PATIENTS' ACADEMY FOR RESEARCH ADVOCACY

Patient Advocacy in Research

Deep Dive

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President & CEO
The Patients' Academy for Research Advocacy

Global Liver Institute, November 2, 2019

Today's objectives

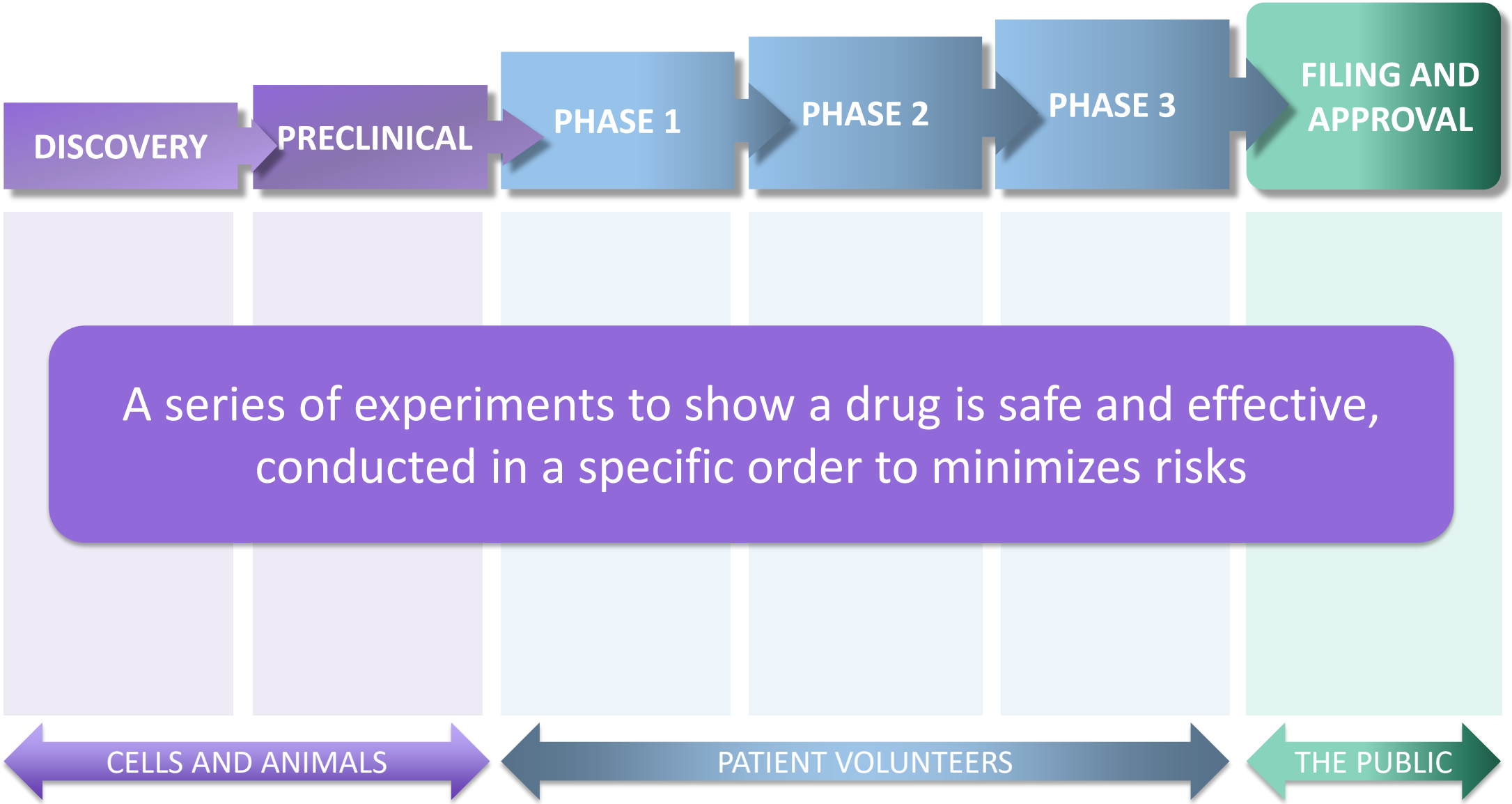
Learn why patient and care partner experience and input are needed to improve R&D

Identify key decision points in R&D where your input can make a difference

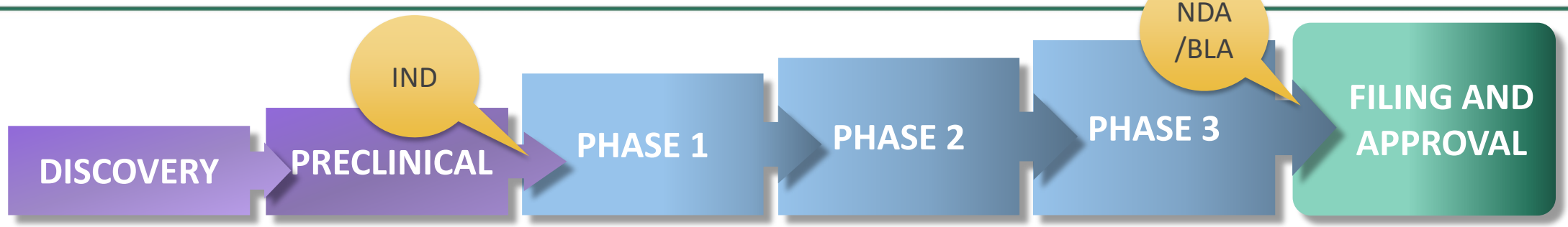
Introduce factors that contribute to good and bad partnerships in R&D

Answer YOUR questions!

