The Evolution of Drugs
Through the Stages of Clinical Trials

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Agenda

- Introduction
- Drug Discovery Process
- Drug Development Process
- Patient Participation
- Conclusion

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What are Clinical Trials?

Clinical trials are research studies intended **to answer scientific questions** and find **better ways to treat or prevent diseases**.

They are fundamental to the development of innovative medicines and vaccines that treat and prevent illness.

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Clinical Trials

Clinical trials are conducted to determine whether **a new treatment is both safe and effective**. Such studies are possible because volunteers (healthy volunteers and patients) agree to participate and try new medicines or vaccines.

Drugs tested in clinical trials can be:

- Drugs that have not yet been approved by health authorities
- Drugs that are currently available for sale, and are being tested to improve existing formulations or evaluate the potential of the drug to treat other

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What Happens During Clinical Trials

- The process of clinical trial depends on the type of trial being conducted. Commonly, **the clinical trial team** includes doctors and nurses as well as social workers and other health care professionals. This team is responsible for the following:
  - checking the health of participants at the beginning of the trial,
  - giving specific instructions for participating in the trial
  - monitoring the particular carefully during the trial, and
  - staying in touch after the trial is completed.
- Some clinical trials **involve more tests or done at a more regular frequency** as well as more doctor visits than the participant would normally have for an illness or condition. For all types of trials, the participant works with a research team.
- Clinical trial participation is most successful when the carefully followed and there is frequent contact with the research staff.

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Types of Clinical Trials

- **Treatment trials** test experimental treatments, new combinations of drugs, or new approaches to surgery or radiation therapy.
- **Prevention trials** look for better ways to prevent disease in people who have never had the disease or to prevent a disease from returning. These approaches may include medicines, vaccines, vitamins, minerals, or lifestyle changes.
- **Diagnostic trials** are conducted to find better tests or procedures for diagnosing a particular disease or condition.
- **Screening trials test** the best way to detect certain diseases or health conditions.
- **Quality of Life trials** (or Supportive Care trials) explore ways to improve comfort and the quality of life for individuals with a chronic illness.

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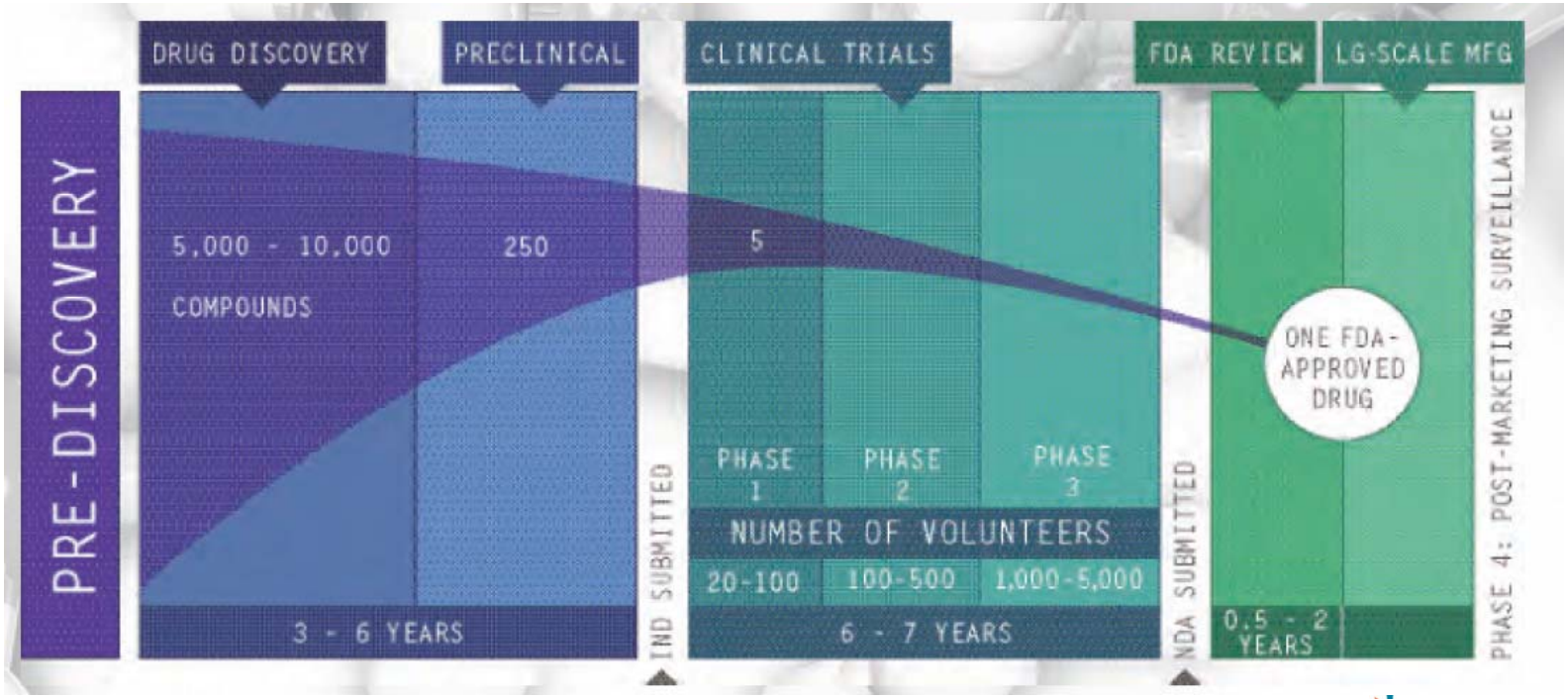
Drug Discovery and Development

