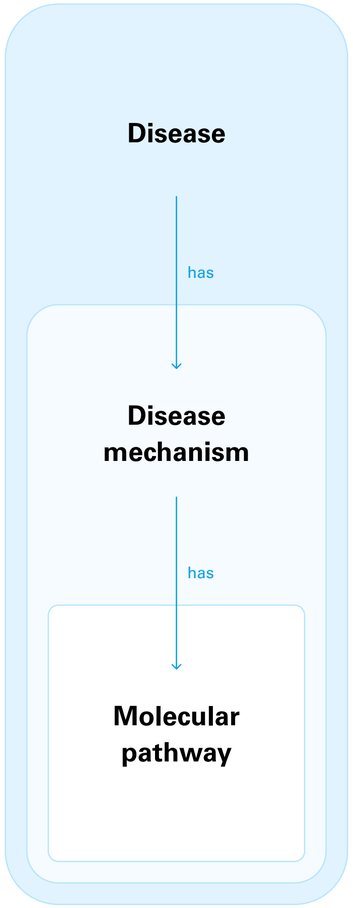
July 9, 2024

Understanding Clinical Trials
A Social-Technical System Deployed to Improve Public Health

Dubberly Design Office

Discovery and development of new drugs and other treatments often benefits from improving disease models.

A disease has mechanisms through which it affects the human body.
Disease mechanisms often involve certain molecular pathways.



Researchers use maps and models to represent their understanding of how a disease works and run simulations to study disease progression, mechanisms, and treatments.

Disease

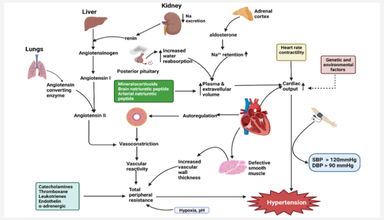
has

Disease mechanisms

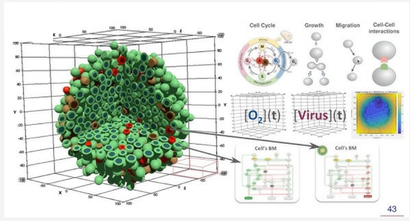
have

Molecular pathways

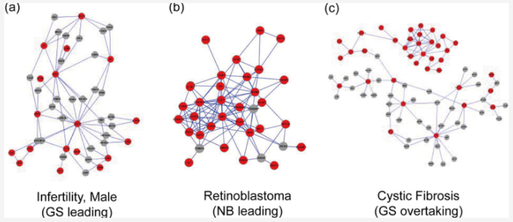
represented by → **Disease maps**

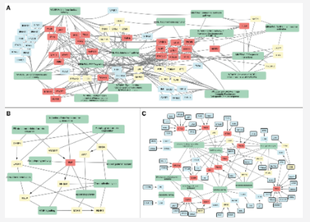


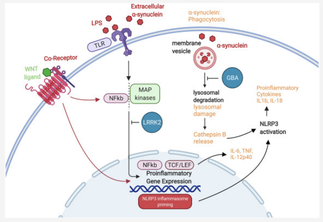
simulated with → **Disease models**



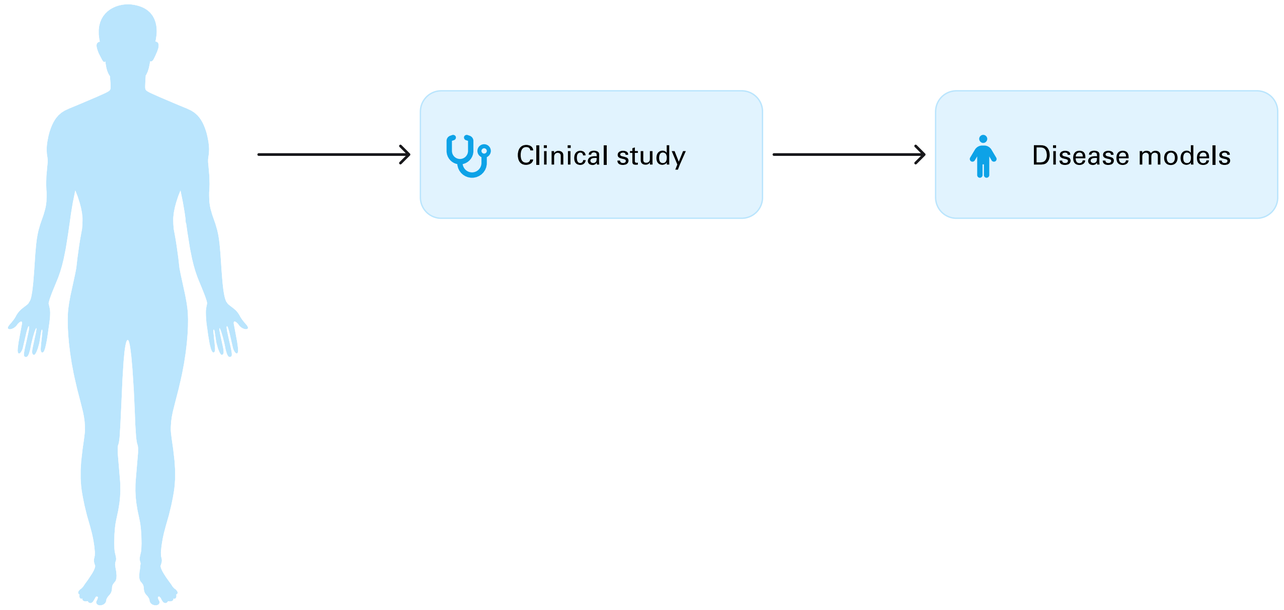
represented by → **Pathway models**







Disease models are developed based on findings from clinical (or preclinical) study



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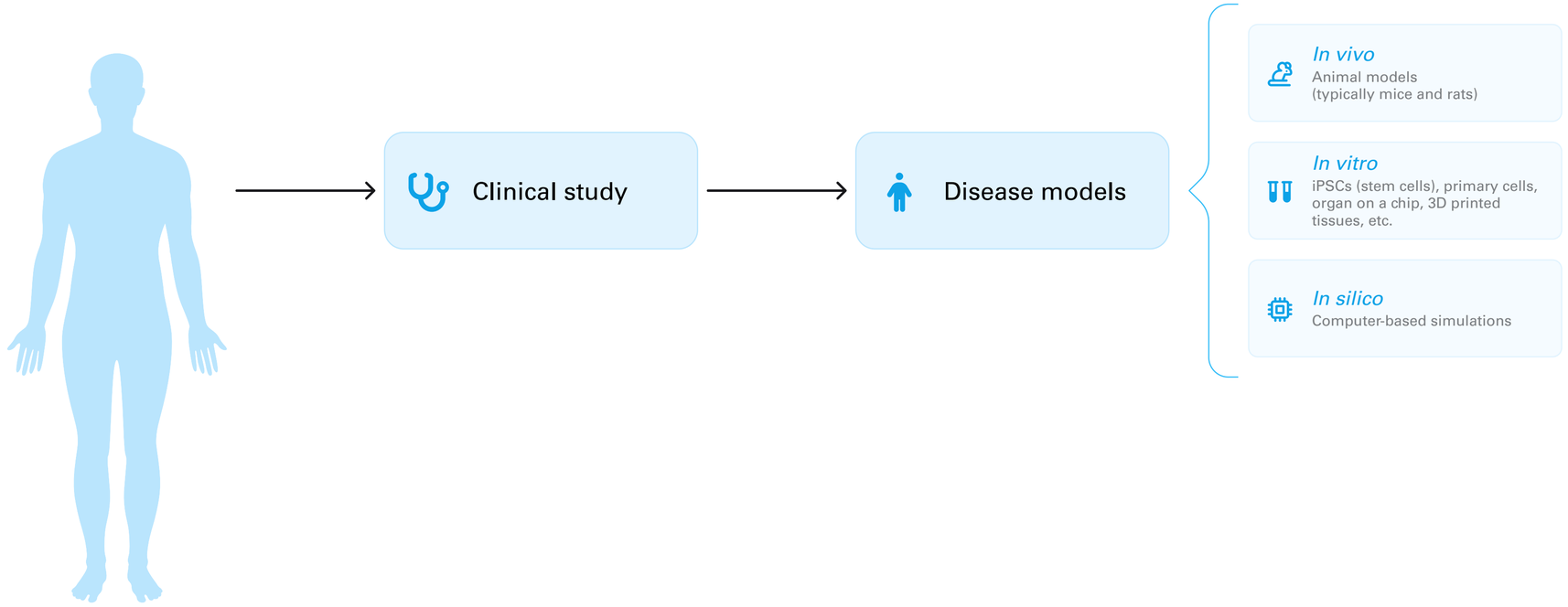
Disease models are developed based on findings from clinical (or preclinical) study — they can be in vivo (animal models), in vitro (cell cultures), or in silico (computer simulations).



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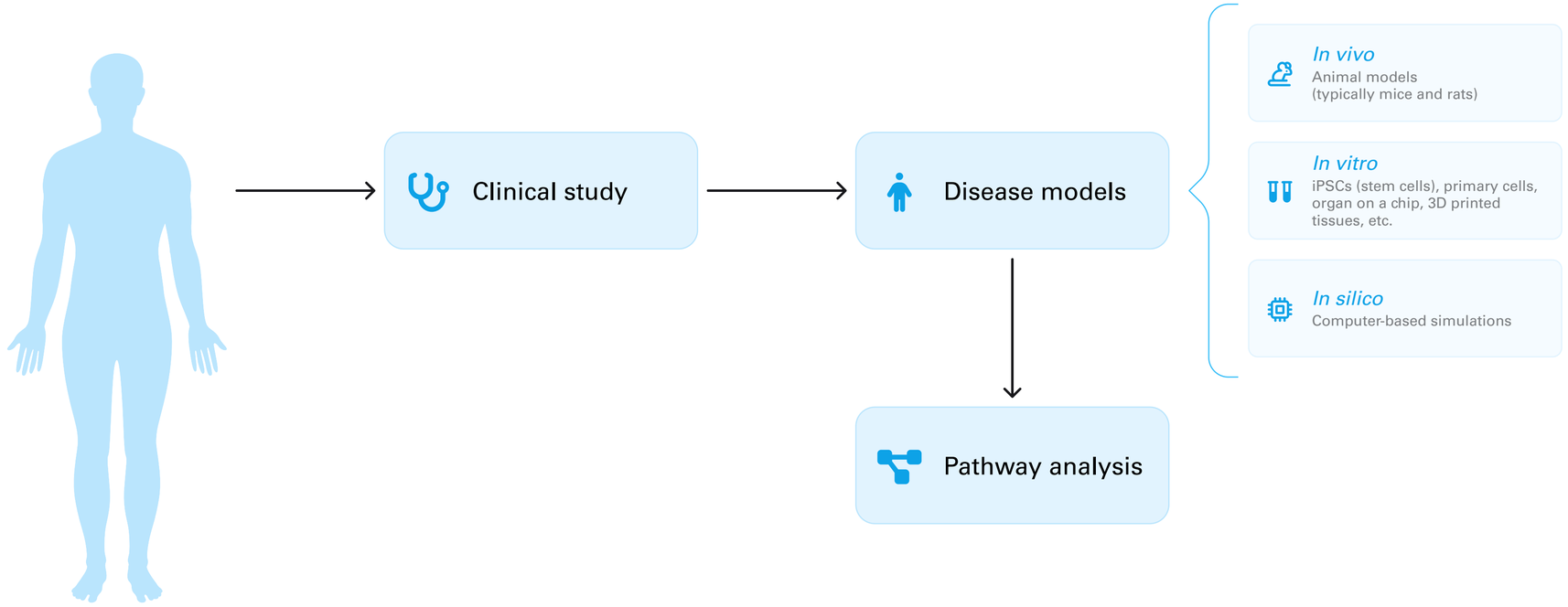
Researchers can use disease models to study a disease's underlying molecular pathways.



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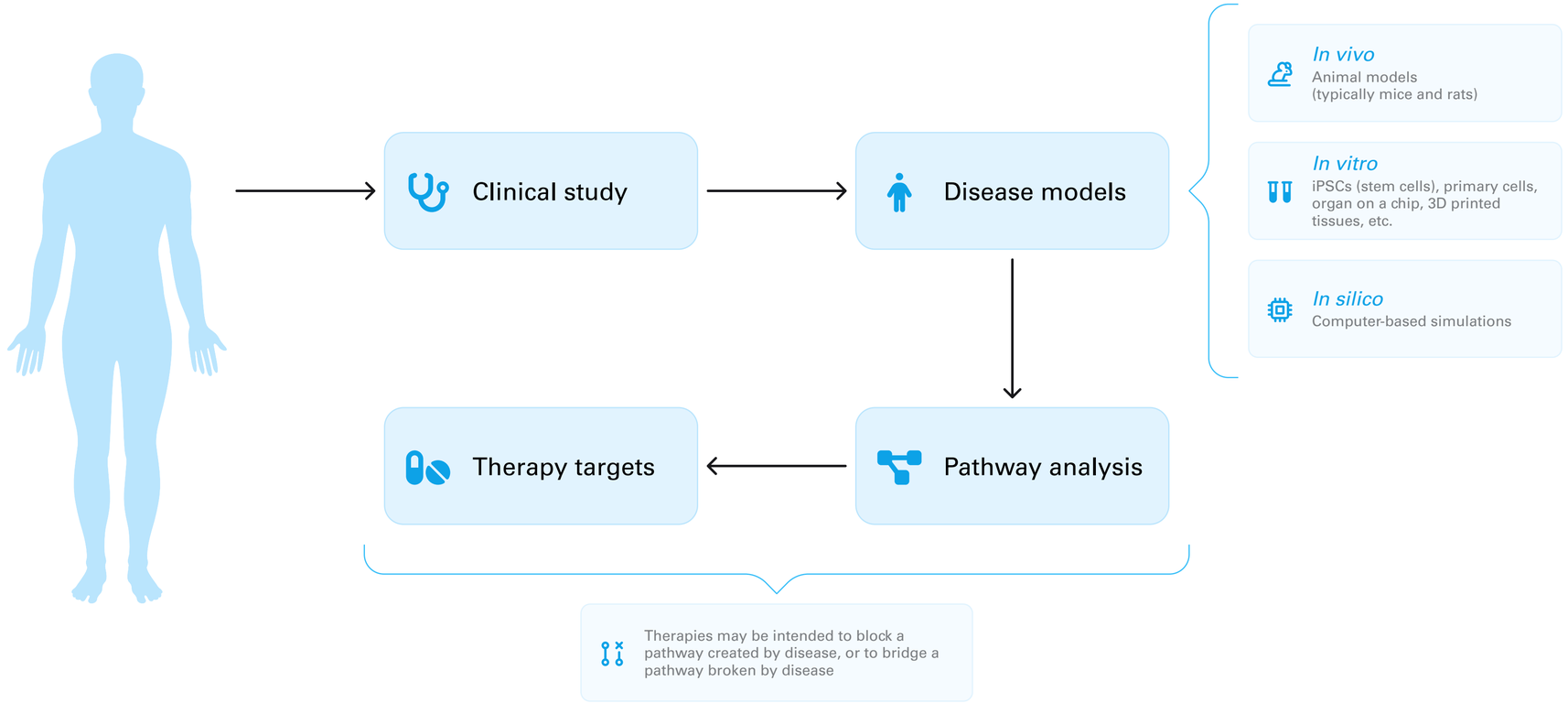
Understanding the disease's molecular pathways enables them to identify potential targets for therapies.



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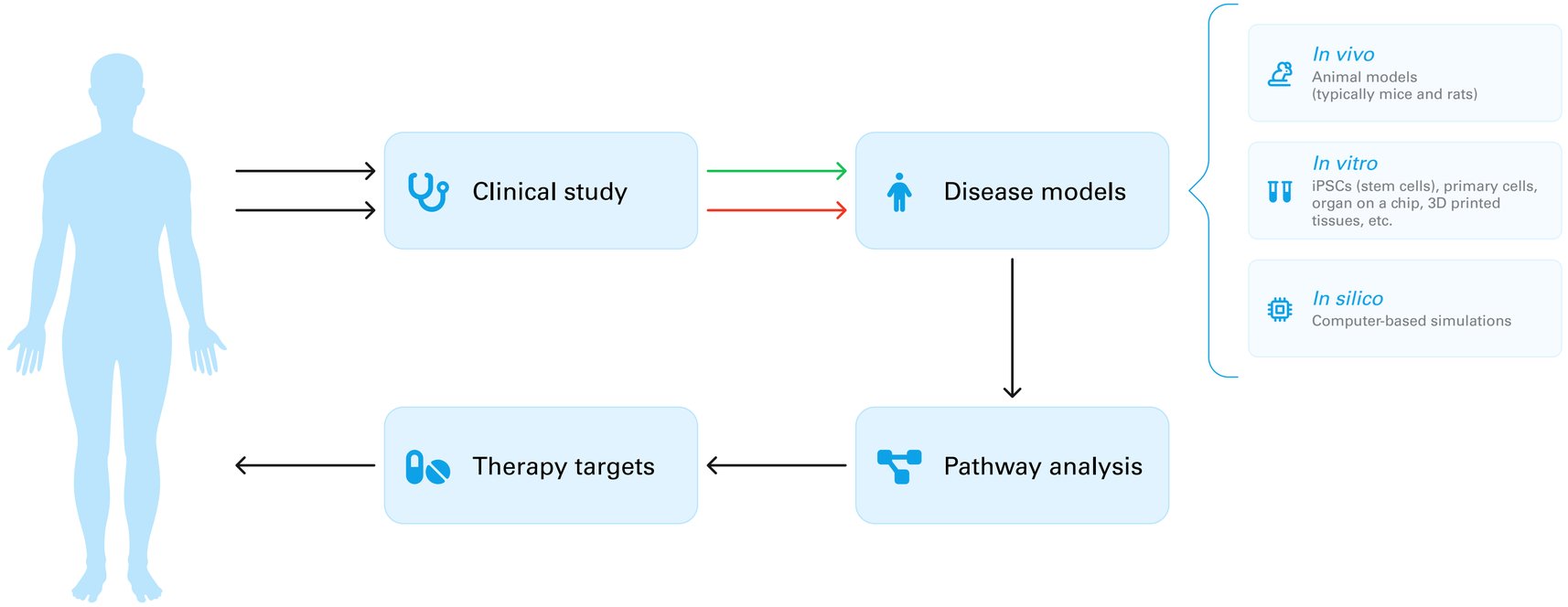
Potential therapies are then tested in clinical study.