A definition of drug R&D



Each step builds knowledge and reduces risk



DISCOVERY	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	FILING AND APPROVAL
Find a molecule that has chemical and biological properties that could treat a disease	Learn how the drug works Determine whether it is safe enough to test in people	Test for safety in people Study PK—what happens to the molecule in the body Decide which doses to study in Phase 2	Test for efficacy—does it work in the disease? Determine what doses to test in Phase 3 Decide on route of administration & formulation	Confirm efficacy in more people Confirm safety with longer exposure Demonstrate appropriate use	Gain approval to market the drug • For a specific use • In specific people • With a specific disease

CELLS AND ANIMALS

PATIENT VOLUNTEERS

THE PUBLIC

Several layers of patient protection

INSTITUTIONAL REVIEW BOARD

Study cannot start until IRB reviews it to ensure it is acceptable medically, ethically, and legal

IRB ensures informed consent form is accurate, complete, and easy to understand

INFORMED CONSENT

Volunteers cannot join the study until they have been given all the facts about the trial and consented to participate

DATA SAFETY MONITORING

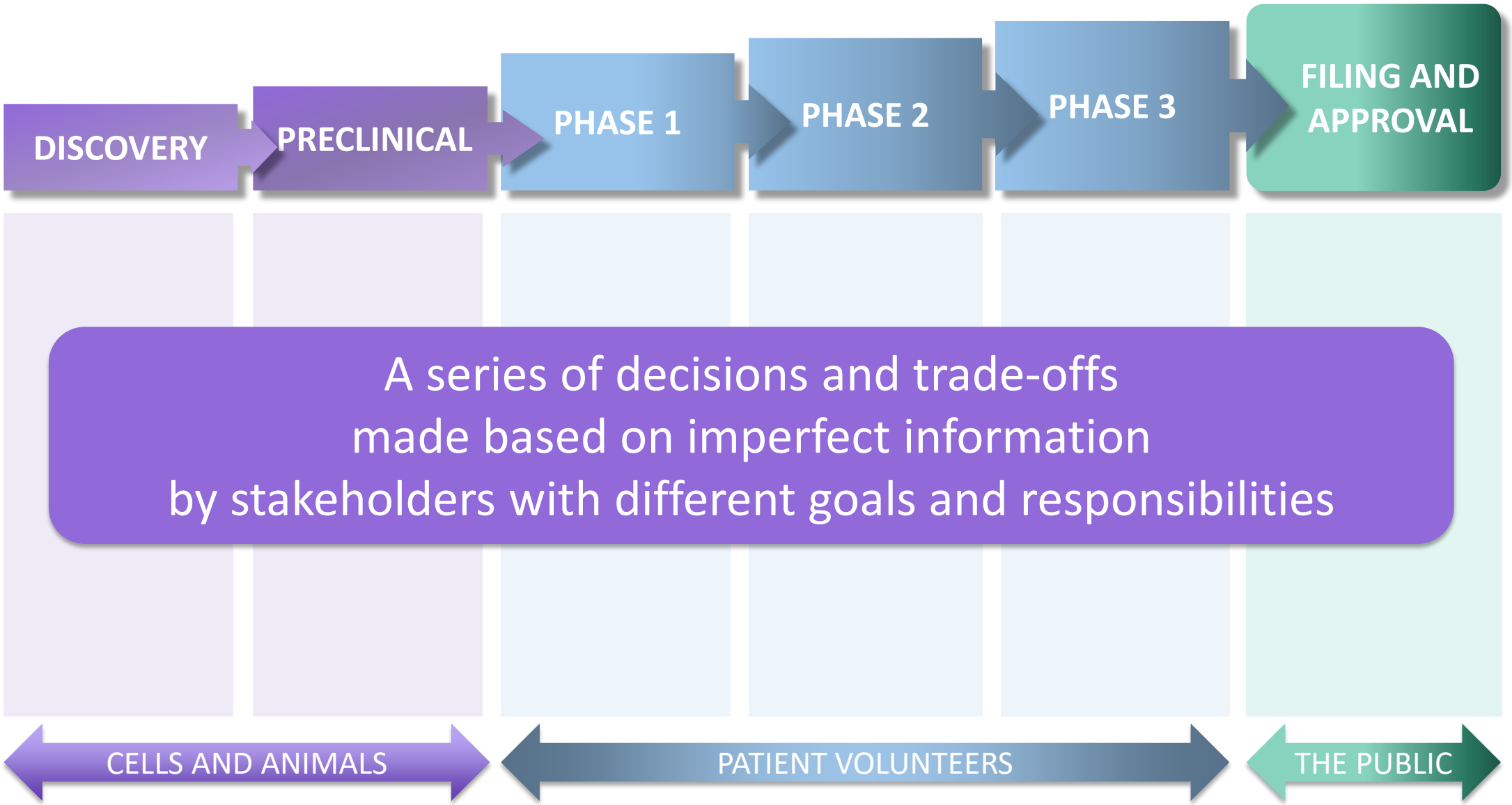
A scientific committee monitors the data at different points during the trial to decide if it should continue

The more is known, the more patients get access

PHASE 1	PHASE 2	PHASE 3	FILING AND APPROVAL
10s	100s	1,000s	10,000s? 100,000s? 1,000,000s?

1. DiMasi, J., et al. "Innovation in the pharmaceutical industry: New estimates of R&D costs." *Journal of Health Economics* (2016)
2. U.S.. Food and Drug Administration. "Prescription Drug User Fee Rates for Fiscal Year 2020." (2019)

Another way to look at it



Key decision-makers

DRUG SPONSORS

Help patients with disease

Earn profits

- Which disease?
- Which molecules to test?
- What studies to conduct?
- Which patients to include?
- What outcomes to measure/data to collect?
- Stop or keep going?

