11

Randomisation & Unblinding



- Follow trial randomization procedure
- Break code only in accordance with the protocol
- In case of any premature unblinding – promptly document and inform the sponsor

ICH GCP 4.7

Records & Reports

- Data in CRF & other records/reports should be adequate, accurate and consistent (ALCOAC)
- Changes to Records/Reports should be traceable, dated, initialed & explained (if necessary)

ALCOAC

- **Attributable** - It should be clear who has documented the data.
- **Legible** - Readable and signatures identifiable.
- **Contemporaneous** -The information should be documented in the correct time frame along with the flow of events. If a clinical observation cannot be entered when made, chronology should be recorded. Acceptable amount of delay should be defined and justified.
- **Original** - Original, if not original should be exact, certified copy; the first record made by the appropriate person.
- **Accurate** - Accurate, consistent and real representation of facts.
- **Complete** - Complete till that point in time.

Records & Reports

- Direct access must be given to all trial-related records (to monitors, auditors & regulatory agencies)
- Trial documents/Essential Documents (GCP chapter 8) should be kept (25 years)

Progress Reports

- Written report on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects to sponsor, EC, institution (if applicable) – promptly
- Written summary of the trial status (annually or more frequently if requested)

ICH GCP 4.10

Final Reports (CSR)

Investigational Medicinal Product (IMP)

- A **pharmaceutical form of an active ingredient or placebo** being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

GCP 1.33

- IMP should be manufactured, handled and stored in accordance with applicable **Good Manufacturing Practice (GMP)**. They should be used in accordance with protocol.

GCP 2.12

Investigational Medicinal Product (IMP)

Handling IP on Site

- IP must only be used in accordance with protocol
- Correct use of IP must be explained to each subject & subject compliance should be checked regularly
- Some or all IP accountability can be delegated to an appropriate pharmacist/ individual, but investigator retains overall responsibility
- IP should be stored as specified by sponsor, e.g., secure, refrigerated etc.
- Records should be kept of:
  - Delivery to site
  - Amount at site
  - Storage conditions
  - Dispensation/Use/Return details by each subject
  - Return to sponsor/alternate disposition

ICH GCP 4.6

Summary

- The investigator has numerous responsibilities defined by:
  - Guidelines (e.g. ICH GCP)
  - EU Regulations / Directives
  - Local regulation
  - Protocol
  - Contracts
- **The principal investigator is ultimately responsible** for the conduct of the trial, even if activities are delegated to other personnel
- Clinical Research Associate (CRA, monitor) and Site coordinator cooperation is crucial

Clinical Study Coordinator

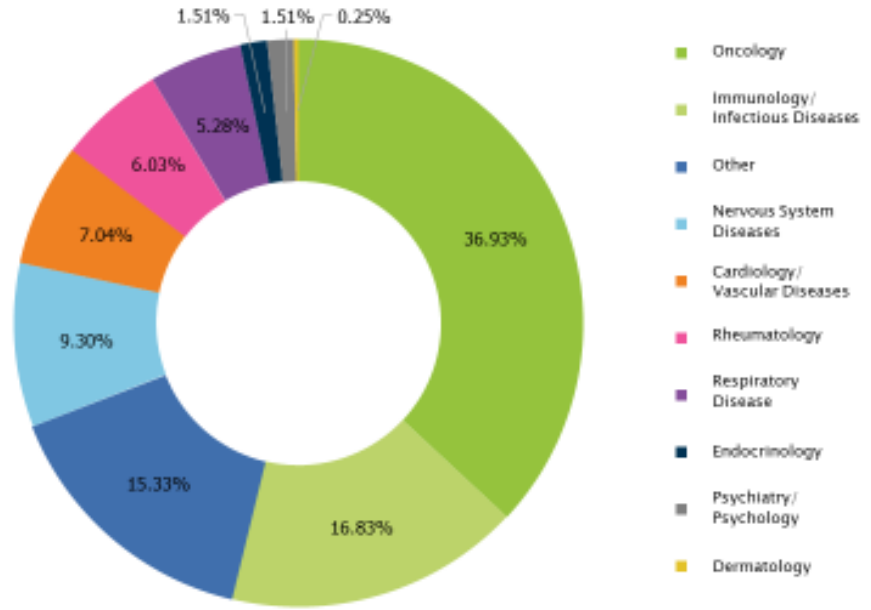
- **Key person for the relisation of the clinical trials on site**
- Site has to have the time, staff & facilities to conduct the trial
- Main contact point for the stakeholders (sponsor/site/investigator/patients)
- Different duties according to the type of the institution/site
- Helps the PI to ensure that all staff are adequately informed about protocol, investigational product, & trial duties
- Helps sponsors to realise the study on site from the feasibility to final reporting
- Acts on behlaf of sponsor for the institution own clinical investigations (IIT - investigators initiated trials/academic research)