If study outcomes align with researchers' expectations it validates the disease model — if they do not align, researchers can then refine the disease model based on the findings.



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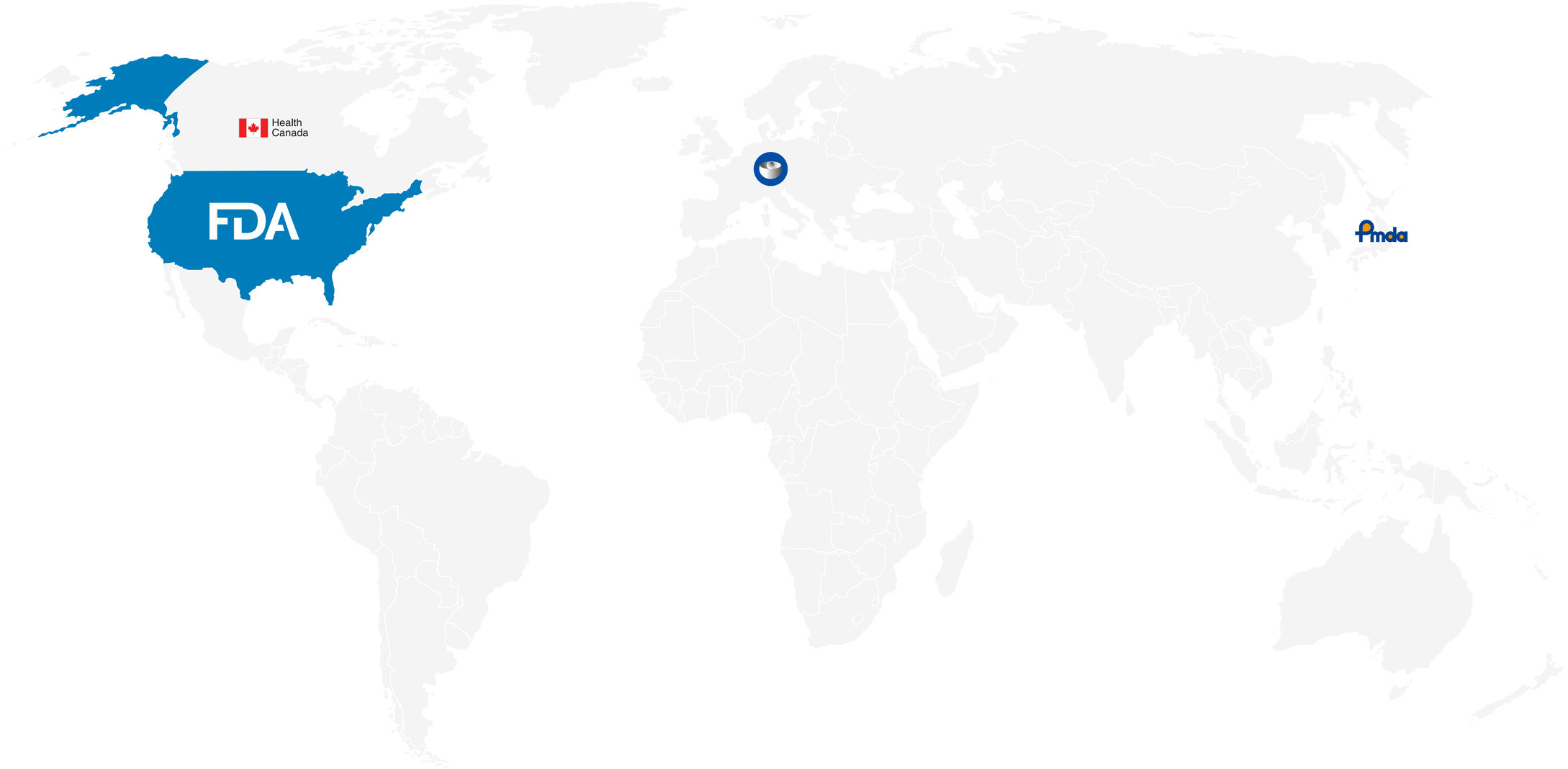
**In order for a new drug
or other treatment
to be used to help patients,
it must first be tested in clinical trials
to ensure that it's safe and effective.**

We’ll cover some key aspects of clinical trials at various levels of detail:

1. **An introduction to clinical trials** with a high-level overview of what they are and who’s involved.
2. **The scientific method** and its role in ensuring the validity of clinical trial results.
3. **The process of conducting a clinical trial** in greater detail using a Phase 3 trial as an example.
4. **Developing a study protocol** and how feedback and iteration are involved in the process.
5. **Study design** in Randomized Controlled Trials.
6. **Pfizer’s COVID-19 vaccine** as a case study of clinical trials.
7. **Comparing study outcomes** to determine whether a drug is effective.

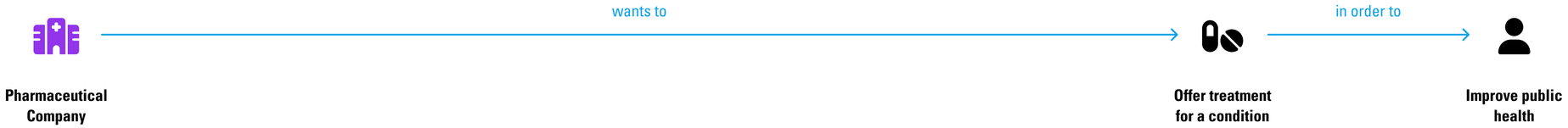
This document focuses primarily on clinical trials in the United States under the Food and Drug Administration (FDA).
However, much of the information is also generally applicable to other regulatory bodies,
such as the European Medicines Agency (EMA), due to their similar processes.



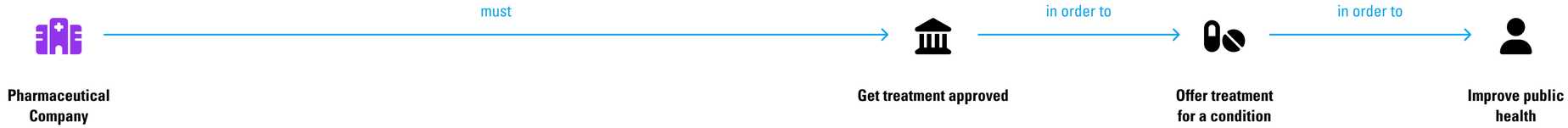
PART ONE

Let’s start with a high-level introduction to clinical trials.

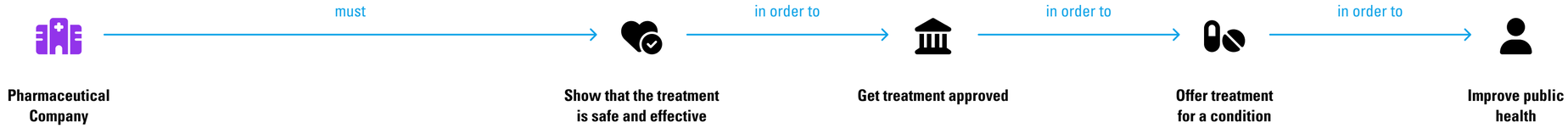
A pharmaceutical company develops a drug to treat patients with a particular medical condition.



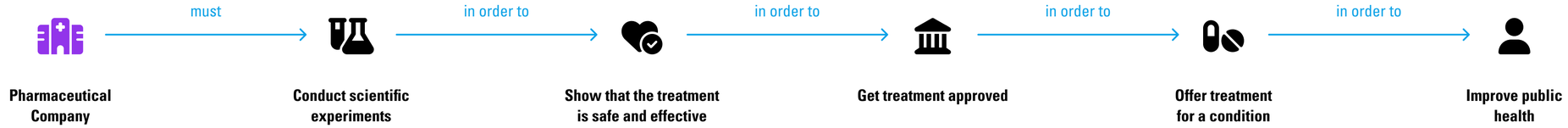
Before the company can use the drug to treat patients, they need to get it approved by the FDA.



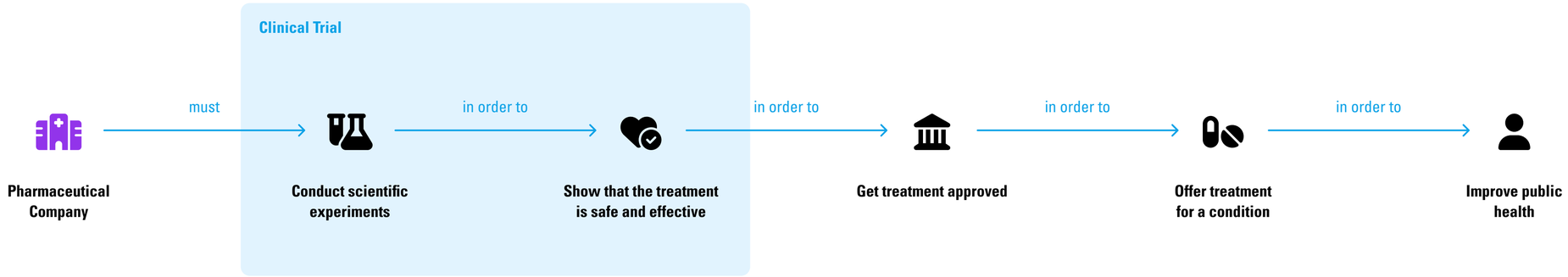
In order to get FDA approval,
they must demonstrate that the treatment is both safe and effective.



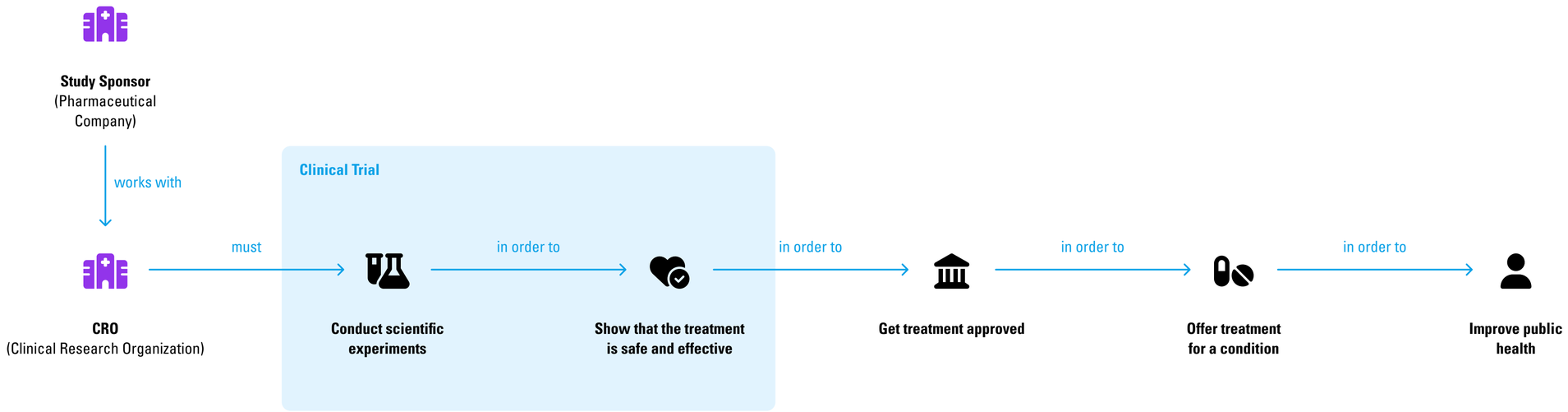
To get determine whether the treatment is safe and effective, the company must conduct scientific experiments to test the drug in a sample of human subjects.



These experiments are clinical trials.



The pharmaceutical company that produces the drug might not conduct a clinical trial on its own — typically, they are the ‘study sponsor’ and work with one or more organizations who specialize in running trials called CROs (‘clinical research organizations’ or ‘contract research organizations’).



The CRO itself includes several different teams who design the study, oversee its operations, and interface with regulators.

Admin & Regulation

Study Sponsor

Clinical Research Organizations (CRO)

Clinical Development Team

Clinical Operations Team

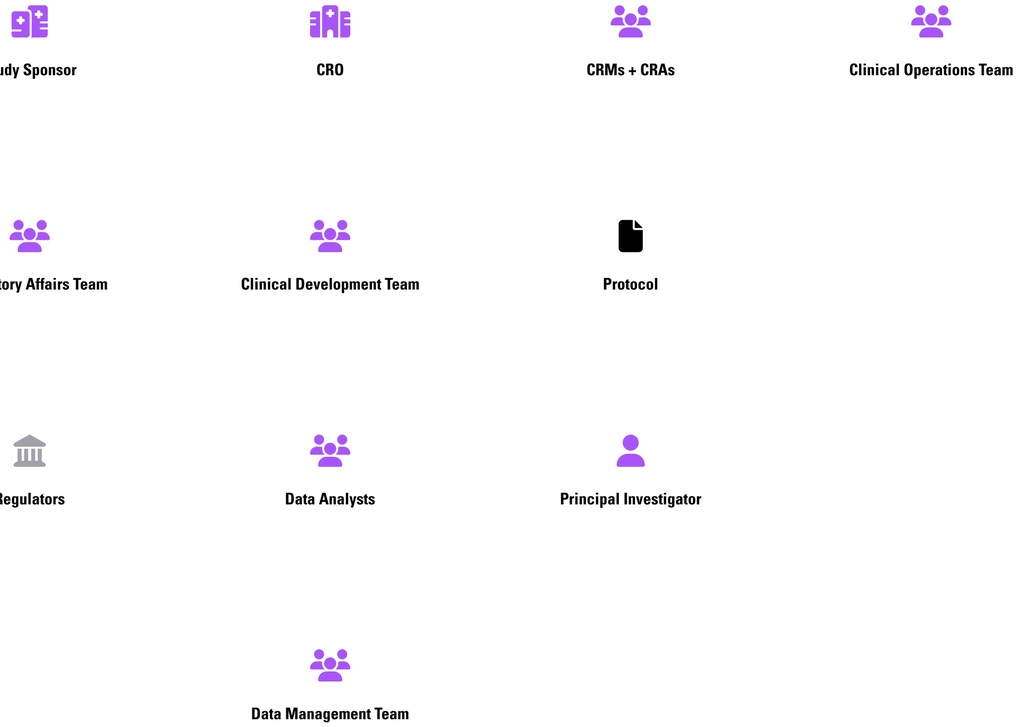
Principal Investigator (PI)

Clinical Research Monitor (CRM)

Clinical Research Associate (CRA)

Regulators (e.g., FDA)

Data Management Team



Researchers recruit participants to study sites managed by study site coordinators. Pharmacists often dispense the treatment (or placebo) and ensure it's administered according to the study protocol.

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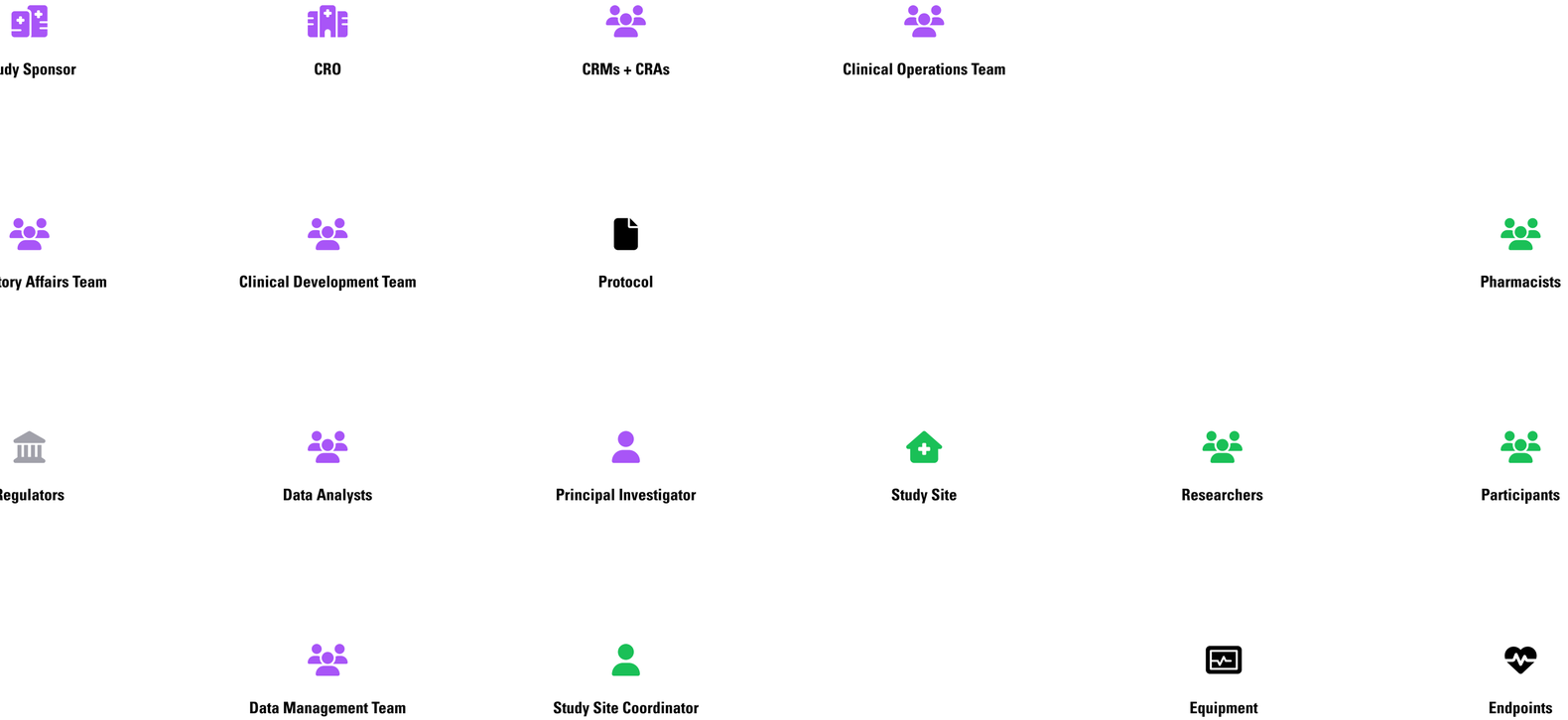
Study Site

Patients (Study Participants)

Study Site Coordinators

Pharmacists

Researchers



Supply chains need to be established for providing study sites with testing equipment, medical supplies, and other materials. In some cases, researchers may also need to be trained and certified to use certain equipment.