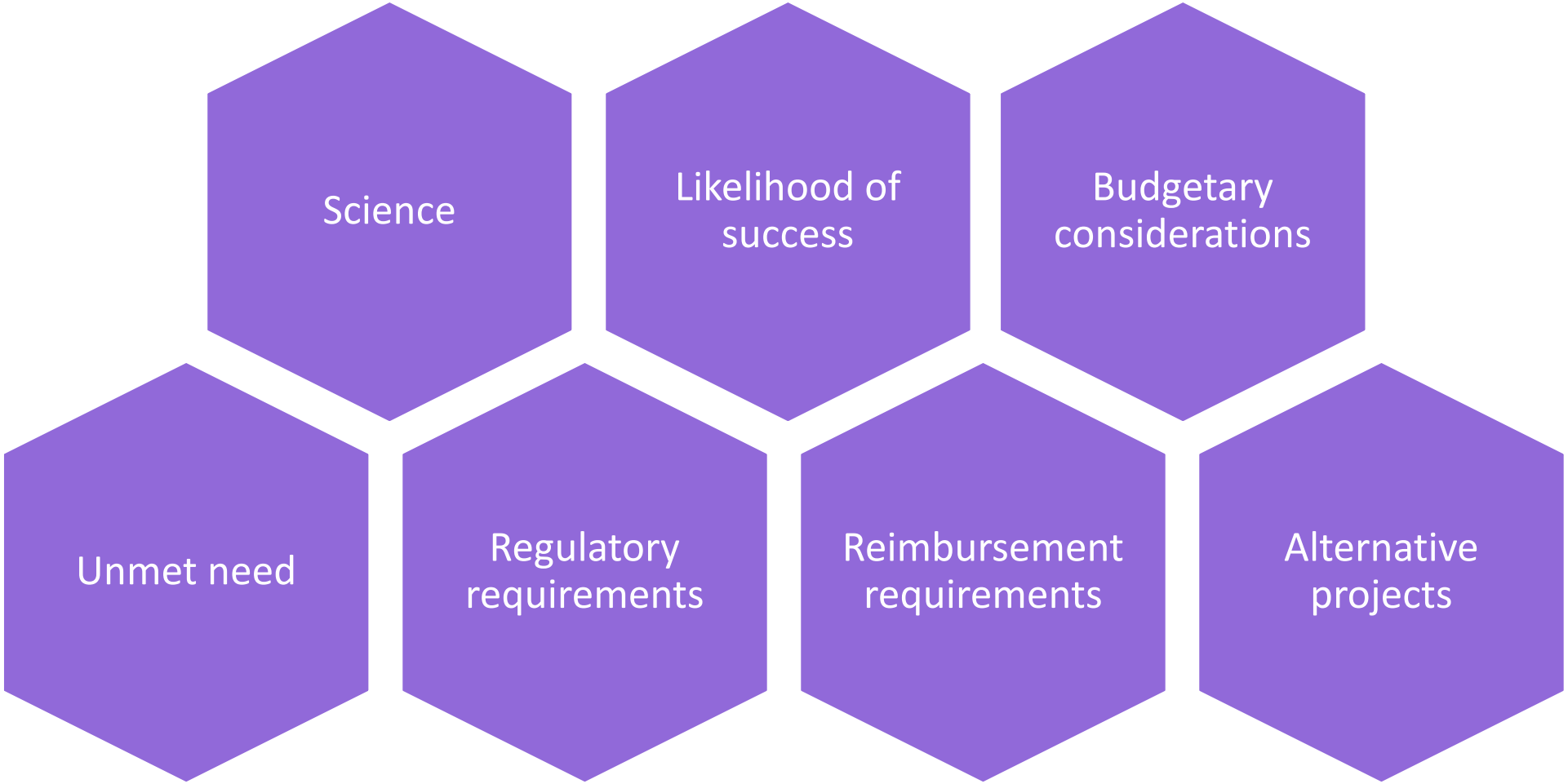
REGULATORS

Protect patients from harm

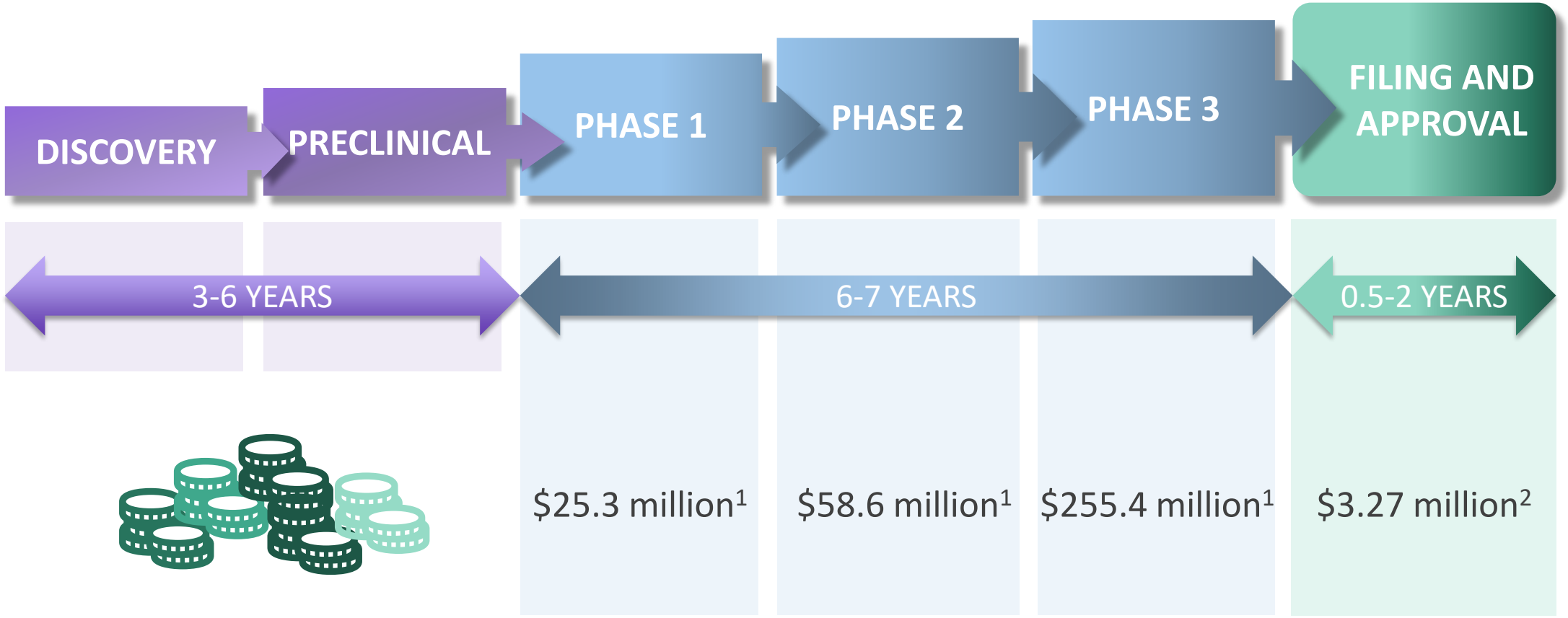
Promote public health

- What evidence is needed to allow clinical testing?
- What studies and outcomes are required for approval?
- What risk-benefit justifies approval?
- What drug sponsors can say about the drug's uses, benefits, and risks?