- The total time it takes to develop **one new medicine** from the time it is discovered to when it is available for treating patients is **10-15 years**
- The **average cost to research** and develop **each successful drug** is estimated to be $800 million to $1 billion. This number includes the cost of the thousands of failures: **For every 5,000- 10,000 compounds** that enter the research and development (R&D) pipeline, ultimately only one receives approval.



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The Discovery Process

- Before new medicines can be discovered, **scientists must first understand the disease to be treated**, and to unravel the underlying cause of the condition.
- They do so by attempting to understand how the genes are altered, how that affects the proteins they encode and how those proteins interact with each other in living cells, how those affected cells change the specific tissue they are in and finally how the disease affects the entire patient.
- **The accumulation of this knowledge is the basis for treating the problem.**

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The Development Process

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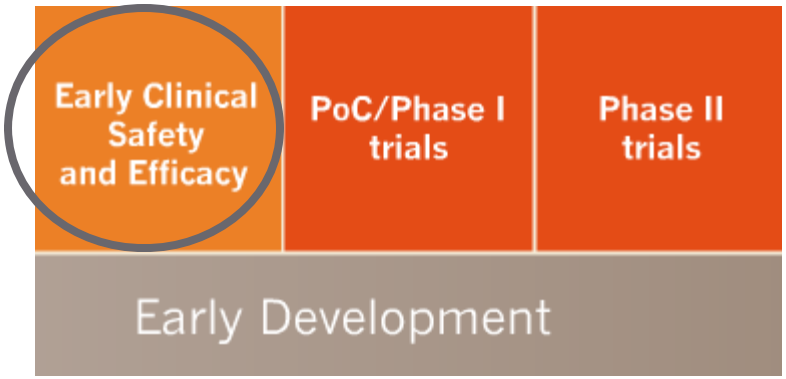
Early Development

Early Clinical Safety and Efficacy

To establish **an initial safety profile** of the drug, extensive toxicological and safety pharmacological profiles are done **using appropriate cell and animal models.**



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Early Safety Tests

Lead compounds must go through multiple tests to provide an early assessment of the safety of the compound. Scientists test Absorption, Distribution, Metabolism, Excretion and Toxicological (ADME/Tox) properties, or “pharmacokinetics,” of each lead.

Successful drugs must be:

- absorbed into the bloodstream
- distributed to the proper site of action in the body
- metabolized efficiently and effectively
- successfully excreted from the body and
- demonstrated to be not toxic

The Development Process

- Any clinical trials performed worldwide has to follow the International Conference Harmonization (ICH) guidelines.
  - These dictate how a clinical trial should be conducted
- Approval of respective Health Authority before **the start** of a clinical trial :
  - In Canada, it is the TPD (Therapeutic Products Directorate) of Health Canada:
  - Review of information submitted in the clinical trial application such as protocol and patient consent forms
- This application **requests permission to distribute the drug** to responsible clinical investigators that are named in the application. Included in the clinical trial application are the **results from preclinical tests, production methods, dosage form** and **information regarding the investigators** who will be conducting the study.