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Study Site

Patients (Study Participants)

Study Site Coordinators

Pharmacists

Researchers

Supplies & Logistics

Equipment Suppliers

Logistics Teams

Equipment Operation Trainers

Study Sponsor

CRO

CRMs + CRAs

Clinical Operations Team

Regulatory Affairs Team

Clinical Development Team

Protocol

Trainers

Pharmacists

Regulators

Data Analysts

Principal Investigator

Study Site

Researchers

Participants

Data Management Team

Study Site Coordinator

Logistics Teams

Equipment

Endpoints

Equipment Suppliers / Data Providers

Data quality control (QC) may also be conducted by another team before transferring study data to the CRO's data management team.

Admin & Regulation

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Study Sponsor

CRO

CRMs + CRAs

Clinical Operations Team

Regulatory Affairs Team

Clinical Development Team

Protocol

Trainers

Pharmacists

Study Site

Patients (Study Participants)

Study Site Coordinators

Pharmacists

Researchers

Regulators

Data Analysts

Principal Investigator

Study Site

Researchers

Participants

Supplies & Logistics

Equipment Suppliers

Logistics Teams

Equipment Operation Trainers

Data Management Team

Study Site Coordinator

Logistics Teams

Equipment

Endpoints

Data Analysis

Data Analysts

Data Readers / Quality Control (QC) Teams

Data Readers / QC Team

Equipment Suppliers / Data Providers

A clinical trial is a social-technical system which requires coordination between hundreds or even thousands of people.
Each plays a role in ensuring that the trial is run smoothly and ethically, and that high-quality data is collected.

Admin & Regulation

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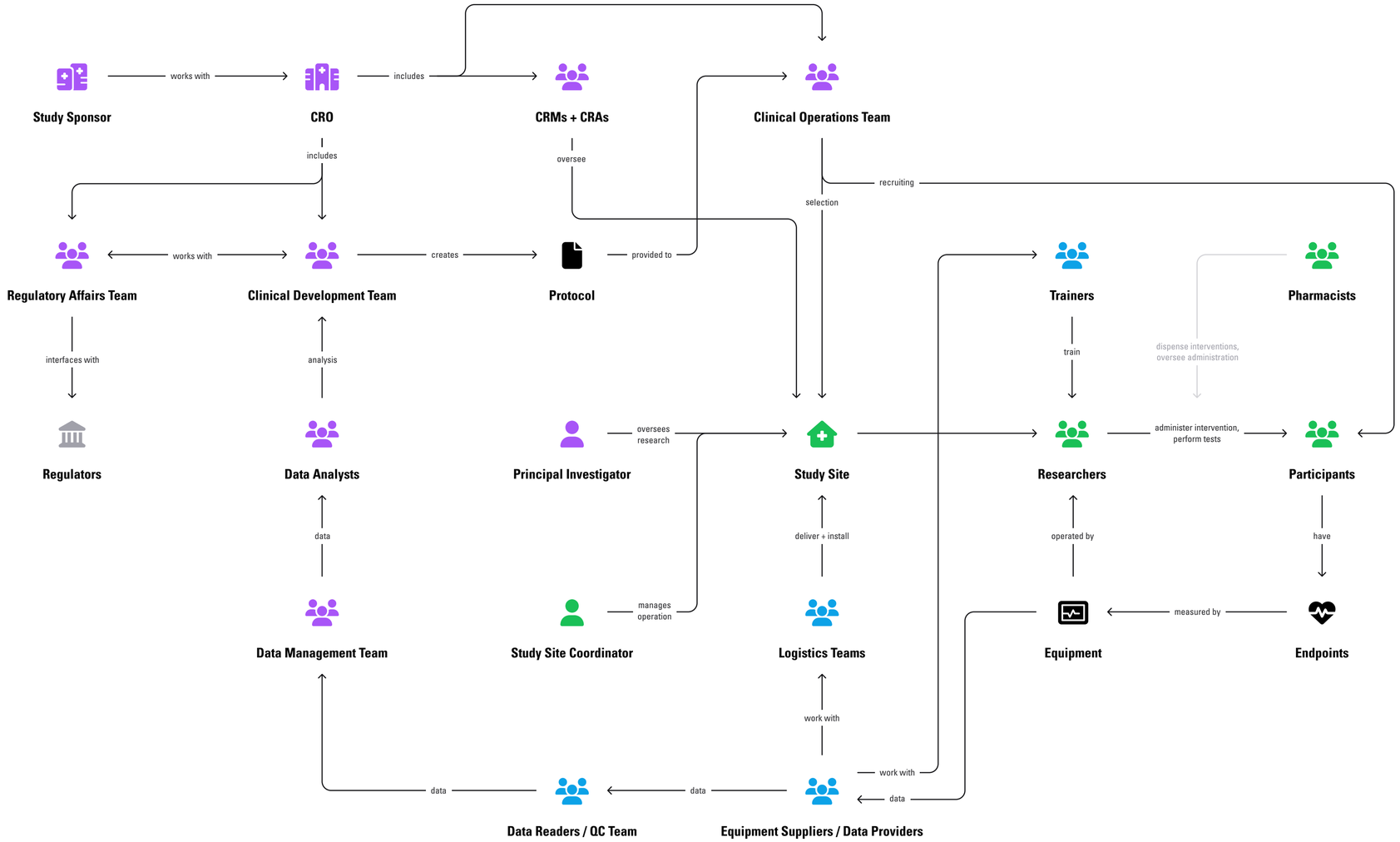


PART TWO

The scientific method serves as the backbone for conducting clinical trials.

A simplified model of the scientific method might begin with a testable hypothesis built on the foundation of existing theory, followed by an experiment, an observation of the results, and finally the formation of a conclusion.

Theory

The initial stage where an existing body of knowledge or a conceptual framework is used to make predictions about natural phenomena. This step involves understanding current theories and models related to the subject of interest.

Hypothesis

A specific, testable prediction derived from the theory. It proposes a possible outcome or explanation that the experiment will test. A hypothesis often takes the form of a statement predicting a relationship between variables.

Experiment

The process of testing the hypothesis through controlled and repeatable procedures. Experiments are designed to isolate and manipulate variables to observe their effects on the system being studied.

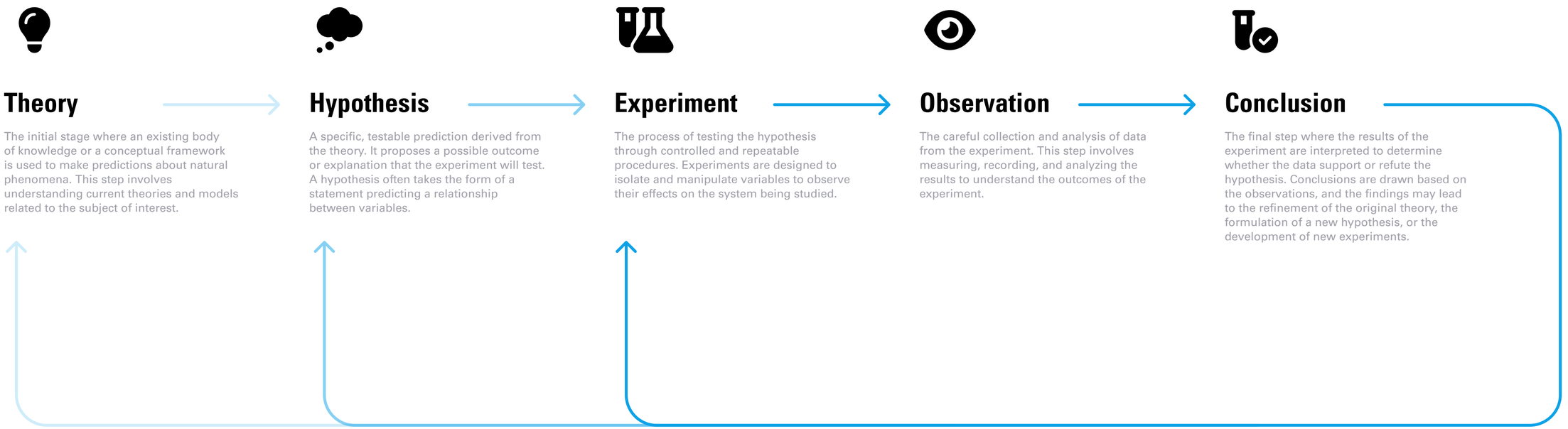
Observation

The careful collection and analysis of data from the experiment. This step involves measuring, recording, and analyzing the results to understand the outcomes of the experiment.

Conclusion

The final step where the results of the experiment are interpreted to determine whether the data support or refute the hypothesis. Conclusions are drawn based on the observations, and the findings may lead to the refinement of the original theory, the formulation of a new hypothesis, or the development of new experiments.

The scientific method is iterative,
with the conclusion of one experiment leading to new experiments, new hypotheses, or even new theories.



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Before clinical trials, preclinical research is conducted in computer models, cell cultures, or animal subjects to determine whether a drug has potential to be safe and useful for humans.

Preclinical

Basic safety and usefulness.

Subjects:
In silico, in vitro, lab animals

Duration:
Variable, months to years

Involves laboratory research and tests on cell cultures and animal models to determine if the treatment is potentially safe and effective. Researchers study the pharmacokinetics (how the body affects the drug) and pharmacodynamics (how the drug affects the body) to understand the drug's effects, including its toxicity, metabolism, and mechanism of action. The goal is to gather enough data to justify the transition to human trials. This phase is critical for identifying possible side effects and determining the safe dosage levels for the next phase of trials.

Once a drug is approved for human testing, Phase I trials are conducted to determine dosage and evaluate safety in a small group of human subjects.

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Phase I

Dosage, safety, and side effects.

Subjects:
20-100 patients or healthy volunteers

Duration:
Less than 1 year

Phase 1 trials are the first stage of testing in human subjects. Typically involving a small group of 20 to 100 healthy volunteers or sometimes patients (in the case of cancer drugs), the primary goal is to evaluate the safety of the drug. This includes determining a safe dosage range and identifying side effects. The focus is on assessing the drug's pharmacokinetics, pharmacodynamics, side effects, and how it is absorbed, metabolized, and excreted by the body. Phase 1 helps to decide whether the drug is safe for further investigation in Phase 2.

Phase 2 trials further evaluate safety, and begin to look at the drug’s efficacy in treating a condition in a larger group of participants over 1-2 years.

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Phase II

Safety and efficacy.

Subjects:
100-300 patients

Duration:
1-2 years

Phase 2 trials test the efficacy of the drug, along with further safety evaluation, in a larger group of people (usually 100 to 300). These participants typically have the condition that the drug is intended to treat. Phase 2 aims to obtain preliminary data on whether the drug works in people who have a certain disease or condition. These trials also continue to study safety, including short-term side effects and risks associated with the drug. Dosage or treatment protocols may also be refined in this phase.

Phase 3 trials evaluate safety and efficacy over a longer period of time, studying the drug’s effects over 1-4 years in thousands of participants.

Preclinical

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Subjects:
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Phase III

Safety and efficacy.

Subjects:
1,000-3,000 patients

Duration:
Up to 4 years

Phase 3 trials involve randomized and blind testing in several hundred to several thousand patients. This large-scale testing provides thorough data on the drug’s effectiveness, benefits, and the range of possible adverse reactions. Phase 3 compares the new drug against the current standard treatment, if one exists, to measure the improvement it offers. The data gathered from this phase is crucial for regulatory approval, as it must demonstrate that the drug’s benefits outweigh any risks.

Finally, the drug is submitted for approval, and regulators review the results and methodology from all clinical phases, as well as manufacturing processes, packaging, and labeling.

Preclinical

Basic safety and usefulness.

Subjects:
In silico, in vitro, lab animals

Duration:
Variable, months to years

Involves laboratory research and tests on cell cultures and animal models to determine if the treatment is potentially safe and effective. Researchers study the pharmacokinetics (how the body affects the drug) and pharmacodynamics (how the drug affects the body) to understand the drug's effects, including its toxicity, metabolism, and mechanism of action. The goal is to gather enough data to justify the transition to human trials. This phase is critical for identifying possible side effects and determining the safe dosage levels for the next phase of trials.

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Approval

Review results & methodology.

Duration:
10-12 months

After successful completion of Phase 3 trials, the drug manufacturer submits a New Drug Application (NDA) or Biologics License Application (BLA) to regulatory authorities, such as the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA). This application includes all the data from the clinical trials, along with details on drug manufacturing, packaging, and labeling. The regulatory authority reviews the application to ensure the drug is safe and effective for its intended use and that the benefits outweigh the risks. Approval from the regulatory body allows the drug to be marketed and prescribed to patients.

After a drug is approved for commercial production, it may go through Phase 4 trials: specific monitoring of the drug's performance in the general population.

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Duration:
1-2 years

Phase 2 trials test the efficacy of the drug, along with further safety evaluation, in a larger group of people (usually 100 to 300). These participants typically have the condition that the drug is intended to treat. Phase 2 aims to obtain preliminary data on whether the drug works in people who have a certain disease or condition. These trials also continue to study safety, including short-term side effects and risks associated with the drug. Dosage or treatment protocols may also be refined in this phase.

Phase III

Safety and efficacy.

Subjects:
1,000-3,000 patients

Duration:
Up to 4 years

Phase 3 trials involve randomized and blind testing in several hundred to several thousand patients. This large-scale testing provides thorough data on the drug's effectiveness, benefits, and the range of possible adverse reactions. Phase 3 compares the new drug against the current standard treatment, if one exists, to measure the improvement it offers. The data gathered from this phase is crucial for regulatory approval, as it must demonstrate that the drug's benefits outweigh any risks.

Approval

Review results & methodology.

Duration:
10-12 months

After successful completion of Phase 3 trials, the drug manufacturer submits a New Drug Application (NDA) or Biologics License Application (BLA) to regulatory authorities, such as the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA). This application includes all the data from the clinical trials, along with details on drug manufacturing, packaging, and labeling. The regulatory authority reviews the application to ensure the drug is safe and effective for its intended use and that the benefits outweigh the risks. Approval from the regulatory body allows the drug to be marketed and prescribed to patients.

Phase IV

Post-approval monitoring.

Subjects:
Thousands of patients

Duration:
Variable, ongoing

Phase 4, also known as post-marketing surveillance, occurs after the drug has been approved for public use. This phase involves the ongoing monitoring of the drug's performance in the general population to identify any long-term or rare side effects. Phase 4 trials can result in further adjustments to the drug's labeling, additional warnings about side effects, or in some cases, withdrawal of the drug from the market. This phase ensures the long-term safety and efficacy of the drug and assesses its impact in various populations.

With increased scale, complexity, and regulatory obligations at each phase, cost increases significantly[1].

Preclinical

Basic safety and usefulness.

Subjects:
Lab animals, in vitro

Duration:
Variable, months to years

$1-2 million

Phase I

Dosage, safety, and side effects.

Subjects:
20-100 patients or healthy volunteers

Duration:
Less than 1 year

$2-6.5 million

Phase II

Safety and efficacy.

Subjects:
100-300 patients

Duration:
1-2 years

$7-20 million

Phase III

Safety and efficacy.

Subjects:
1,000-3,000 patients

Duration:
Up to 4 years

$11-53 million

Approval

Review results & methodology.

Duration:
10-12 months

$2-5 million

Phase IV

Post-approval monitoring.

Subjects:
Thousands of patients

Duration:
Variable, ongoing

$5-20 million

1. https://pubmed.ncbi.nlm.nih.gov/26908540/

With each phase's success rate, only about 7% of drugs that are approved for human testing make it to the market.

Preclinical

Basic safety and usefulness.

Less than **1%** of compounds are approved for human testing.

Phase I

Dosage, safety, and side effects.

Approximately **70%** of drugs move from Phase 1 to Phase 2.

Phase II

Safety and efficacy.

Approximately **33%** of drugs move from Phase 2 to Phase 3.

Phase III

Safety and efficacy.

Approximately **25-30%** of drugs in Phase 3 are submitted for approval.

Approval

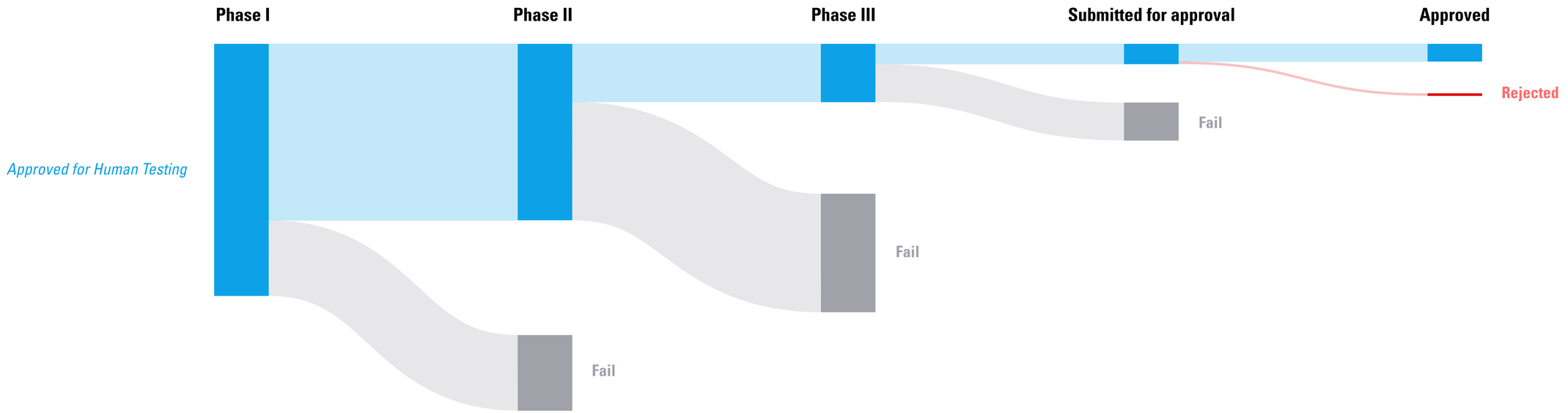
Review results & methodology.