How drug sponsors decide



The stakes are high

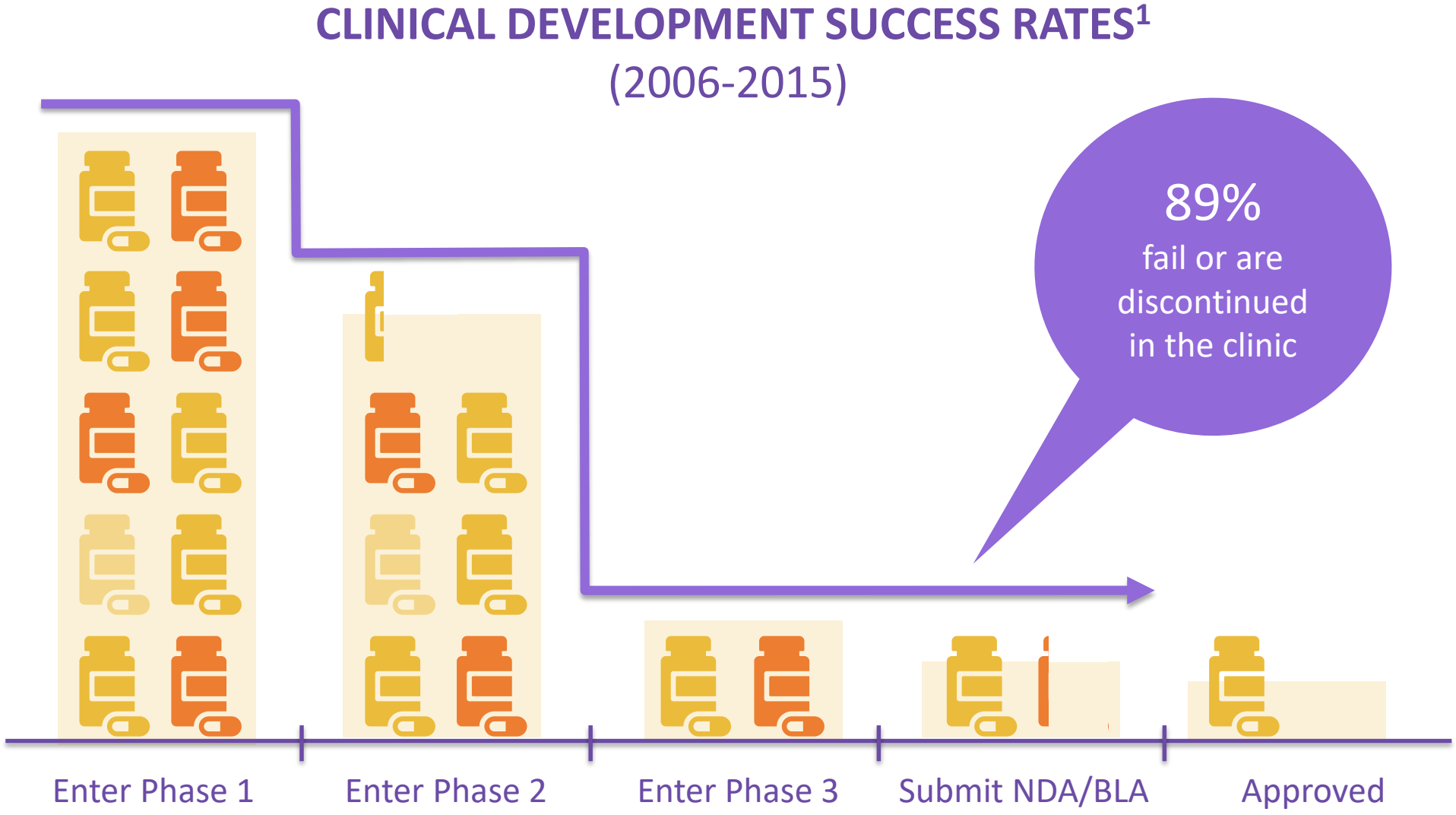


Average time
10 years

Average cost
$1.4 billion[1]