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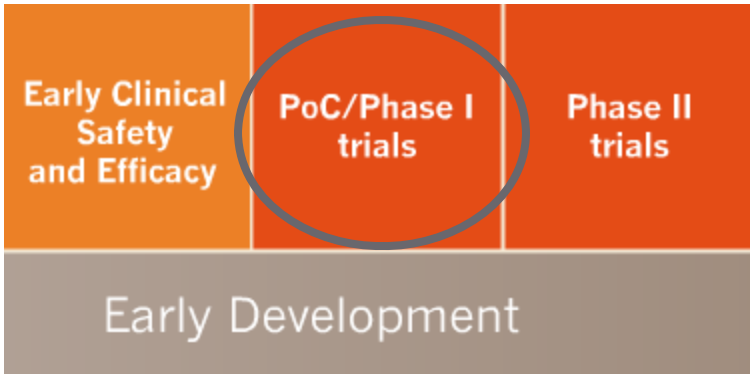
Early Development

Proof of Concept and Phase I trials

In PoC trials, the drug is for the **first time given to humans-** a small group of patients or healthy volunteers – in order to verify the mechanism of action and to **get an early readout of the efficacy of the compound in human disease.**

In Phase I trials, the drug is tested in a small group of patients or healthy volunteers (20-100) to evaluate its safety, determine a safe dosage range, and identify side effects.

PoC and Phase I trials are often combined.



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Design of Trials

- Design is dictated by the goal of the trial
- Choice also depends on the population, knowledge of the intervention
- Proper design is critical, analysis cannot rescue improper design

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Phase I Design

"Standard"

- Observe group of 3 patients
- No toxicity→ increase dose
- Any toxicity → observe 3 or more
  - » One toxicity out of 6 → increase dose
  - » Two or more toxicity (ie 2 out of 3; 2 out of 6) → stop

Bayesian sequential/adaptive designs

As the objective of the phase I is to find the tolerated dose

(Storer, *Biometrics* 45:925-37, 1989)

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Early Development

Phase II trials

In Phase II trials, the drug is given to a larger group of people *(100-500)* to test its effectiveness, to determine the effective dose range and to further evaluate its safety.

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Phase II Design

- Design of Gehan
  - No control
  - Goal is to reject ineffective drugs ASAP

    Decision I: Drug is unlikely to be effective in $\geq$ x% of patients

    Decision II: Drug could be effective in $\geq$ x% of patients

- Many cancer Phase II trials follow Gehan design
- Might also randomize patients into multiple arms each with a different dose – can then get a dose response curve
- **Other two-stage designs based on determining p_1-p_0 > x% where p_0 is the standard care combination**

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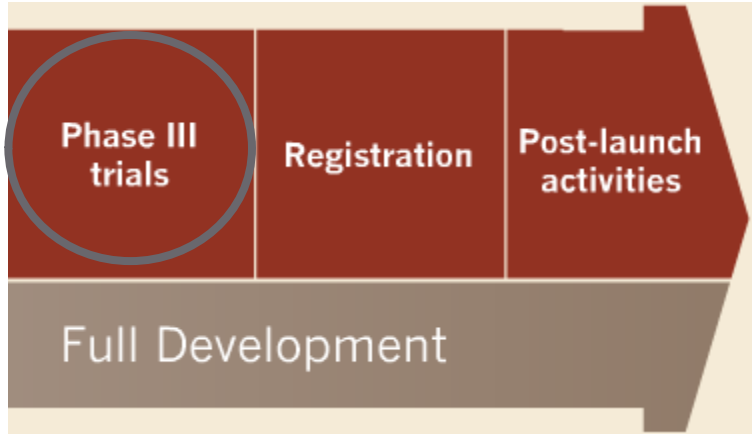
Full Development

Phase III trials

In Phase III trials, the drug is given to large groups of people *(1000-5000)* 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.