Approximately **85-90%** of drugs submitted to the FDA are approved.

Phase IV

Post-approval monitoring.

Success rate:
Approximately **92%** of drugs in Phase 4 trials remain on the market.



Advancements in how we measure clinical endpoints can improve our ability to predict whether a treatment will be successful, enabling study sponsors to better focus their investments on more promising treatments.

Preclinical

Basic safety and usefulness.

Less than **1%** of compounds are approved for human testing.

Phase I

Dosage, safety, and side effects.

Approximately **70%** of drugs move from Phase 1 to Phase 2.

Phase II

Safety and efficacy.

Approximately **33%** of drugs move from Phase 2 to Phase 3.

Phase III

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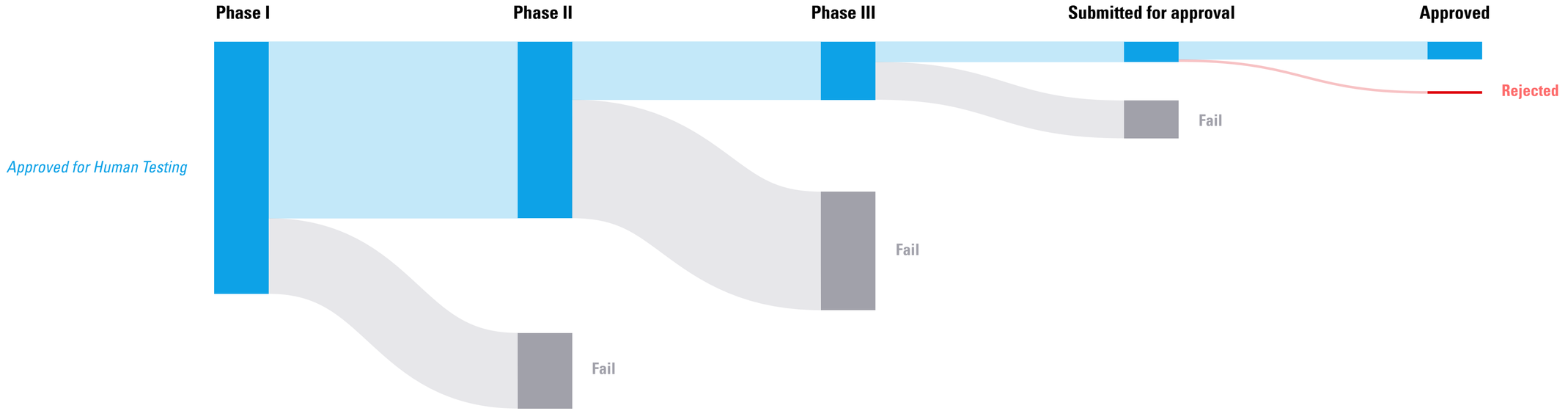
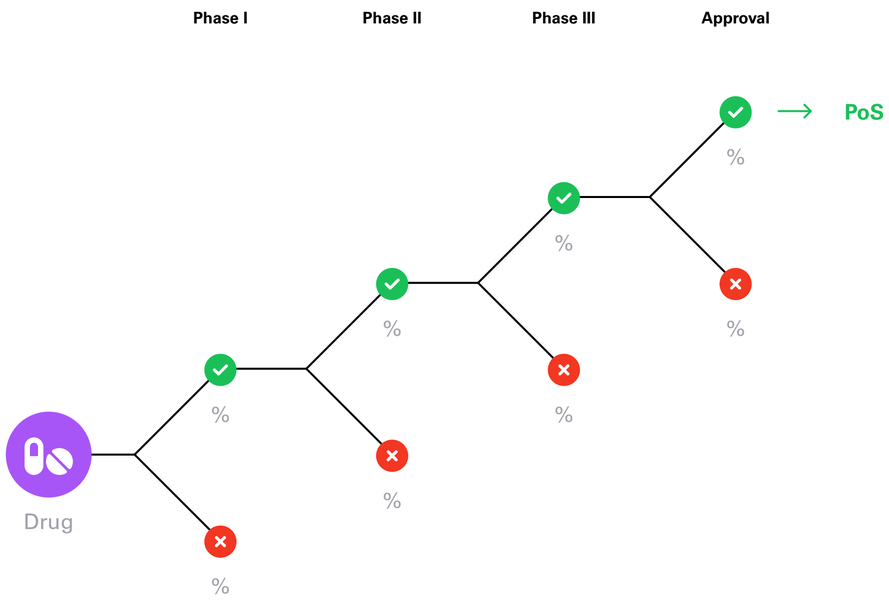
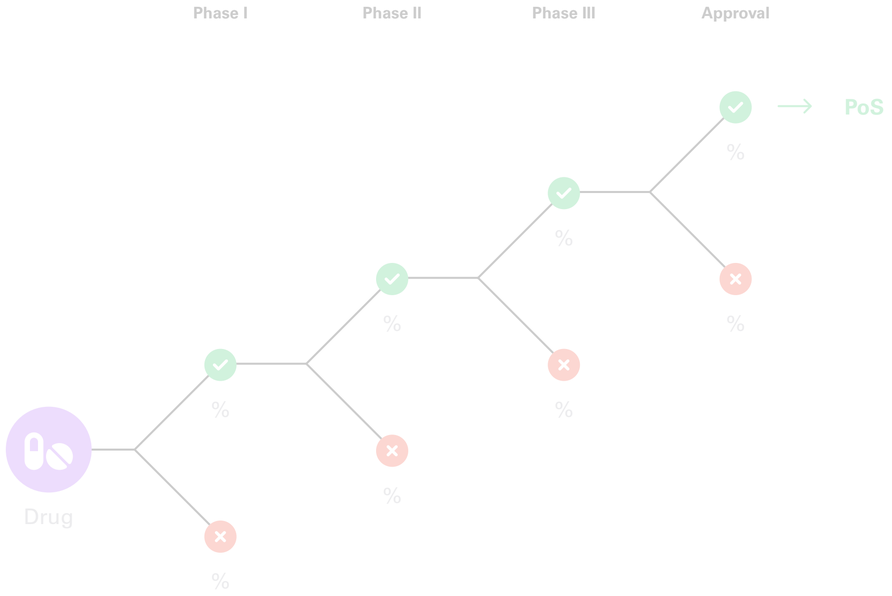


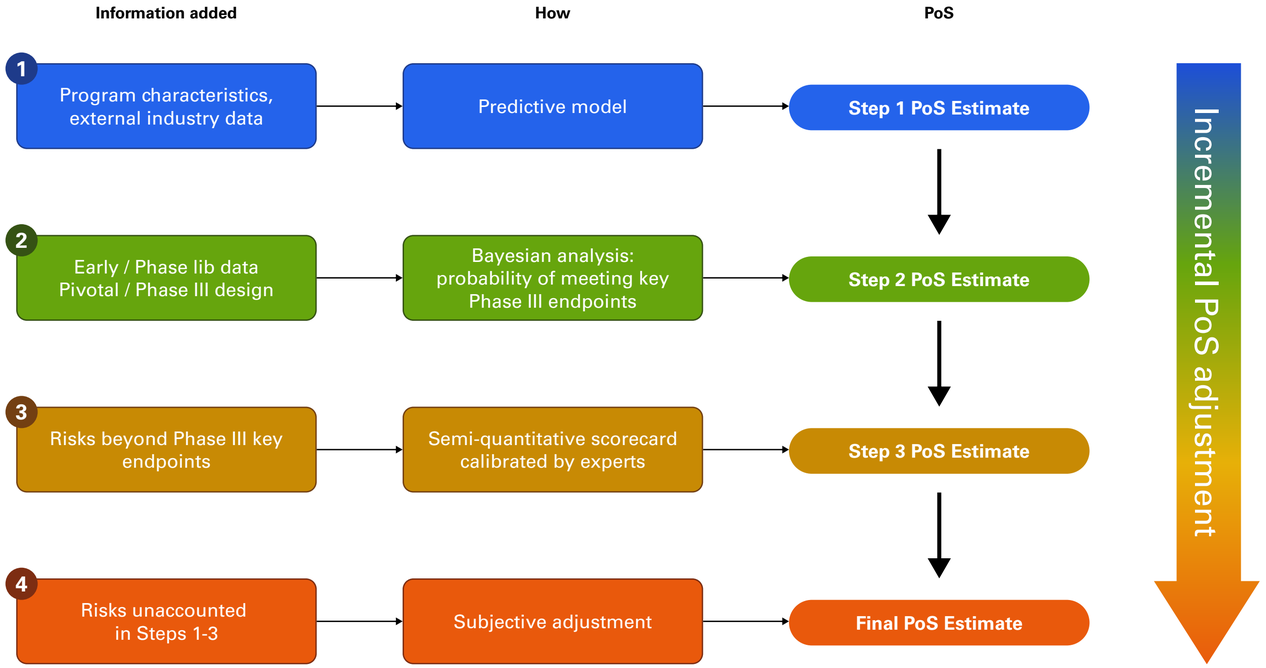
For a given drug, study sponsors need to predict the drug's Probability of Success (PoS) to determine whether the drug has enough potential to be worth dedicating resources to it.



Study sponsors may develop frameworks for calculating a trial's PoS which take into account characteristics of the trial itself, as well as historical data from other trials.



The PoS framework. FDP, Full Development Point; PoS, probability of success.[1]



1. Hampson, L.V., Holzhauer, B., Bornkamp, B., Kahn, J., Lange, M.R., Luo, W.-L., Singh, P., Ballerstedt, S. and Cioppa, G.D. (2022), A New Comprehensive Approach to Assess the Probability of Success of Development Programs Before Pivotal Trials. Clin Pharmacol Ther, 111: 1050-1060. https://doi.org/10.1002/cpt.2488

When a treatment is approved for human testing, the conclusion of preclinical study forms the hypothesis for the following clinical trials

When a treatment is approved for human testing,
the conclusion of preclinical study forms the hypothesis for the following clinical trials:
this drug will be safe and effective for treating a health condition in humans.

The trials that follow are a series of experiments designed to build a body of evidence which either supports or invalidates the hypothesis.

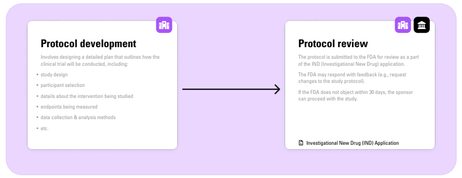
PART THREE

Let’s look at an example of a Phase 3 clinical trial in a bit more detail.

First, the Study Sponsor develops the Study Protocol — a document which outlines how the study will be conducted — then submits it to regulators for review.

SETUP

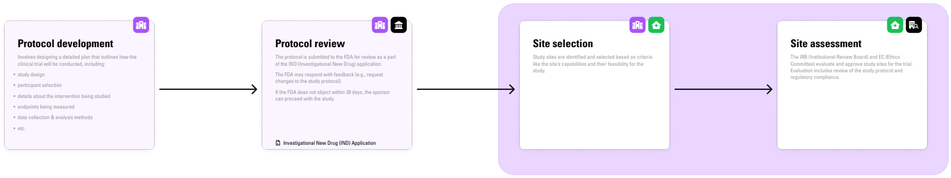
Study Protocol



The CRO identifies study sites, and the Institutional Review Board (IRB) evaluates and approves them for the trial.
Outside of the US, the IRB may be referred to as the ‘Ethics Committee’ (EC).

SETUP

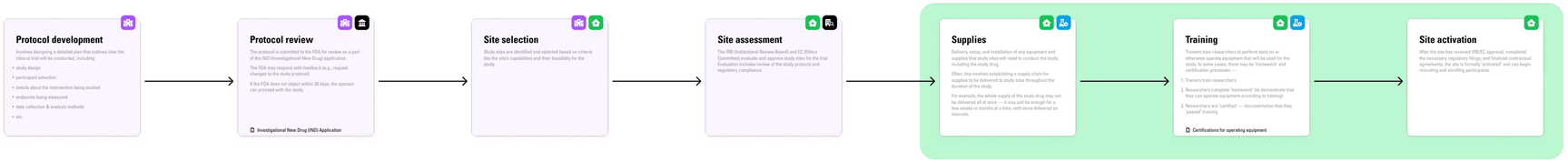
Study Protocol → **Site Selection**



Once a study site is approved, supplies are delivered and researchers receive any necessary training — then the site is ‘activated’ and can begin recruiting participants.

SETUP

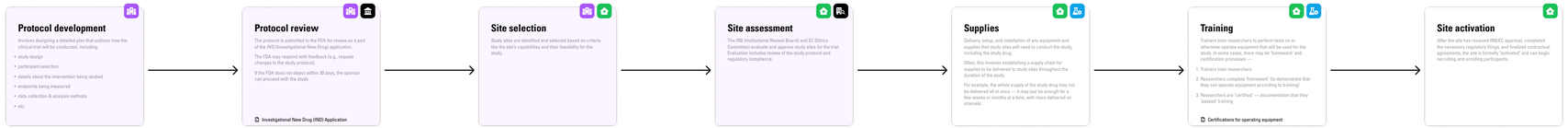
Study Protocol | **Site Selection** | **Site Setup**

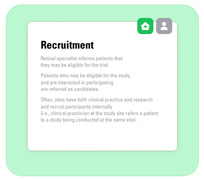


Typically, study participants are recruited by clinical practitioners who refer eligible patients as candidates.

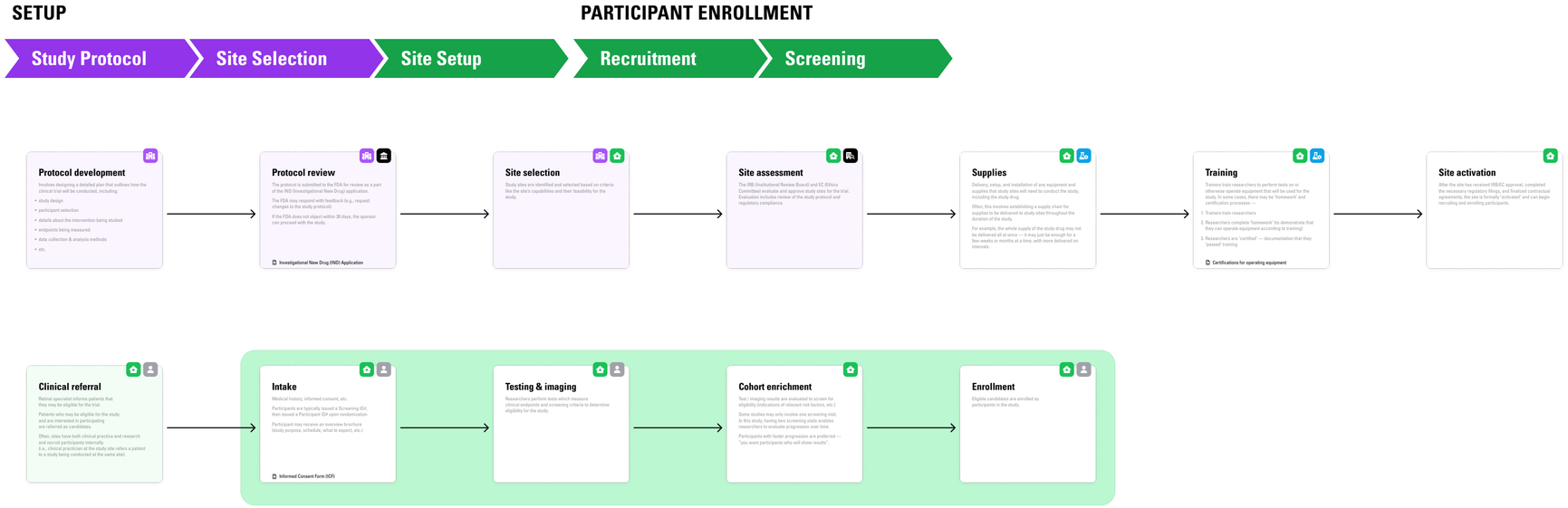
SETUP **PARTICIPANT ENROLLMENT**

Study Protocol | Site Selection | Site Setup | Recruitment

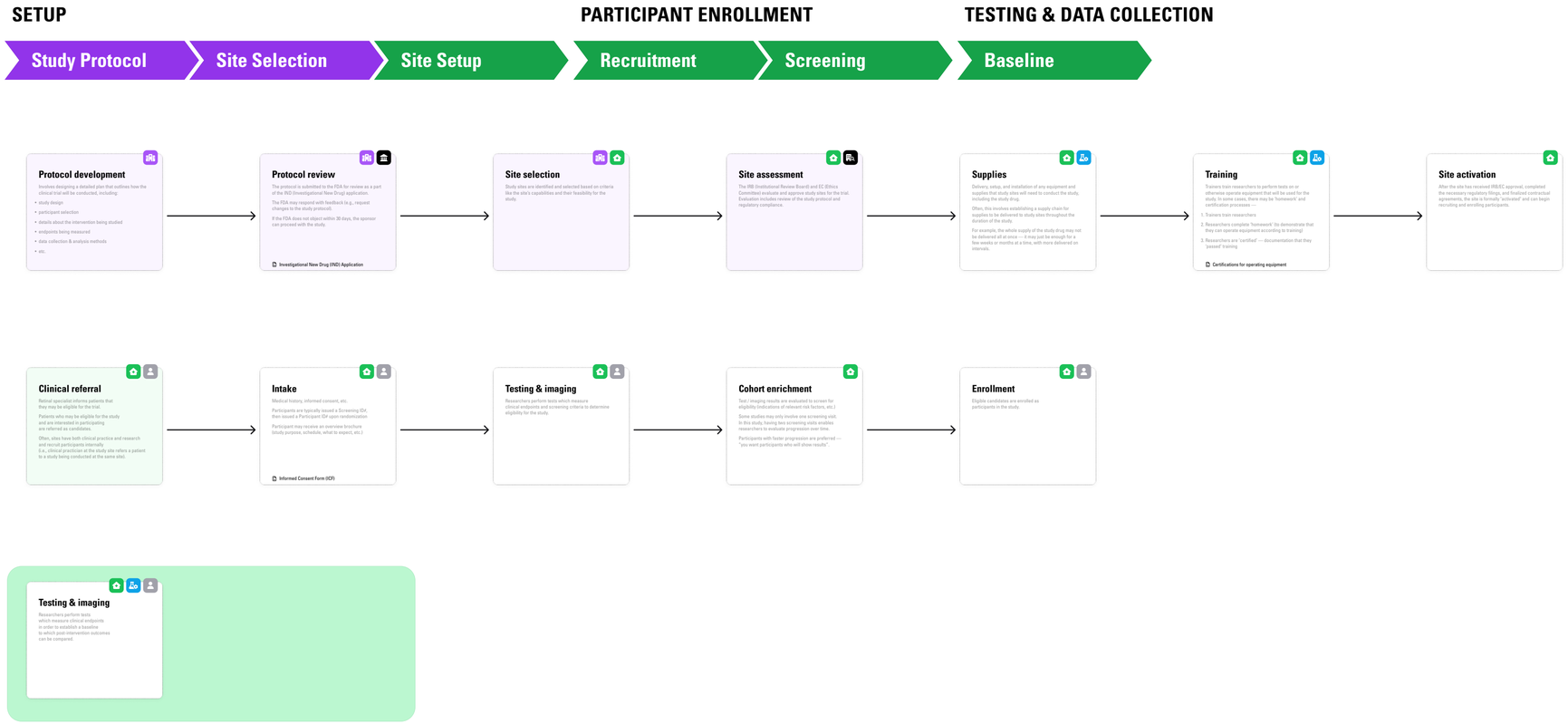




Candidates go through a screening process, which determines eligibility for the study based on medical history and preliminary testing. Eligible candidates are then enrolled as participants.