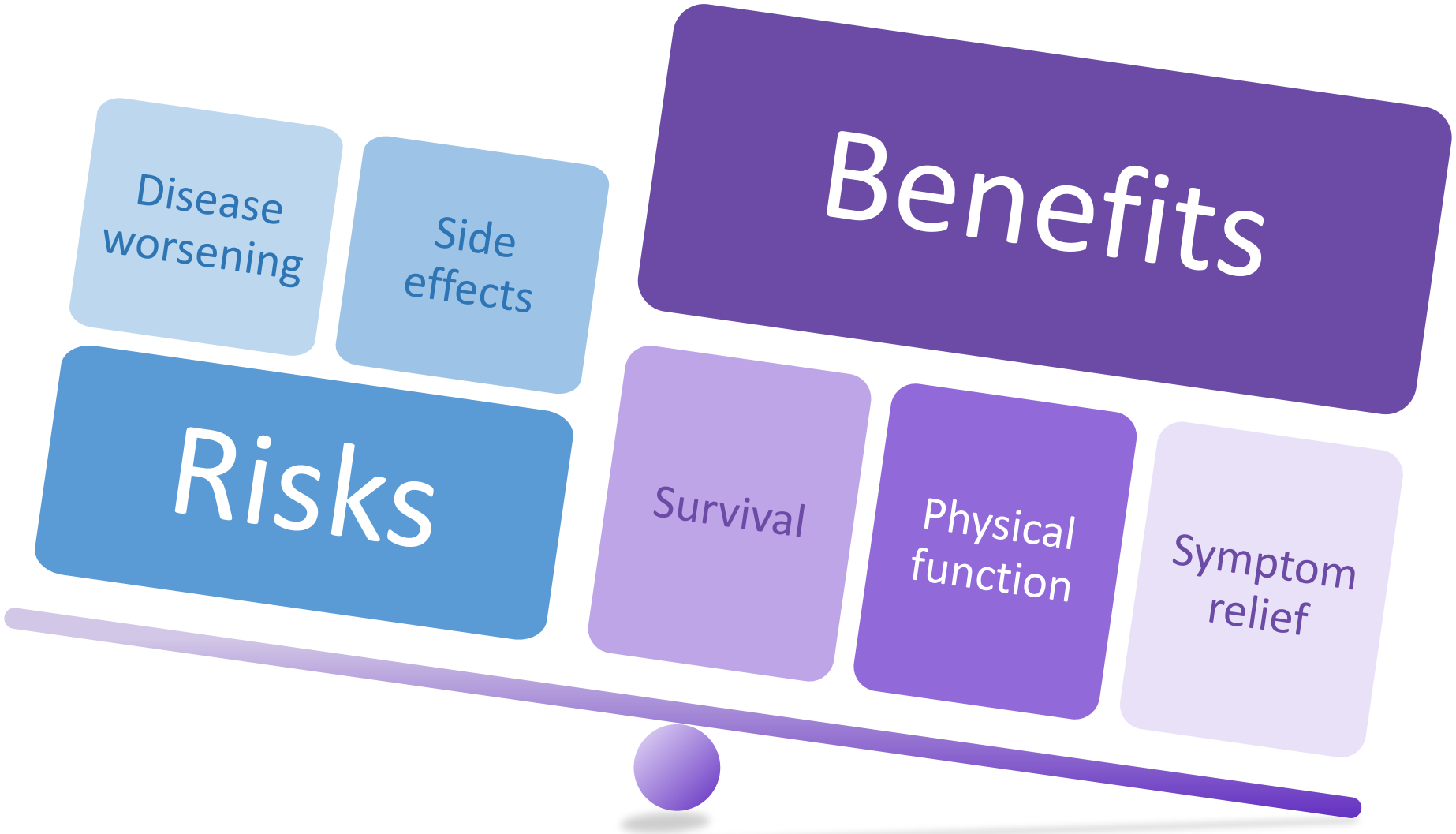
1. DiMasi, J., et al. "Innovation in the pharmaceutical industry: New estimates of R&D costs." *Journal of Health Economics* (2016)
2. U.S.. Food and Drug Administration. "Prescription Drug User Fee Rates for Fiscal Year 2020." (2019)

Few succeed



1. Biotechnology Innovation Organization, et al. "Clinical development success rates 2006-2015." (2016)

How regulators decide



Risk-benefit is a judgment call

> Ultimately, FDA faces a balancing act in evaluating a new drug.

> No matter how much data are available, we often have to make a judgment call, weighing the known benefits against known risks and the potential—and possibly unknown—risks.

FDA

How FDA Evaluates Regulated Products: Drugs
Updated November 28, 2016

You are the experts on risk-benefit …

> Patients are the experts in living with their disease or condition, the outcomes that are most important to them, and how they weigh benefits and risks.

Jeffrey Shuren

FDA's Center for Devices & Radiological Health

May 2, 2019

… And on some of the reasons drugs fail

GOOD FAILURES

STUDY REVEALS NEW INFORMATION
Not safe
Not effective

UNSAFE/INEFFECTIVE DRUG REJECTED
Lacks benefits patients want
Has unacceptable side effects

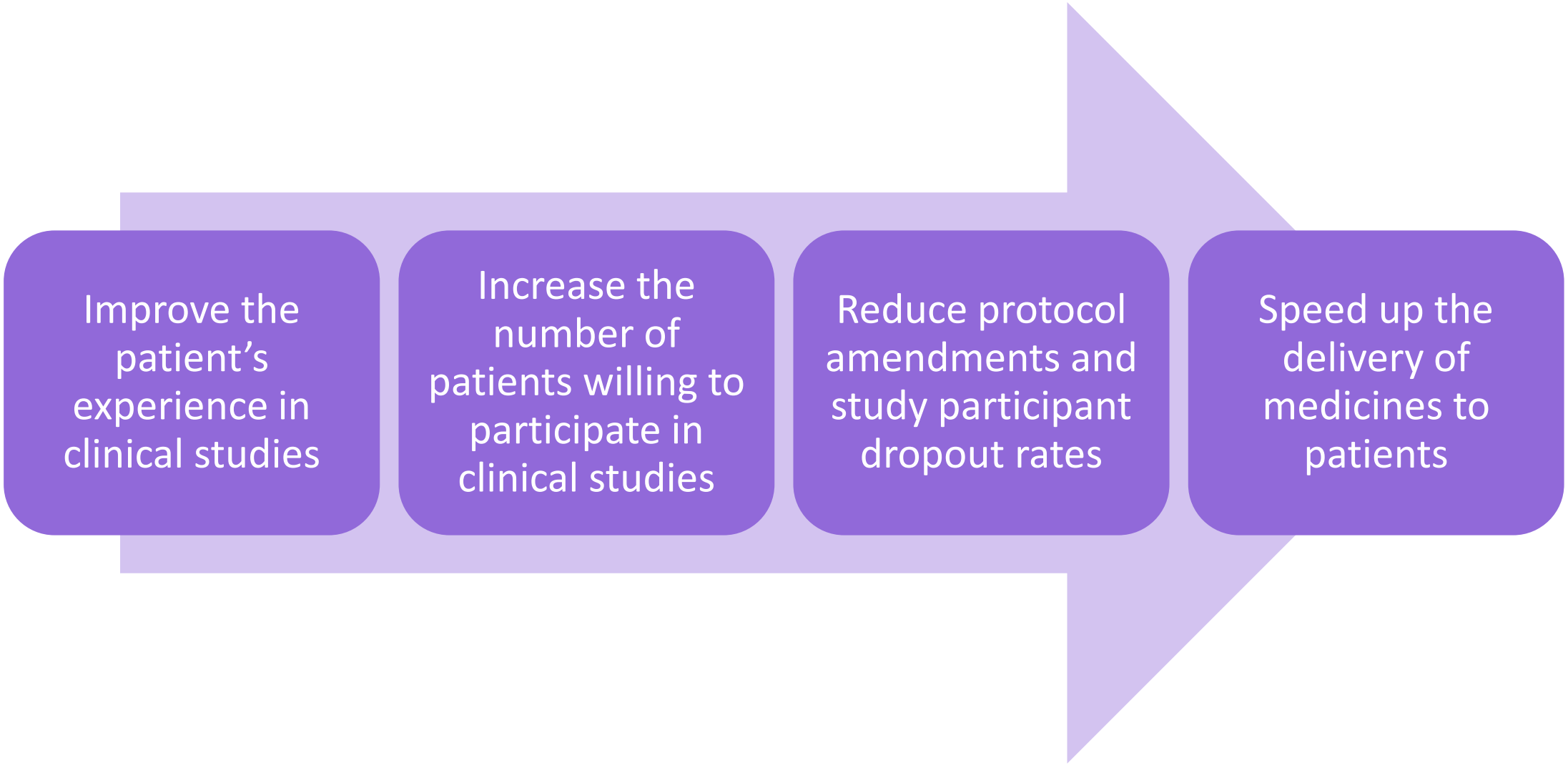
PREVENTABLE FAILURES?