Clinical Trials in numbers

AIFP Survey 2021 CZE

CLINICAL TRIALS BY THERAPEUTIC AREA

Structure of CTs conducted by AIFP members in 2021 by therapeutic area



Oncology and immunology surpass the other therapeutic areas in terms of the number of clinical trials. Oncological clinical trials represented in 2021 more than one-third of all clinical trials and, together with immunological and infectious disease clinical trials, **51% of all clinical trials in the CR.**

- **Oncology** shows the highest percentage of CTs (almost **37%**) and this percentage keeps steadily **growing** since 2015. Oncology represented **21** % of CTs in **2015** and **33** % of CTs in **2019.**
- On the other hand, the number of **immunological** clinical trials **dropped** from **22** % in 2019 to **17** % in 2021. **The number of cardiological CTs also dropped** - from **10**% in 2019 to **7**% in 2021.
- The high percentage of CTs concerning the "**other**" area is due to the fact that relatively many CTs were conducted in gastroenterology (mainly Crohn's disease and ulcerative colitis) and "non-tumoral" hematology (mainly hemophilia).
- **The low presence of "traditional" areas, such as cardiology, endocrinology (including diabetes) and respiratory diseases, is significant and interesting.**

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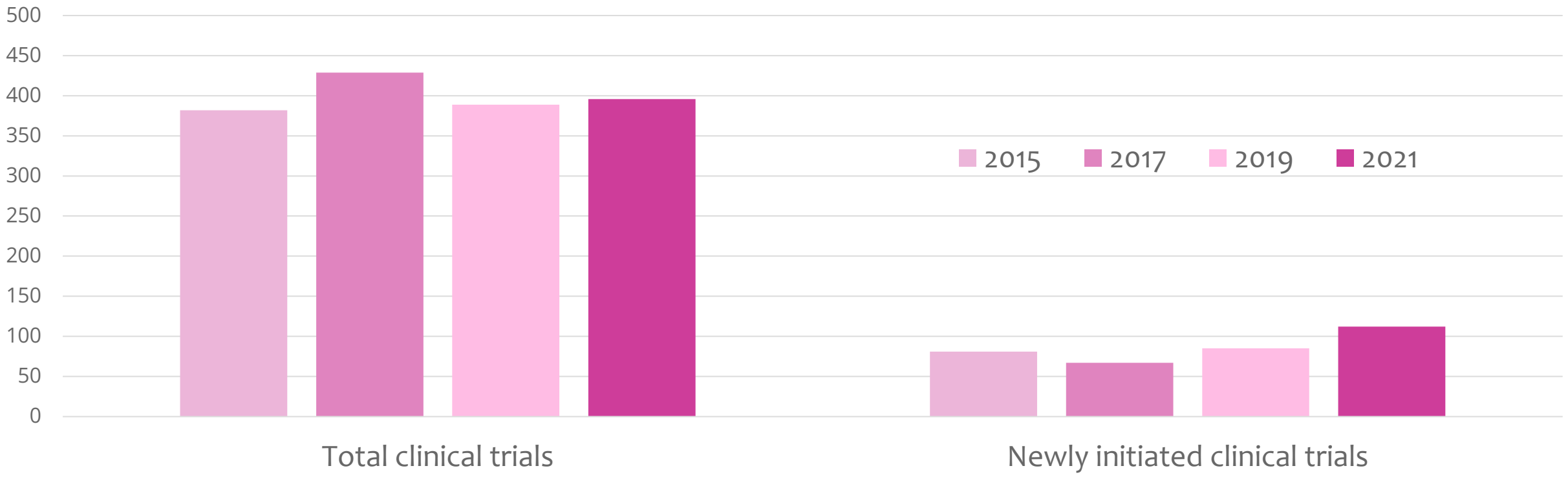
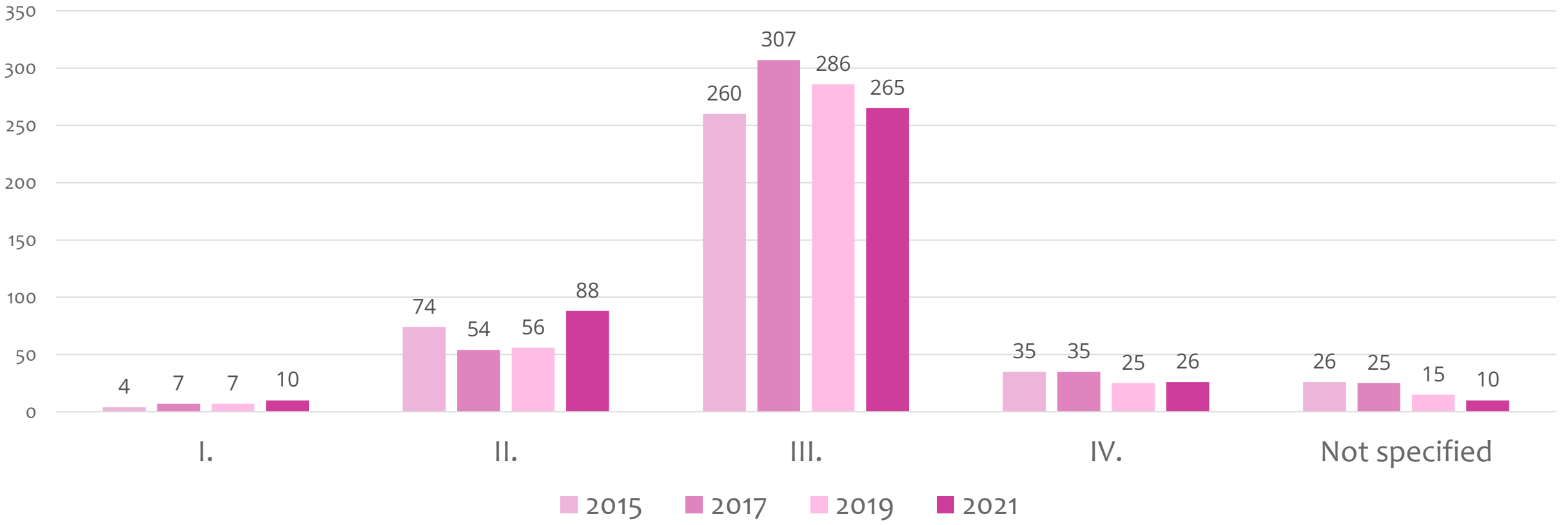
INNOVATION FOR LIFE