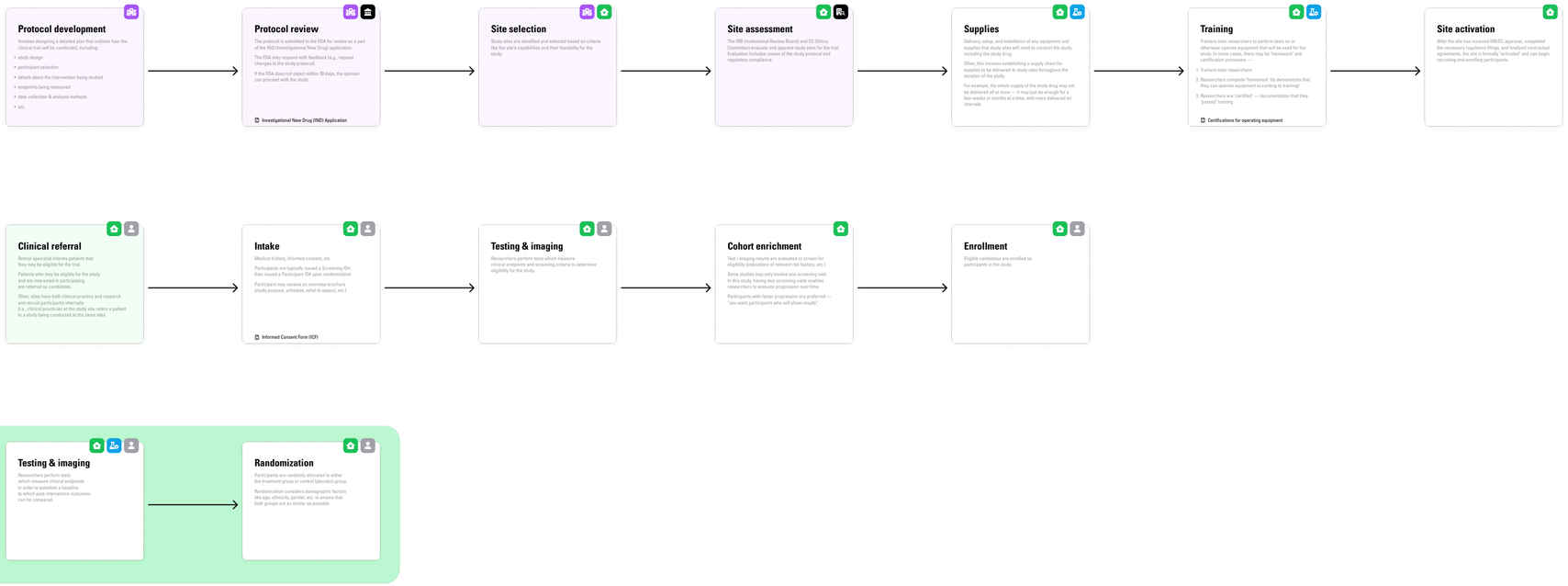
The participants go through testing and imaging to measure clinical endpoints. This testing establishes a baseline to which researchers can later compare study outcomes.



In a Randomized* Controlled Trial, participants are then randomly assigned to treatment or control groups.

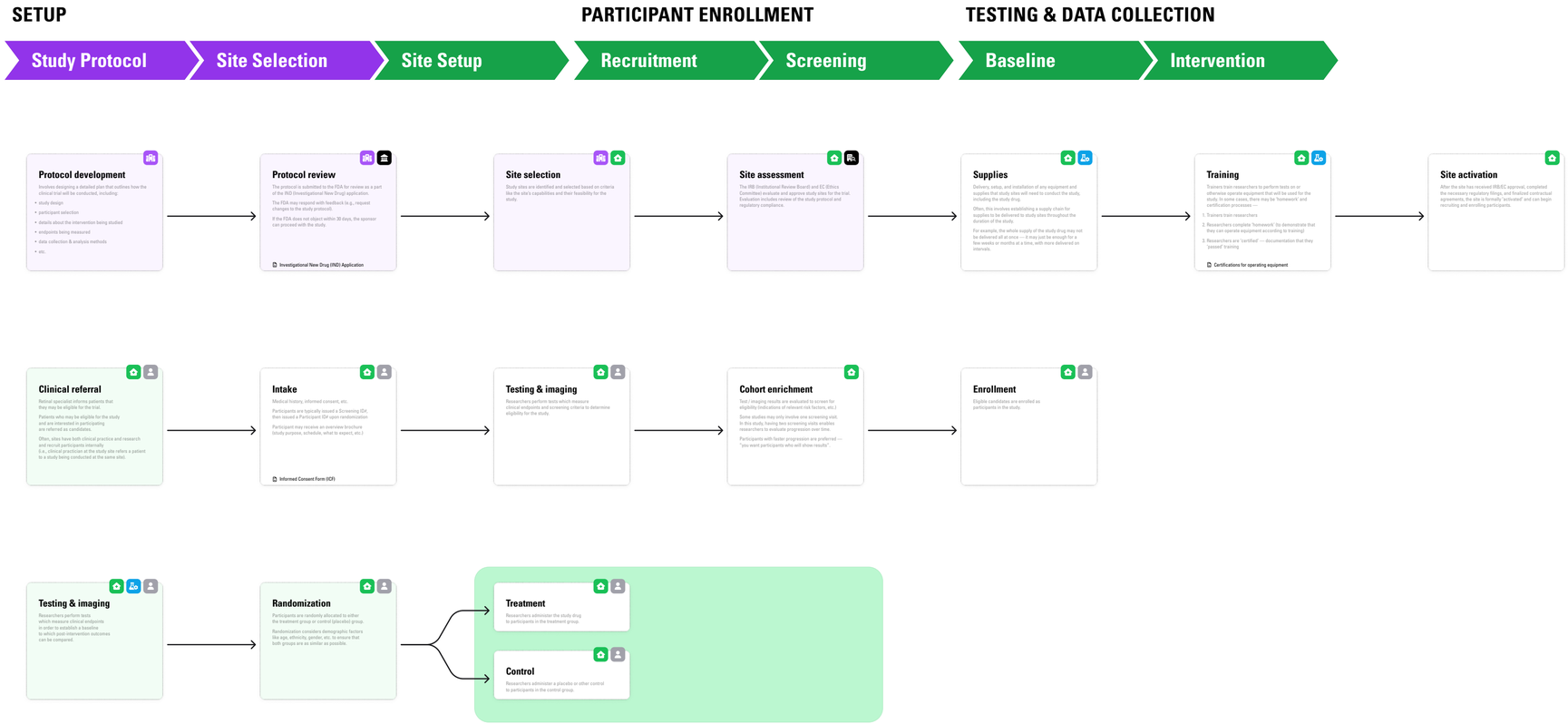
SETUP | **PARTICIPANT ENROLLMENT** | **TESTING & DATA COLLECTION**

Study Protocol → Site Selection → Site Setup → Recruitment → Screening → Baseline

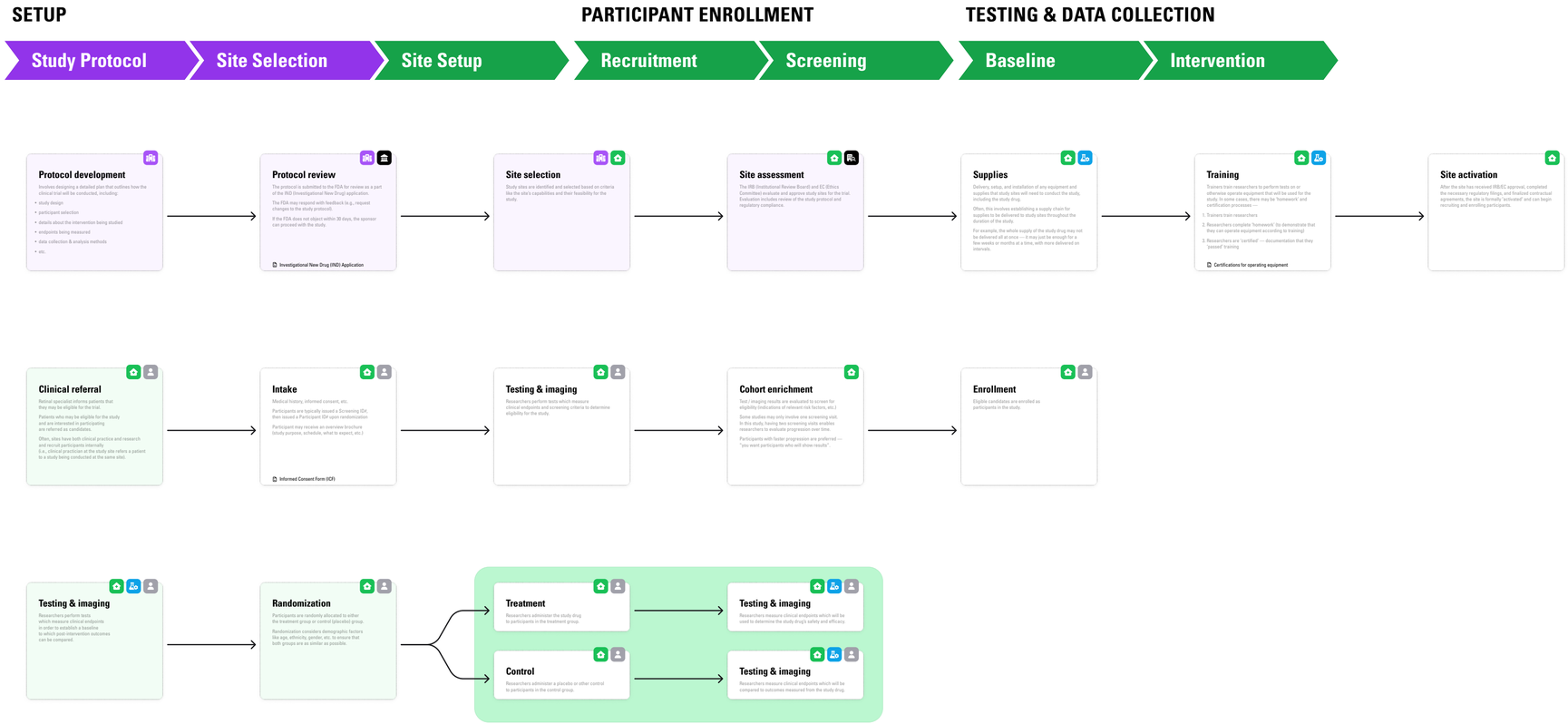


* More detail on study design in Part Five.

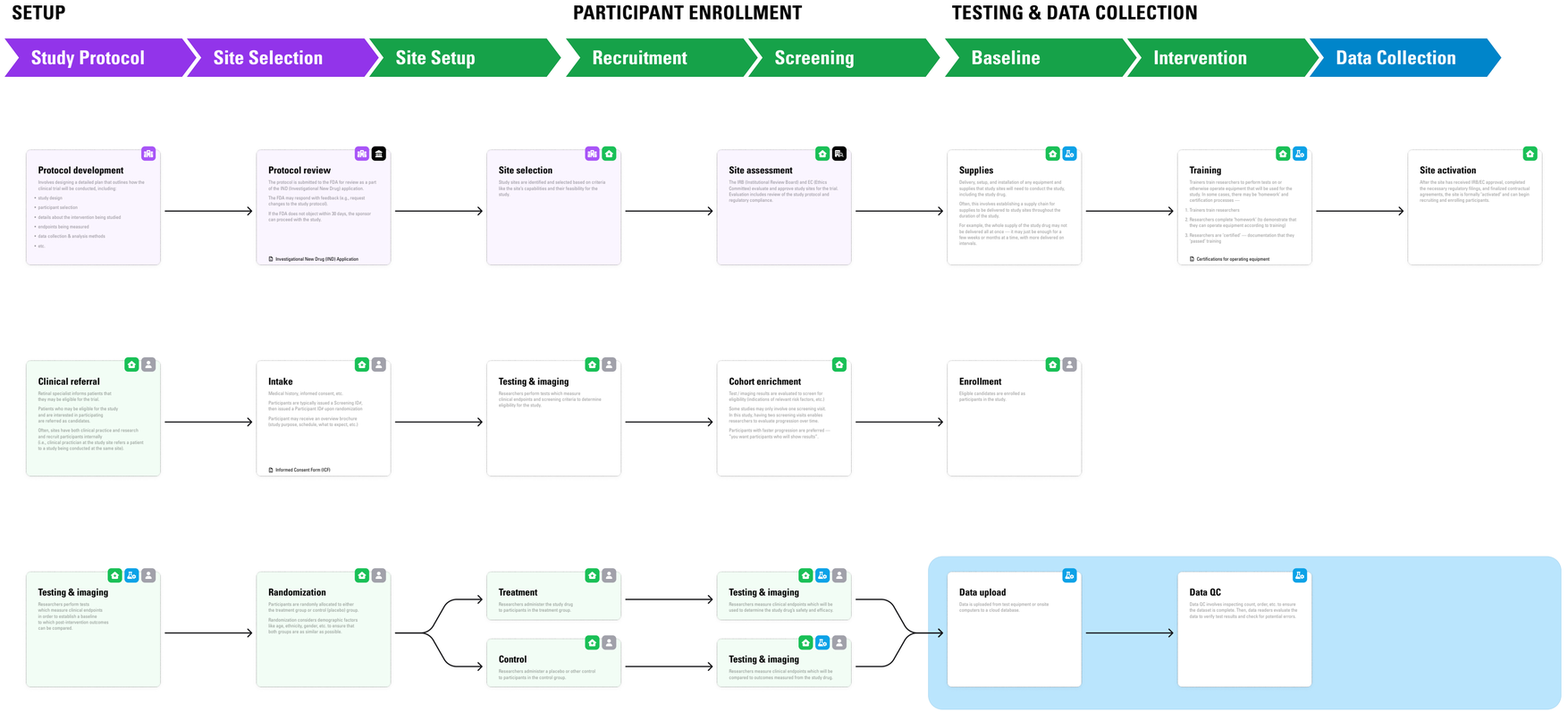
Each group receives an intervention:
the treatment group receives the drug being studied, while the control group receives a placebo or an existing treatment.