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Phase III Design

- Comparative Studies
  - Experimental Group vs. Control Group
- Establishing a Control
  - Historical
  - Randomized
- Randomized Control Trial (RCT) is the gold standard
  - Eliminates several sources of bias
  - To allow discrimination of patient outcomes caused by test treatment from those caused by other factors
  - Natural progression of disease
  - Observer/patient expectations
  - Other treatment
- Fair comparisons
  - Necessary to be informative

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Phase III Design

- Superiority Trials
  - A controlled trial may demonstrate efficacy of the test treatment by showing that it is superior to the control
    - No treatment
    - Best standard of care
- Non-Inferiority Trials
  - Controlled trial may demonstrate efficacy by showing the test treatment is similar in efficacy to a known effective treatment
    - The active control has to be effective under the conditions of the trials
    - New treatment cannot be worse by a pre-specified amount
    - New treatment may not be better than the standard but may have other advantages
      - Cost
      - Toxicity
      - Invasiveness

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Use of Placebo Control

- The “placebo effect” is well documented
- Could be
  - No treatment + placebo
  - Standard care + placebo
- Matched placebos are necessary so patients and investigators cannot decode the treatment assignment
- E.g. Vitamin C trial for common cold
  - Placebo was used, but was distinguishable
  - Many on placebo dropped out of study – not blinded
  - Those who knew they were on vitamin C reported fewer cold symptoms and duration than those on vitamin who didn't know

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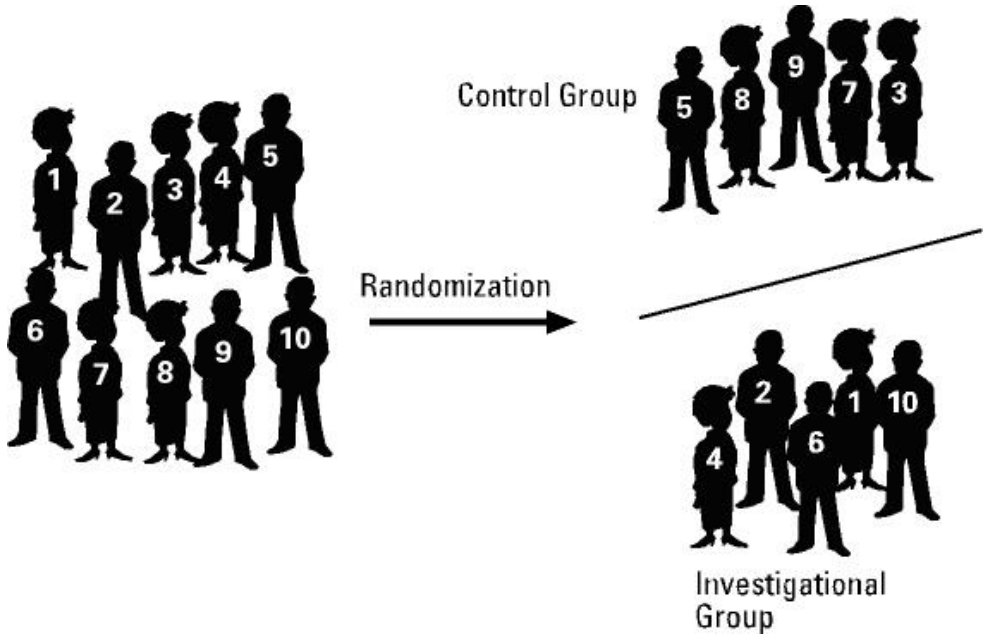
Randomized Trials

Participants have an equal chance to be assigned to one of two or more groups:

- One gets the most widely accepted treatment (standard treatment)
- The other gets the new treatment being tested, which researchers hope and have reason to believe will be better than the standard treatment
- Provides the best way to prove the effectiveness of a new agent or intervention



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Comparing Treatments

- Fundamental principle
  - Groups must be alike in all important aspects and only differ in the treatment each group receives
  - In practical terms, “comparable treatment groups” means “alike on the average”
- Randomization
  - Each patient has the same chance of receiving any of the treatments under study
  - Allocation of treatments to participants is carried out using a chance mechanism so that neither the patient nor the physician know in advance which therapy will be assigned
- Blinding
  - Avoidance of psychological influence
  - Fair evaluation of outcomes

Full Development

Registration

For the registration of a new drug, the results of all preclinical and clinical studies, the quality data and the description of the manufacturing process are compiled and submitted for review to the regulatory authorities. If the regulators agree that the data prove the quality, efficacy and safety of the drug, a marketing authorization is granted. From then on, a new drug can be made commercially available to patients.