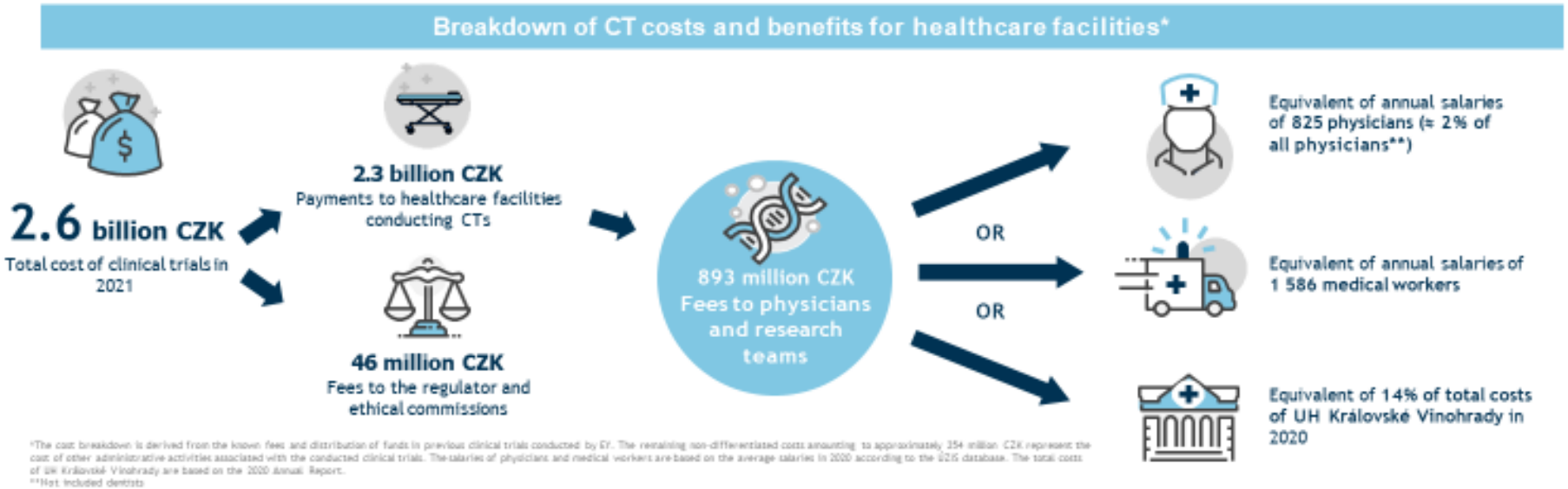
Clinical Trials conducted in the Czech Republic

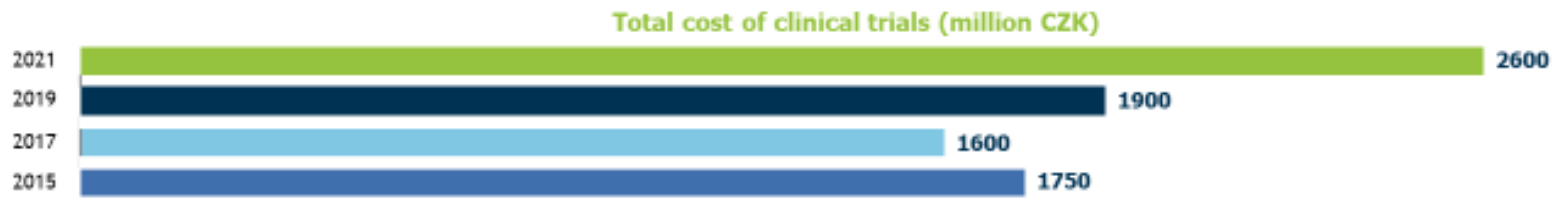


Clinical Trials conducted in the Czech Republic – by phase



FINANCIAL BENEFITS OF CLINICAL TRIALS





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Thank you
for being a part of CT community!

Masarykův onkologický ústav

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Narodowy Instytut Onkologii im. Marii Skłodowskiej-Curie Państwowy Instytut Badawczy

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NÁRODNÝ ONKOLOGICKÝ ÚSTAV umenie liečiť

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