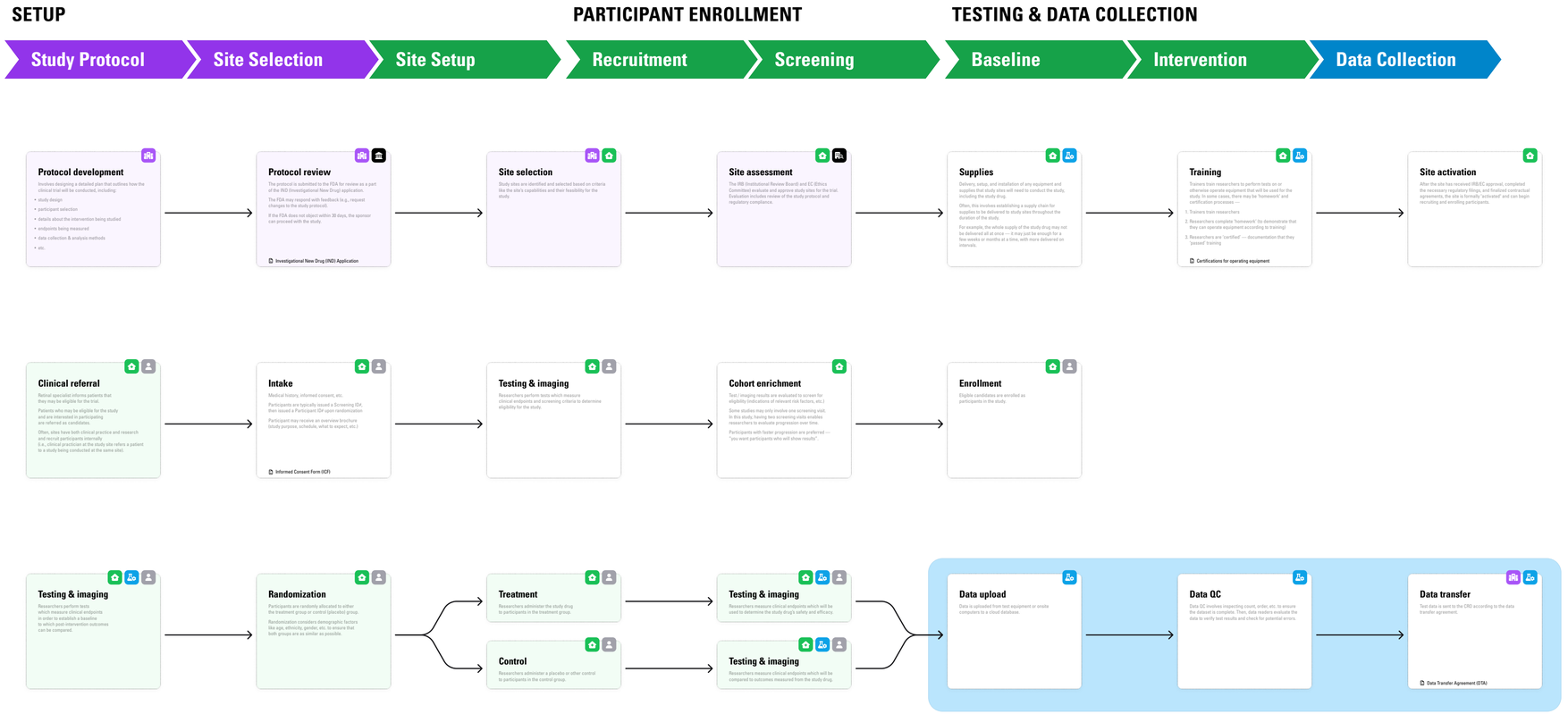
After administering the intervention, researchers measure clinical endpoints again.



Data collected from testing is uploaded to a database then goes through a QC process.

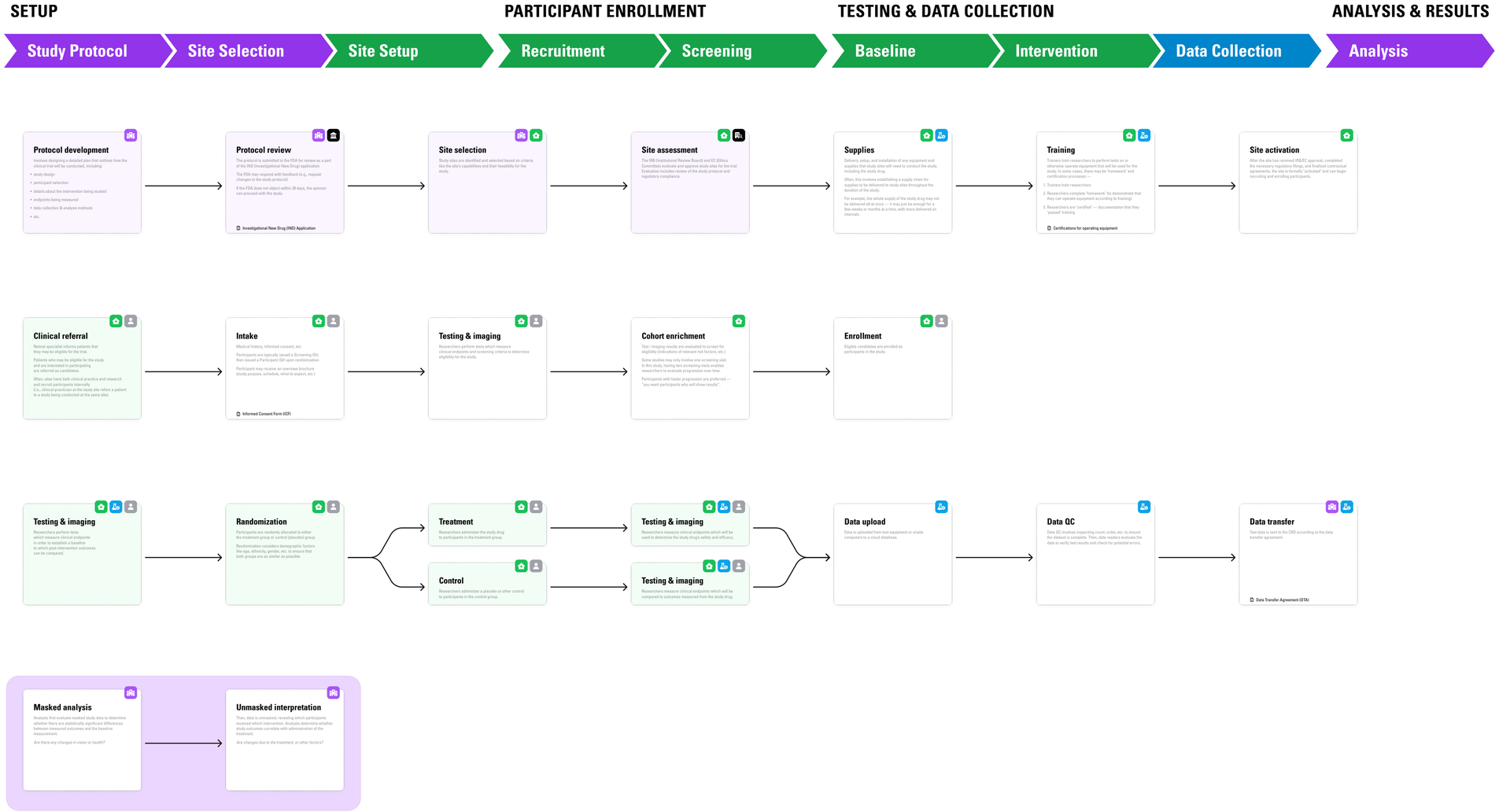


If the data is collected by a third party, the quality-checked data is then transferred to the CRO.
Data providers often enter into a Data Transfer Agreement with the CRO.



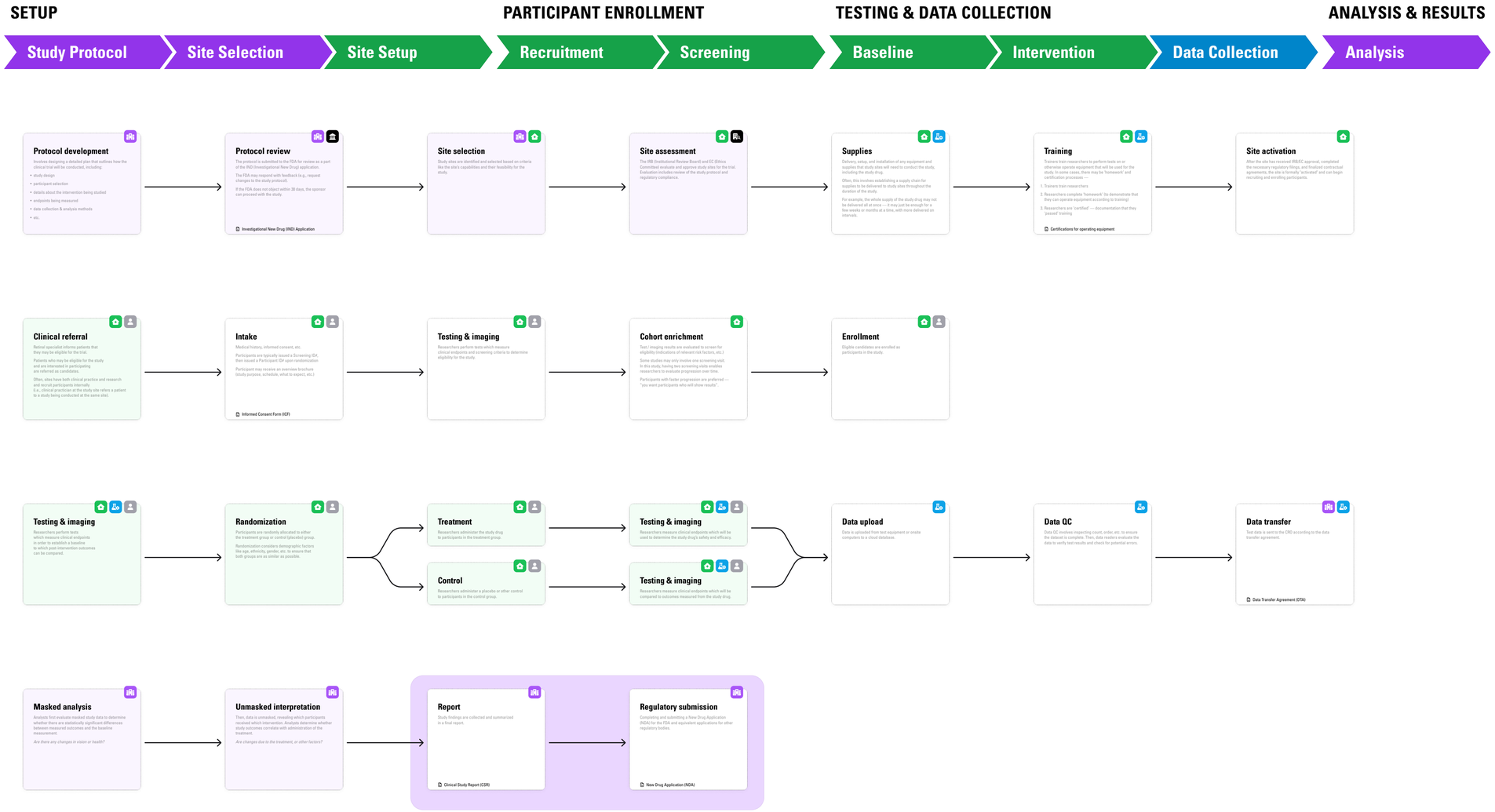
Analysts then evaluate the data.

First, they compare study outcomes to the baseline measurement to identify whether there were significant changes — then, they ‘unmask’ the data to determine whether those changes were correlated with the study drug.

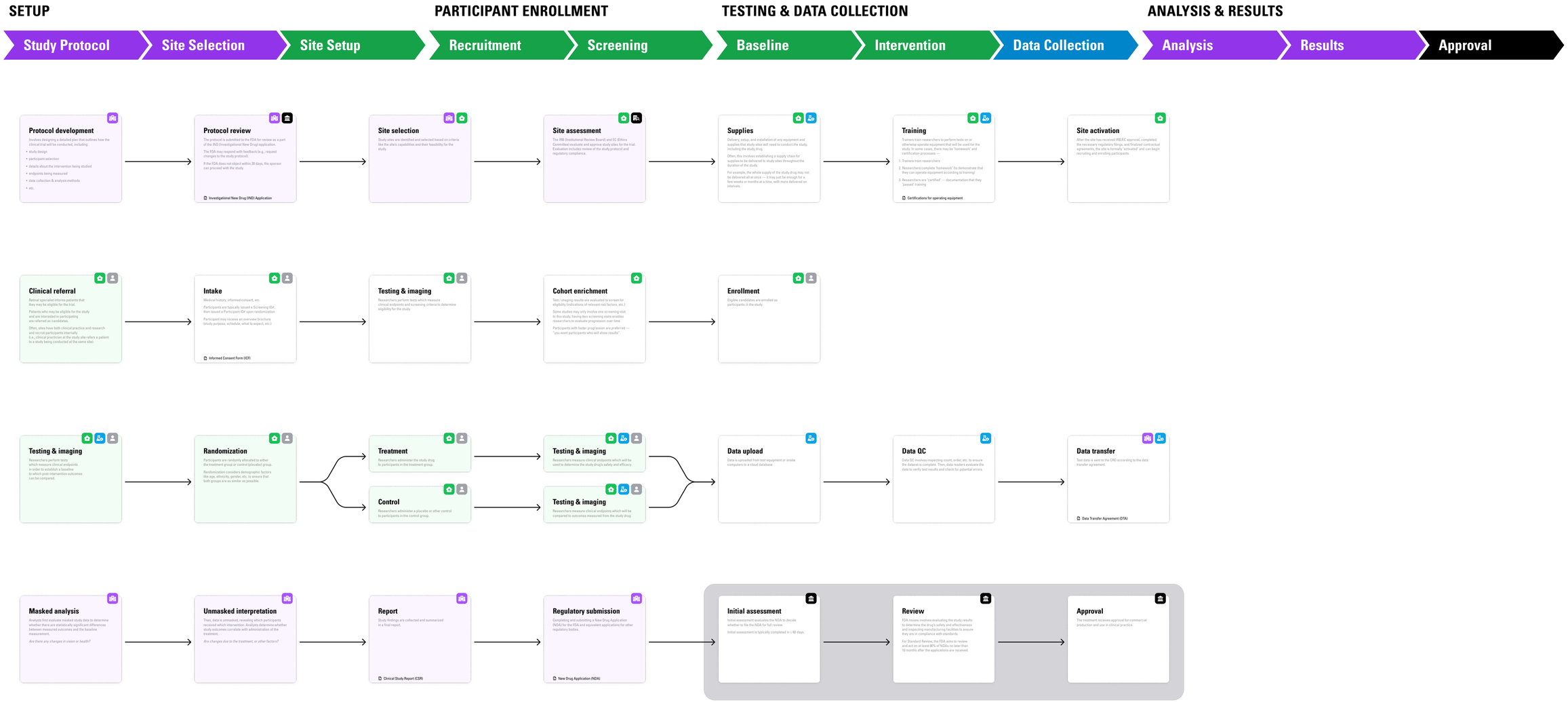


Often, trials will include an ‘Interim Analysis’. “An interim analysis is a planned analysis conducted before the final planned analysis, which allows the study sponsor to evaluate the trial's success probability while controlling the overall statistical error rates.” https://www.sciencedirect.com/topics/medicine-and-dentistry/interim-analysis

After analysis is complete, the Clinical Development Team forms a conclusion — they compile a report of the results and submit an application for final approval to regulatory bodies (e.g., the FDA, EMA).



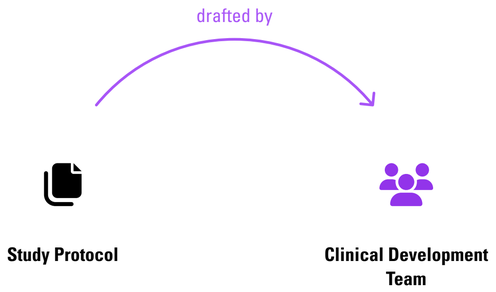
After an initial assessment, regulators perform a thorough review of the application. Finally, they may approve the drug for commercial production and use in clinical practice.



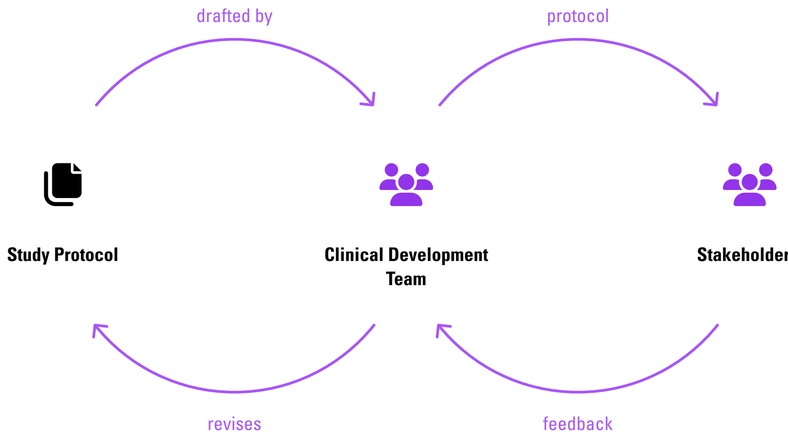
PART FOUR

Developing a study protocol involves feedback and iteration.

The study protocol is created by the Study Sponsor’s Clinical Development Team.



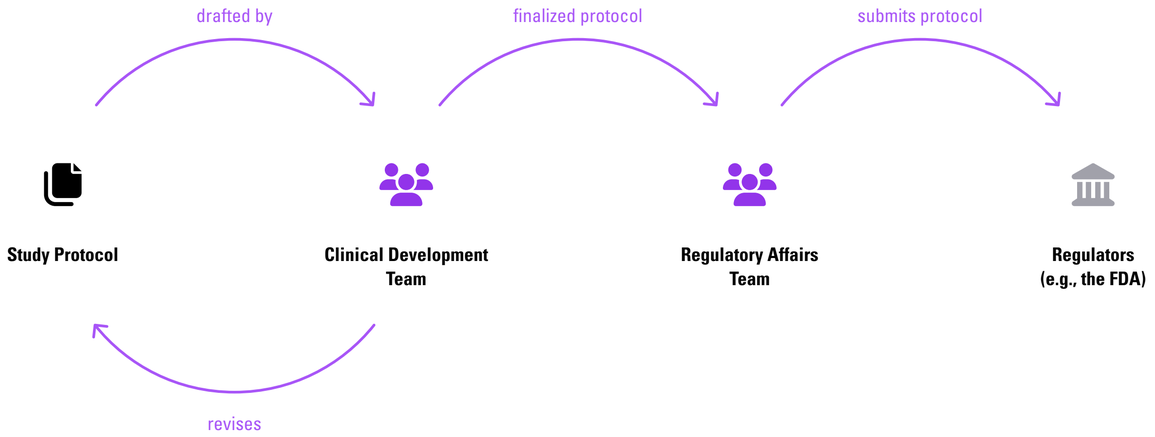
After drafting the protocol, they revise it based on feedback from various stakeholders to ensure the protocol is scientifically rigorous, feasible, ethical, and complies with regulatory requirements.