USEFUL DRUG DENIED OR DELAYED
Benefits undervalued
Risks given too much weight

STUDY DID NOT WORK FOR PATIENTS
Not feasible
Not relevant or attractive

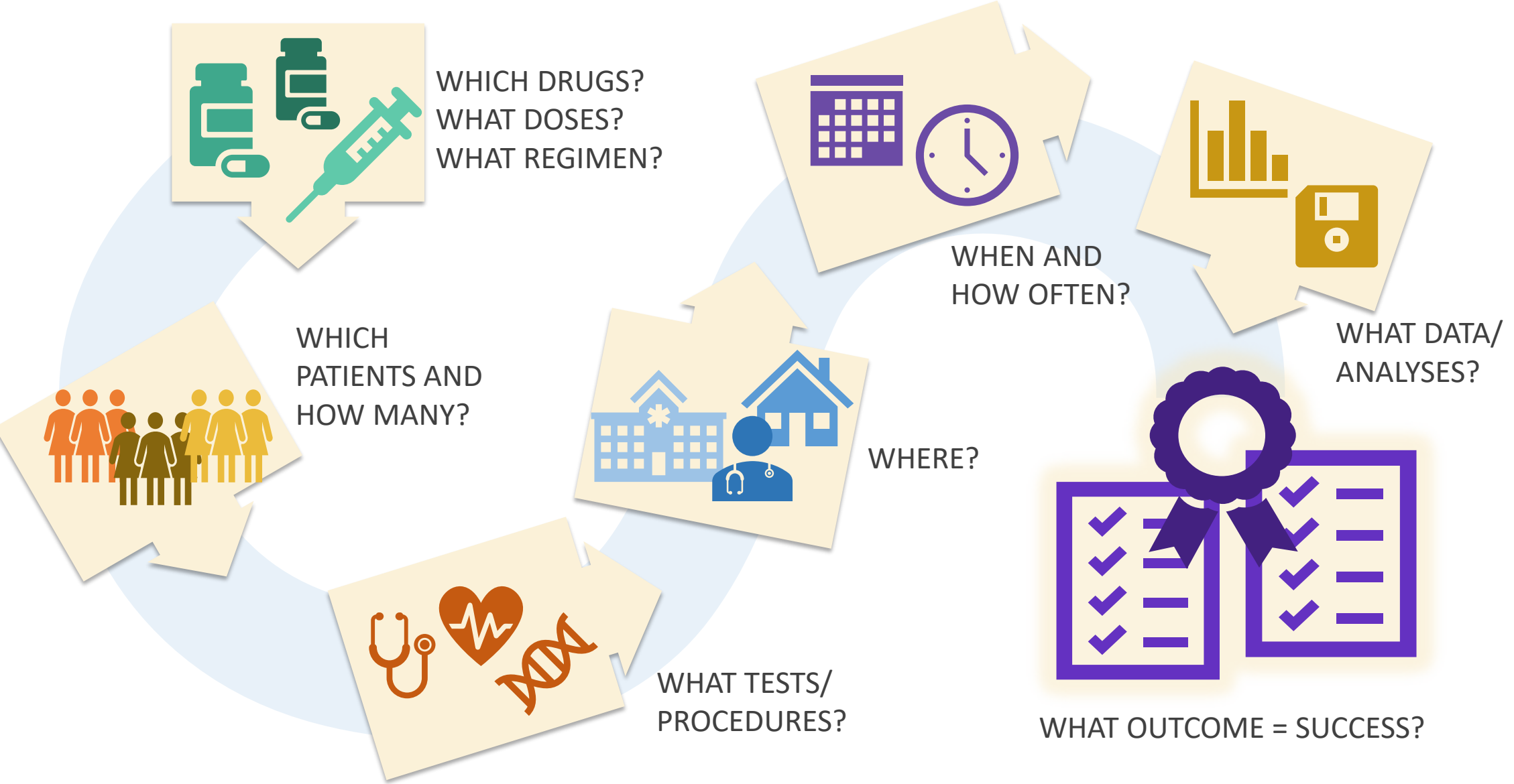
STUDY WAS FLAWED
Measured the wrong things
Was too small
Enrolled the wrong patients