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Review Process for a Drug

1. When a sponsor decides that it would like to market a drug in Canada, it files **a "New Drug Submission"** with the TPD (Therapeutic Products Directorate of Health Canada). This contains information and data about the **drug's safety, effectiveness and quality.** It includes the results of the preclinical and clinical studies, details regarding the production of the drug, packaging and labelling details, and information regarding therapeutic claims and side effects.

2. The TPD performs a thorough review of the submitted information, sometimes using **external consultants and advisory committees.**

3. The TPD evaluates the safety, efficacy and quality data to assess **the potential benefits and risks of the drug.**

4. The TPD reviews the information that the sponsor proposes to provide to health care practitioners and consumers about the drug (e.g. the label, product brochure).

5. If, at the completion of the review, the conclusion is that the benefits outweigh the risks and that the risks can be mitigated, **the drug is issued a Notice of Compliance (NOC),** as well as a Drug Identification Number (DIN) which permits the sponsor to market the drug in Canada and indicates the drug's official approval in Canada.

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Full Development

Post-launch activities

Once a drug is on the market, adverse effects need to be constantly monitored and reported to the regulatory authorities. In addition, life-cycle programs – including Phase IV clinical trials - are often undertaken to add new indications or improve existing formulations of the drug.

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Clinical Trial Participation – WHO?

- Using inclusion/exclusion criteria is an important principle of medical research that helps to produce reliable results.
- The factors that allow someone to participate in a clinical trial are called **"inclusion criteria"** and those that disallow someone from participating are **called "exclusion criteria**". These criteria are based on such factors as age, gender, the type and stage of a disease, previous treatment history, and other medical conditions.
- Some research studies seek participants **with illnesses or conditions** to be studied in the clinical trial, while others need **healthy participants**.
- It is important to note that inclusion and exclusion criteria are not used to reject people personally. **Instead, the criteria are used to identify appropriate participants and keep them safe.** The criteria help ensure that researchers will be able to answer the questions they plan to study.
- These have been discussed with and are supported by medical expert as well as with the health authorities having the objective to minimize the risk of exposure to a new treatment

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Informed Consent

- Informed consent is the process of learning the key facts about a clinical trial before deciding whether or not to participate.
- To help someone decide whether or not to participate, the doctors and nurses involved in the trial explain the details of the study.
- If the participant's native language is not English, translation assistance can be provided.
- The participant then decides whether or not to sign the document.
- It is also a continuing process throughout the study to provide information for participants.
- Informed consent is not a contract, and **the participant may withdraw from the trial at any time.**

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Clinical Trial Participation

Benefits

Clinical trials that are well-designed and well-executed are the best approach for eligible participants to: Play an active role in their own health care.

- Gain access to new research treatments before they are widely available.
- Obtain expert medical care at leading health care facilities during the trial.
- Help others by contributing to medical research.

Risks

There are risks to clinical trials. There may be unpleasant, serious or even life-threatening side effects to experimental treatment.

- The experimental treatment may not be effective for the participant.
- The protocol may require more of their time and attention than would a non-protocol treatment, including trips to the study site, more treatments, hospital stays or complex dosage requirements.

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Considerations Before Participating in a Trial

- What should people consider before participating in a trial?

  People should know as much as possible about the clinical trial and feel comfortable asking the members of the health care team questions about it, the care expected while in a trial, and the cost of the trial. Questions to ask:

- What is being studied?
- Why do researchers believe the intervention being tested might be effective? Why might it not be effective? Has it been tested before?
- What are the possible interventions that I might receive during the trial?
- Who will know which intervention I receive during the trial? Will I know? Will members of the research team know?
- How do the possible risks, side effects, and benefits of this trial compare with those of my current treatment?
- What tests and procedures are involved?
- How long will the study last?
- Who will pay for my participation?
- Will I be reimbursed for other expenses?

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Conclusion

- The conduct of clinical trials follows strict and rigourous regulations and processes
- The sponsor are being auditted to make sure that these steps are well followed
- The sponsor is also verifying the patient eligibility and provide protocol training to the participating study team at the hospitals
- The patients have a key role into this whole process

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More Information

- www.clinicaltrials.gov
- Health Canada
  - http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/cta_intro-eng.php
- Your Health Care Provider

Thank you!

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