Stakeholders:

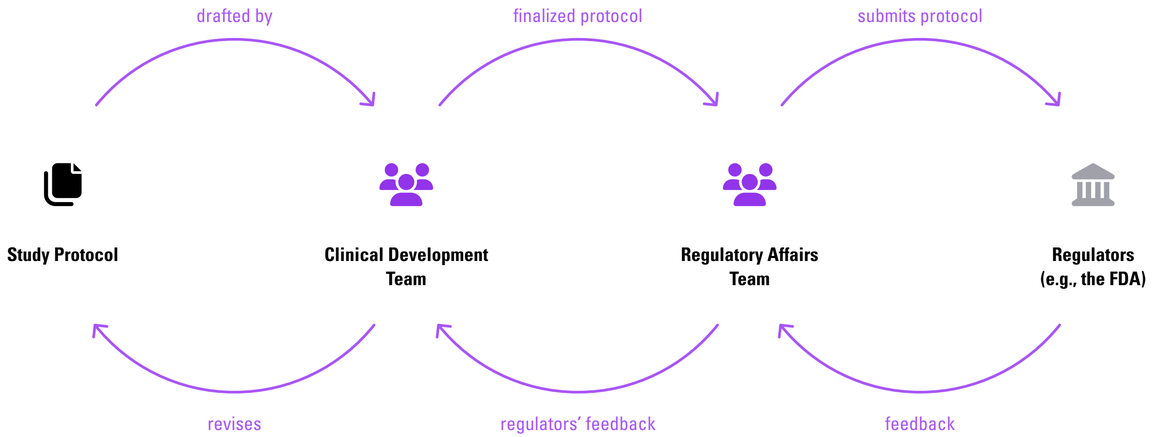
Regulatory Affairs Team
Medical Affairs Team
Operations and Logistics Teams
Pharmacologists and Toxicologists
Patient Advocacy Groups

Once all stakeholders are satisfied, the protocol is finalized and handed off to the Regulatory Affairs team who submits it to regulators for review.



In the US, if the FDA doesn't respond or place the trial on hold within 30 days, the study may proceed.

Regulators may also have feedback, and request that changes be made to the study protocol. The Regulatory Affairs Team communicates FDA feedback to the Clinical Development Team, who then revises the protocol.



FDA Special Protocol Assessments (SPAs)

For Phase 3 trials, the Regulatory Affairs Team will often request a Special Protocol Assessment (SPA), a more thorough review of the study protocol.

SPA Request

The study sponsor submits a request for an SPA, detailing the study protocol and specific questions or areas where they seek FDA agreement.

The team meets with FDA officials and discusses the study protocol in detail and may negotiate aspects of the study design.

SPA Request

The study sponsor submits a request for an SPA, detailing the study protocol and specific questions or areas where they seek FDA agreement.

Meeting & review

The FDA reviews the proposed protocol and meets with the sponsor to discuss the details.

During this meeting, both parties may negotiate aspects of the study design, endpoints, methodologies, and other critical components.

Ultimately, the goal is to reach an agreement with the FDA that the study will support approval if conducted as outlined in the study protocol.

SPA Request

The study sponsor submits a request for an SPA, detailing the study protocol and specific questions or areas where they seek FDA agreement.

Meeting & review

The FDA reviews the proposed protocol and meets with the sponsor to discuss the details.

During this meeting, both parties may negotiate aspects of the study design, endpoints, methodologies, and other critical components.

Drafting the agreement

After reaching a consensus during the review and discussions, the FDA prepares a written agreement.

This document captures the agreed-upon study protocol details that the FDA believes are adequate to meet regulatory requirements.

Once both parties are satisfied, the SPA agreement is finalized.

SPA Request

The study sponsor submits a request for an SPA, detailing the study protocol and specific questions or areas where they seek FDA agreement.

Meeting & review

The FDA reviews the proposed protocol and meets with the sponsor to discuss the details.

During this meeting, both parties may negotiate aspects of the study design, endpoints, methodologies, and other critical components.

Drafting the agreement

After reaching a consensus during the review and discussions, the FDA prepares a written agreement.

This document captures the agreed-upon study protocol details that the FDA believes are adequate to meet regulatory requirements.

Finalization & approval

The sponsor reviews this document, and any final adjustments are made. Once both parties are satisfied, the agreement is finalized.

The process of drafting the SPA agreement involves similar iteration and feedback. SPA discussions may also lead to further revision of the study protocol.

The scope of the SPA is limited to aspects of the study protocol, and the SPA agreement provides some assurance that the protocol itself will support final approval.

Scope of the **Special Protocol Assessment (SPA) Agreement**

Trial design
The setup of the clinical study, including its type (e.g., randomized, placebo-controlled).

Endpoints
Primary and secondary outcomes the study aims to measure.

Statistical analysis methodology
Detailed plans for how data will be processed and analyzed.

Patient population
Inclusion and exclusion criteria for study participants.

However the SPA agreement does not guarantee approval — the scope of the New Drug Application (for final approval) is much broader than the SPA.

Scope of the **New Drug Application (NDA)**

Considerations for the final approval of a new drug after Phase III trials.

Preclinical data
Toxicology, pharmacokinetics, and pharmacodynamics data.

Clinical outcomes
Comprehensive results from all clinical trial phases demonstrating the drug's safety and efficacy.

Manufacturing information
Descriptions of the manufacturing process, facilities, and controls to ensure consistent drug quality.

Labeling
Information on the drug's intended use, dosage, risks, and instructions.

Regulatory compliance
Ensuring that all aspects of the drug development process meet FDA regulations.

Risk management
Plans to monitor and mitigate risks post-marketing.

Marketing plans
Strategies for the drug's distribution and sales.

Financial disclosure
Details regarding the financial aspects related to the drug's development and potential conflicts of interest.

Scope of the **Special Protocol Assessment (SPA) Agreement**

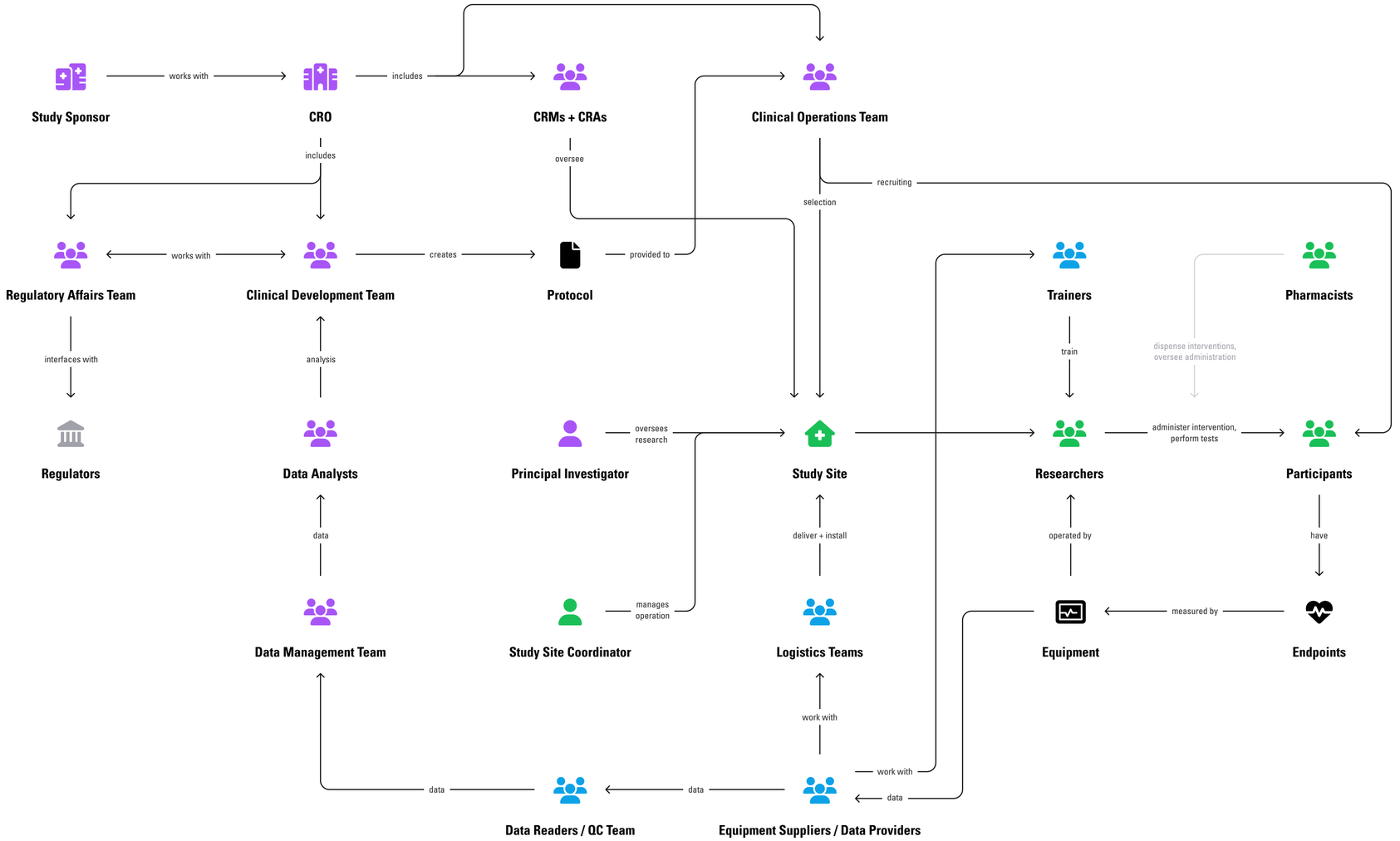
Trial design
The setup of the clinical study, including its type (e.g., randomized, placebo-controlled).

Endpoints
Primary and secondary outcomes the study aims to measure.

Statistical analysis methodology
Detailed plans for how data will be processed and analyzed.

Patient population
Inclusion and exclusion criteria for study participants.

A clinical trial is a social-technical system which requires coordination between hundreds or even thousands of people.
Each plays a role in ensuring that the trial is run smoothly and ethically, and that high-quality data is collected.



Clinical trials are conducted in phases and built on the foundation of the scientific method.

Basic safety and usefulness.

Subjects:
In silico, in vitro, lab animals

Duration:
Variable, months to years

Dosage, safety, and side effects.

Subjects:
20-100 patients or healthy volunteers

Duration:
Less than 1 year

Safety and efficacy.

Subjects:
100-300 patients

Duration:
1-2 years

Safety and efficacy.

Subjects:
1,000-3,000 patients

Duration:
Up to 4 years

Review results & methodology.

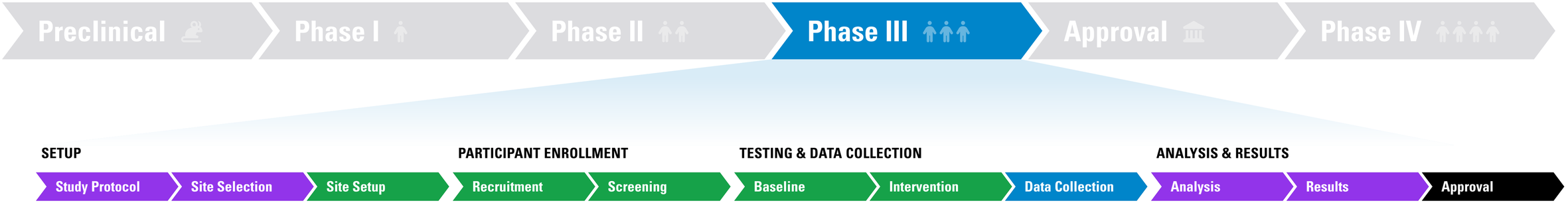
Duration:
10-12 months

Post-approval monitoring.

Subjects:
Thousands of patients

Duration:
Variable, ongoing

A single clinical trial includes many processes beyond the research itself — it requires large-scale preparation and data analysis efforts as well.



Developing a study protocol involves several rounds of iteration based on feedback from many stakeholders.

Preclinical | Phase I | Phase II | **Phase III** | Approval | Phase IV

SETUP

Study Protocol → Site Selection → Site Setup

PARTICIPANT ENROLLMENT

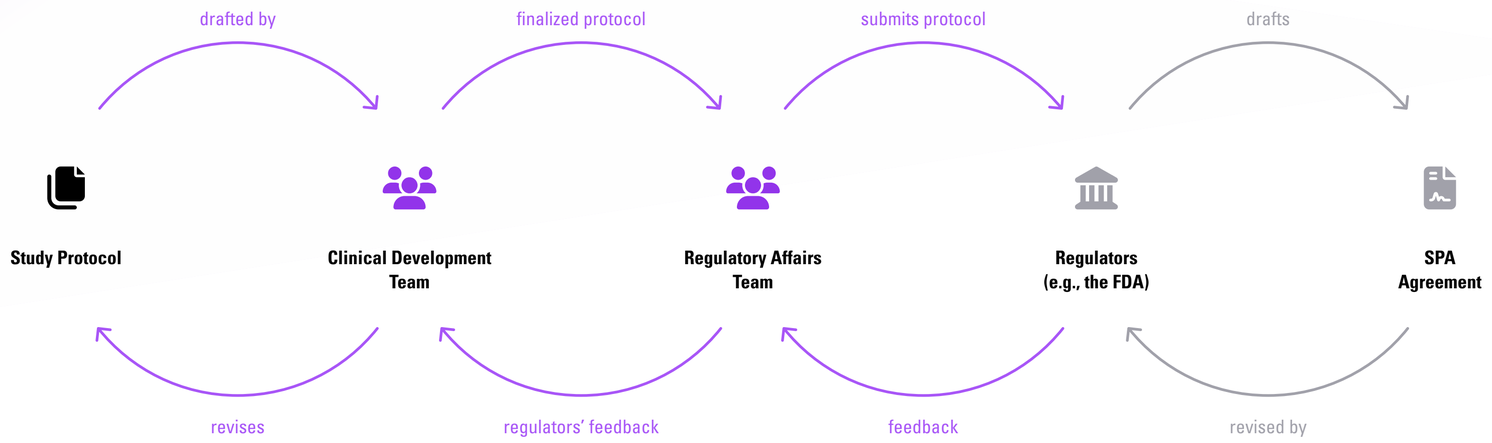
Recruitment → Screening

TESTING & DATA COLLECTION

Baseline → Intervention → Data Collection

ANALYSIS & RESULTS

Analysis → Results → Approval



The protocol outlines how the study will be conducted, including details of the study's design.
Study design is important for ensuring high quality data that can adequately verify whether or not a drug is safe and effective.

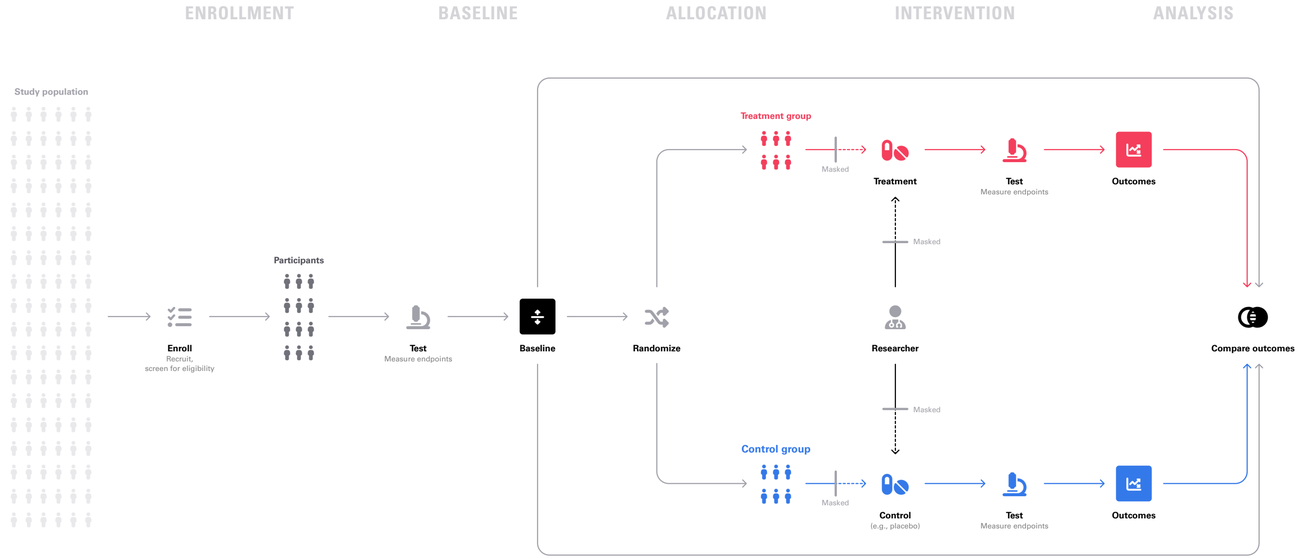
Preclinical | Phase I | Phase II | **Phase III** | Approval | Phase IV

SETUP
Study Protocol | Site Selection | Site Setup

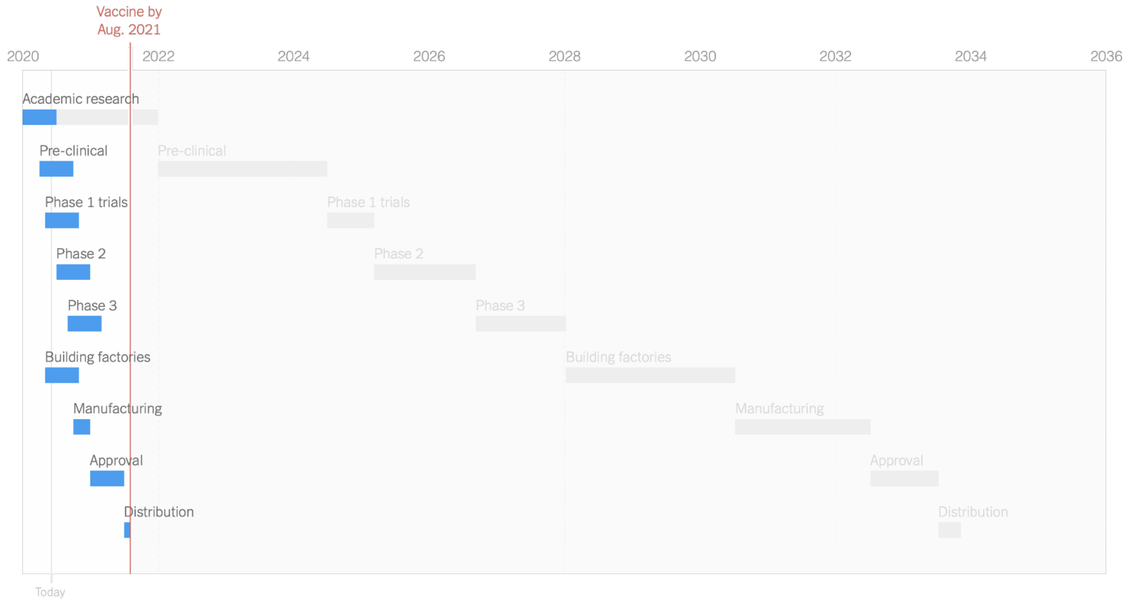
PARTICIPANT ENROLLMENT
Recruitment | Screening