Your advice can improve trials

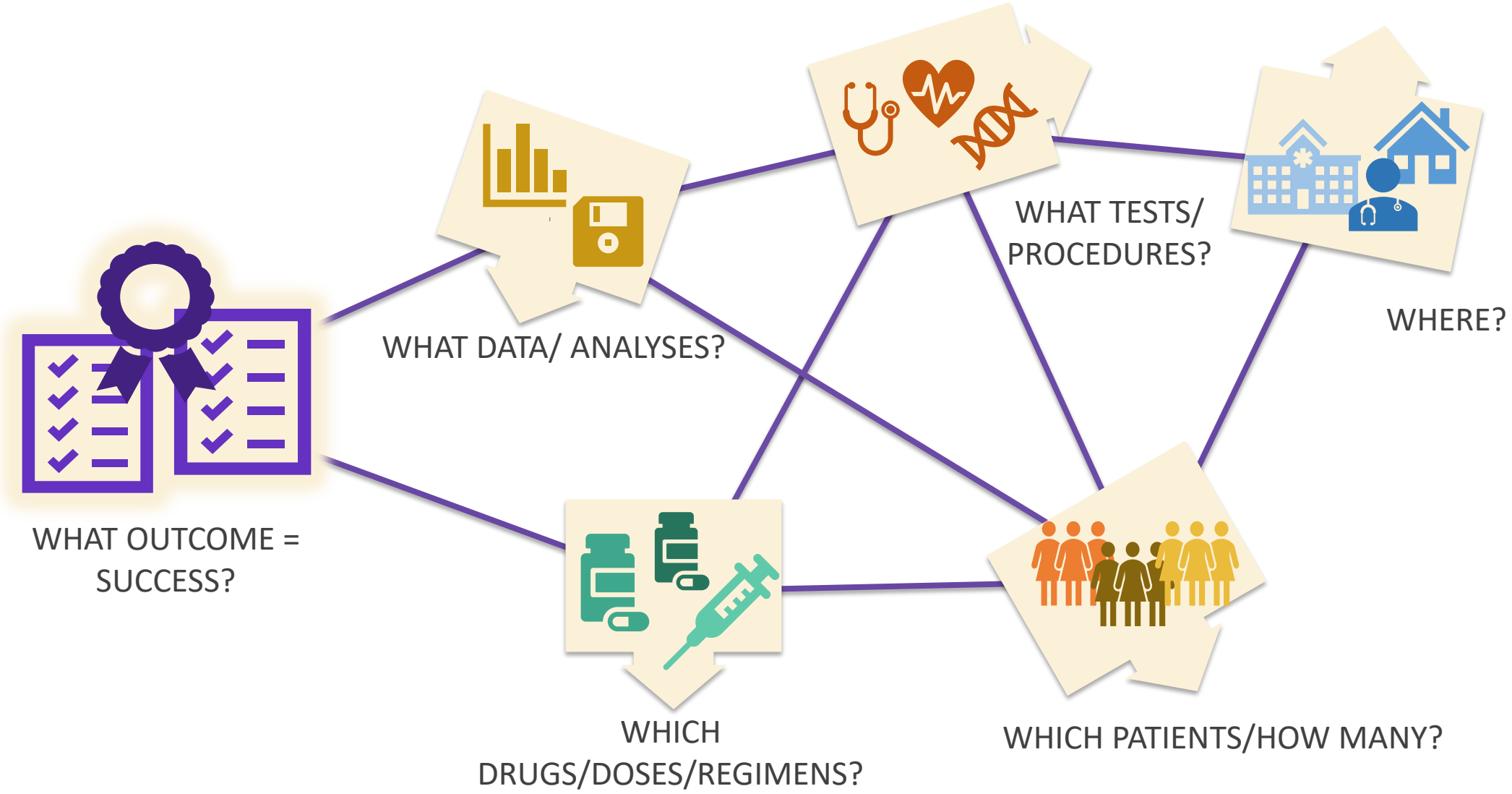


1. TransCelerate Biopharma Inc. "Patient Protocol Engagement Toolkit (P-PET) User Guide." (2019)

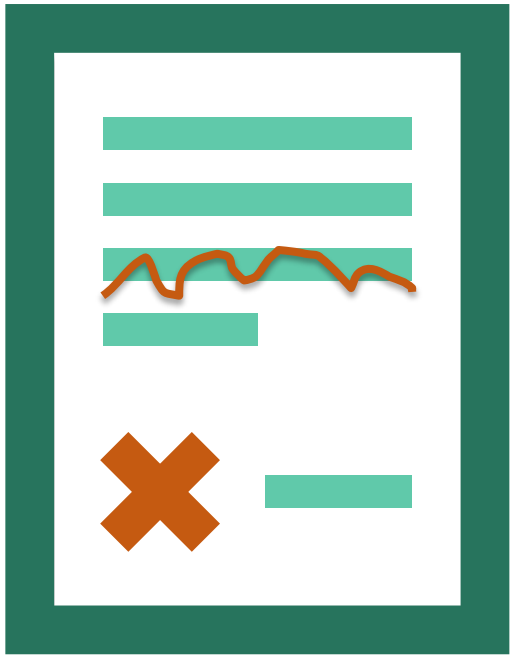
The protocol—anatomy of a clinical trial



Many components are interdependent



Poor enrollment leads to amendments



> The top reason for amending a protocol is to modify study eligibility criteria as a result of changes in study design strategy and difficulties recruiting patients.