TESTING & DATA COLLECTION
Baseline | Intervention | Data Collection

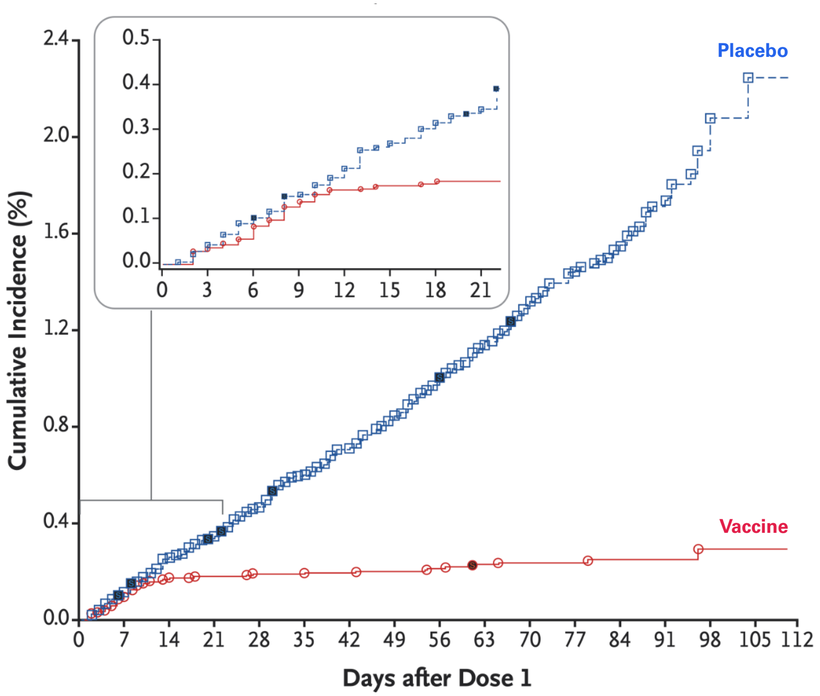
ANALYSIS & RESULTS
Analysis | Results | Approval



Despite an accelerated timeline due to emergency circumstances,
Pfizer's BNT162b2 trials were able to demonstrate that the vaccine was effective at protecting against COVID.



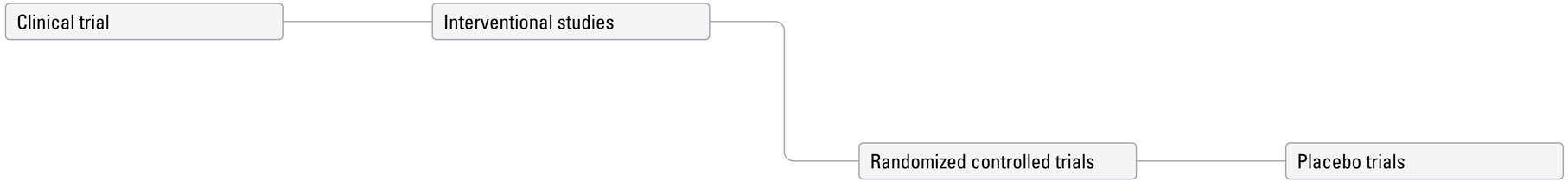
COVID-19 Vaccine Timeline



Pfizer Vaccine Trial Efficacy Results

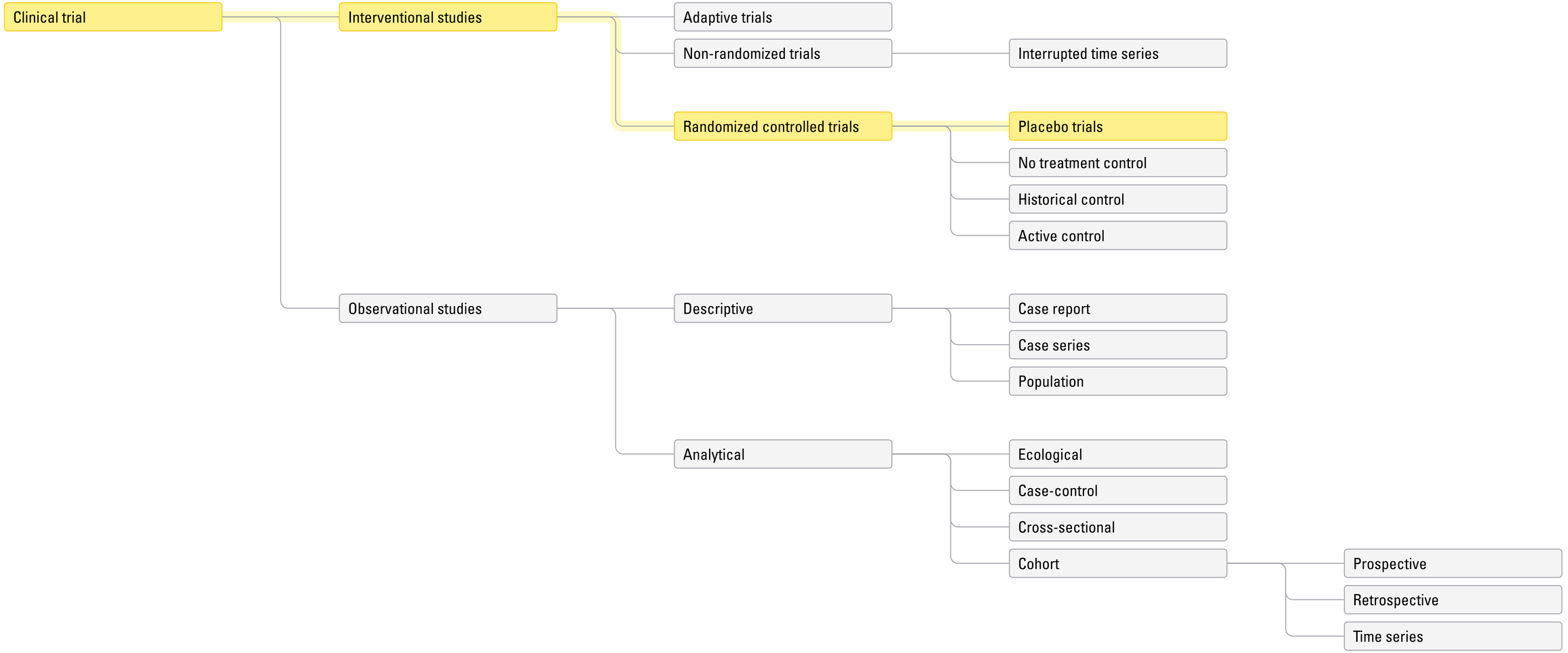
We've described some examples of typical clinical trials, but clinical trials come in different shapes and sizes.

We’ve focused primarily on randomized, placebo-controlled trials like the Pfizer vaccine trials.



https://www.researchgate.net/figure/Flowchart-outline-of-clinical-trial-design-types_fig1_348657614

While randomized controlled trials are considered a ‘gold standard’ and are the most common, there are many other possible study designs for clinical trials.



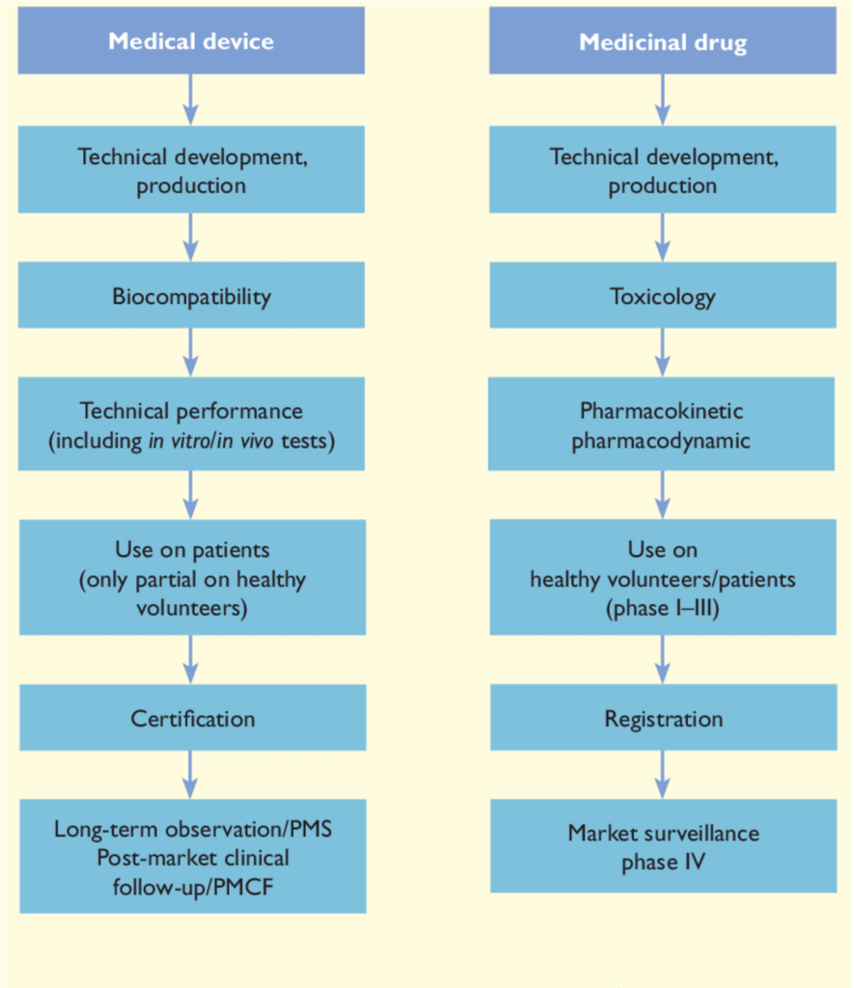
https://www.researchgate.net/figure/Flowchart-outline-of-clinical-trial-design-types_fig1_348657614

For medical devices, the classification of trials and process for conducting them differs slightly from clinical trials for drugs.

Clinical trial classification

Device Studies	Drug Studies
Pilot: Small study (10-30 patients with the condition) to determine preliminary safety and performance	**Phase I:** Small study (20-100 healthy volunteers or people with condition) to determine preliminary safety and dosage
Pivotal: Larger study (150-300 patients with the condition) to determine efficacy and adverse effects	**Phase II:** Larger study (up to several hundred people with the condition) to determine efficacy and adverse effects
Post-approval: Post-approval study to collect long-term data	**Phase III:** *(sometimes known as pivotal study)* Even larger study (up to thousands of people with the condition) to determine efficacy and monitor adverse effects
	Phase IV: Post-marketing study to collect long-term data

https://premier-research.com/blog-medical-devices-vs-drug-trials/



https://www.researchgate.net/figure/Different-development-steps-for-medical-devices-and-medicinal-drugs-in-Europe_fig1_44676847

However they are both subject to much of the same regulatory scrutiny.

Medical Device and Drug Trials Common Threads

	IDE (21 CFR Part 812)	IND (21 CFR Part 312)
Requires appropriate submission be made to the FDA prior to initiating the study	✔	✔
Specifies labeling requirements	✔	✔
Addresses waivers	✔	✔
Describes sponsor responsibilities	✔	✔
Describes investigator responsibilities	✔	✔
Requires selection of qualified investigators	✔	✔
Requires study monitoring	✔	✔
Requires IRB approval prior to initiating the study	✔	✔

https://premier-research.com/blog-comparing-medical-device-and-drug-trials-in-the-u-s-common-threads/

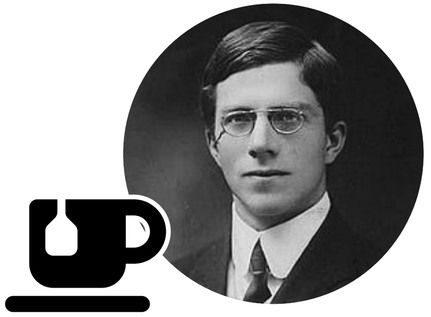
APPENDIX TWO

Ronald Fisher’s ‘Lady Tasting Tea’ experiment.

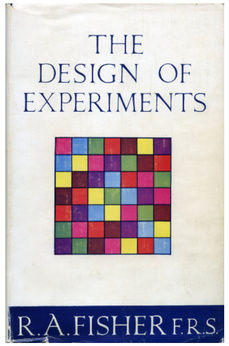
Ronald A. Fisher's 1935 book *The Design of Experiments* recounts a story of a social gathering in the 1920's, at which a colleague named Muriel Bristol requested that her tea be prepared with the milk poured first.

For my tea, could you please pour the milk first?

Muriel Bristol



Ronald Fisher

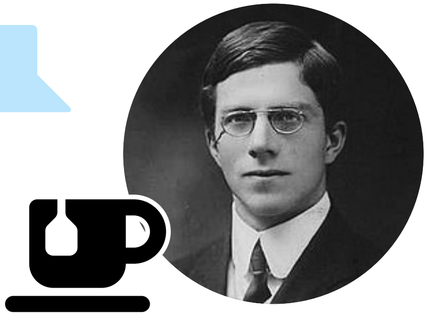


The request sparked a debate among Fisher and the other attendees, who were skeptical of Muriel's claim that she could tell the difference.
Fascinated by the debate, Fisher decided to test her claim with an experiment.

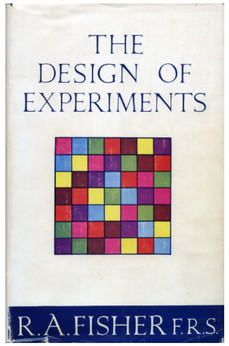
Muriel Bristol

In tea with milk, I can tell the difference between
when the tea was poured first and when the milk was poured first.

I'm skeptical — I'll design an experiment to test your assertion.



Ronald Fisher

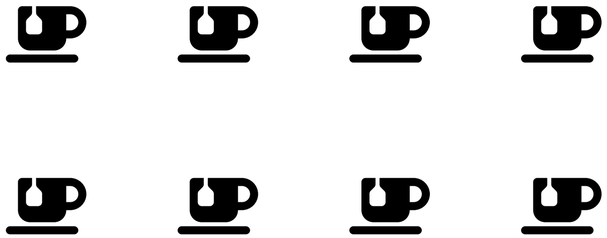


Fisher prepared 8 cups of tea — 4 with milk poured first and 4 with tea poured first — and asked Muriel to guess which ones were which.

Here, I've prepared 8 cups of tea for you. I want you to taste each one, and tell me which ones have had the tea poured first and which ones have had the milk poured first.

Ronald Fisher

Muriel Bristol



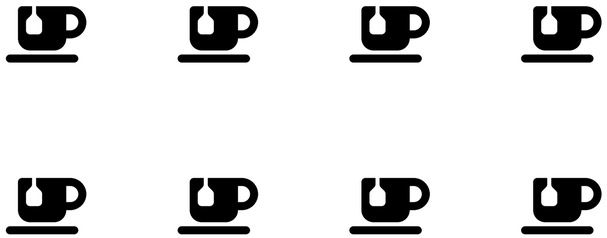
**The concept of a ‘null hypothesis’ is often attributed to Fisher —
here, the null hypothesis was that Muriel could not correctly distinguish between tea preparation methods.**

Here, I’ve prepared 8 cups of tea for you. I want you to taste each one,
and tell me which ones have had the tea poured first
and which ones have had the milk poured first.

Ronald Fisher

H_0: *Muriel cannot distinguish between tea preparation methods better than random guessing.*

Muriel Bristol



However, Muriel correctly guessed on all 8 cups of tea, providing strong evidence against the null hypothesis — she *could* tell the difference.

Tea first	Tea first	Tea first	Tea first	Milk first	Milk first	Milk first	Milk first
Correct	Correct	Correct	Correct	Correct	Correct	Correct	Correct

Muriel Bristol

Fisher's work in this area laid the foundation for modern scientific research.
In addition to the null hypothesis, his experiment employed several other statistical and scientific methdologies.

Null hypothesis

Fisher formulated the null hypothesis (H⊠) that Muriel Bristol could not distinguish between the cups of tea with milk added first and those with tea added first better than random guessing.

Experimental design

Fisher designed a controlled experiment to test Bristol's claim. He prepared a set number of tea cups with milk added first and tea added first, ensuring that the number of each type was equal (four of each).

Randomization

The order in which the cups were presented to Bristol was randomized to prevent any potential bias or pattern recognition that could influence the results.

Blind (or 'masked') testing

To ensure objectivity, the test was conducted in a blind manner where Bristol did not know the method used for each cup, eliminating any influence of expectation or prior knowledge.

Probability and statistical significance

Fisher calculated the probability of Bristol correctly identifying all eight cups by chance alone. This probability was used to determine the statistical significance of the results. If the observed outcome had a low probability of occurring under the null hypothesis, the null hypothesis could be rejected.

Type I error

Fisher considered the potential for a Type I error (rejecting a true null hypothesis) and designed the experiment to minimize this risk by setting a significance level (alpha).

Tea-Tasting Distribution

Success count	Permutations of selection	Number of permutations
0	oooo	1 × 1 = 1
1	ooox, ooxo, oxoo, xooo	4 × 4 = 16
2	ooxx, oxox, oxxo, xoxo, xxoo, xoox	6 × 6 = 36
3	oxxx, xoxx, xxox, xxxo	4 × 4 = 16
4	xxxx	1 × 1 = 1
Total		70

July 9, 2024

Understanding Clinical Trials

A Social-Technical System Deployed to Improve Health

Dubberly Design Office