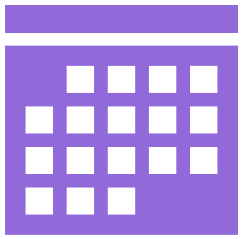
Clinical Trials Transformation Initiative

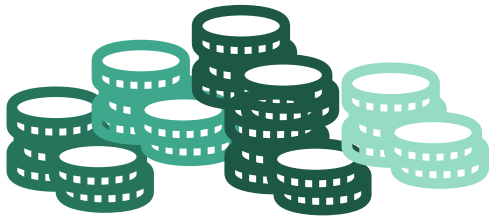
Therapeutic Innovation & Regulatory Science[1]

2017

1. Levitan, B., et al. "Assessing the Financial Value of Patient Engagement: A Quantitative Approach from CTTI's Patient Groups and Clinical Trials Project." (2017)

Amendments cost time and money

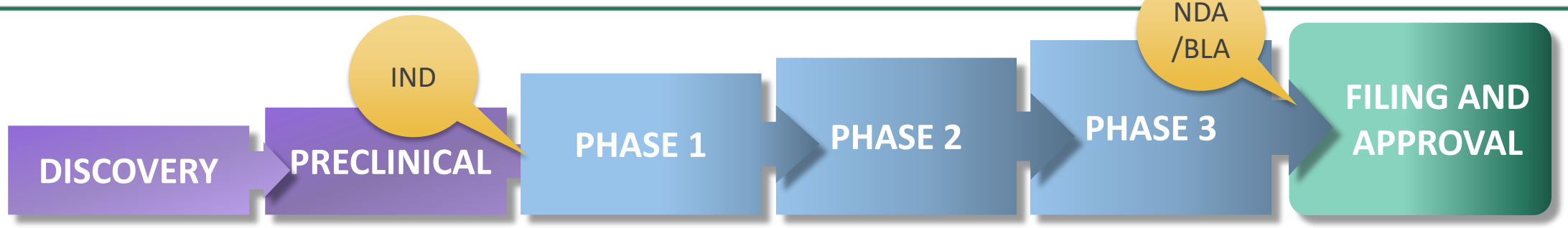




PHASE 2	PHASE 3
90 days[1]	90 days[1]
$0.56 million[1]	$2.1 million[1]

1. Levitan, B., et al. "Assessing the Financial Value of Patient Engagement: A Quantitative Approach from CTTI's Patient Groups and Clinical Trials Project." (2017)

Roles for patients in R&D



Provide information on unmet need, disease burden, and treatment burden

Provide data on expectations of benefit and tolerance for risk

Advise on product characteristics, administration, packaging

Assess relevance of research to patients' needs

Advise on eligibility criteria

Assess barriers to participation

Help design patient materials

Help identify and prioritize endpoints

Help develop patient-reported outcomes

Advise on and assist with recruiting patient volunteers

Provide feedback on patient experience

Provide written comments on regulations and guidances

Testify at FDA hearings

Serve on advisory committees

CELLS AND ANIMALS

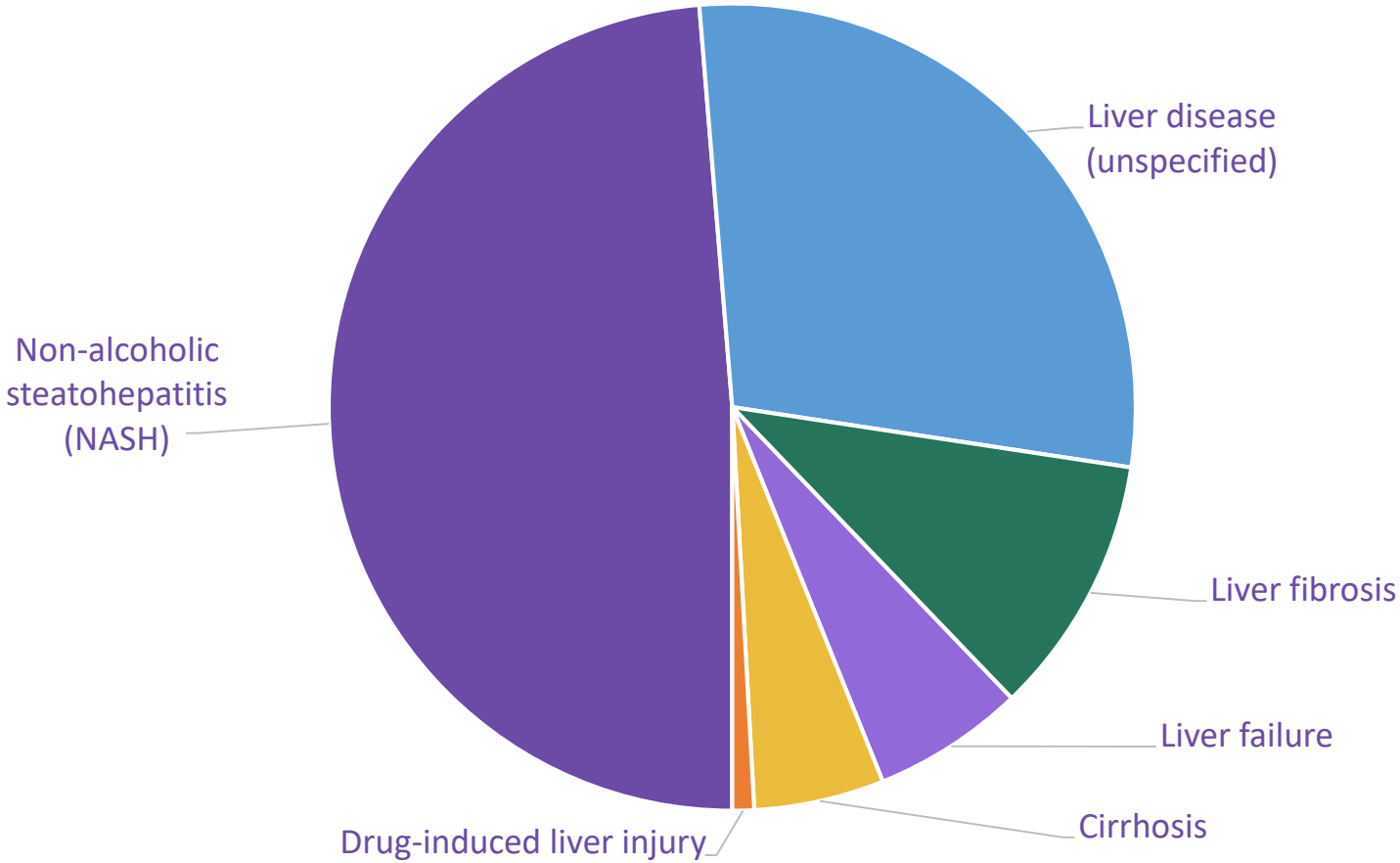
PATIENT VOLUNTEERS

THE PUBLIC

It’s best to start early

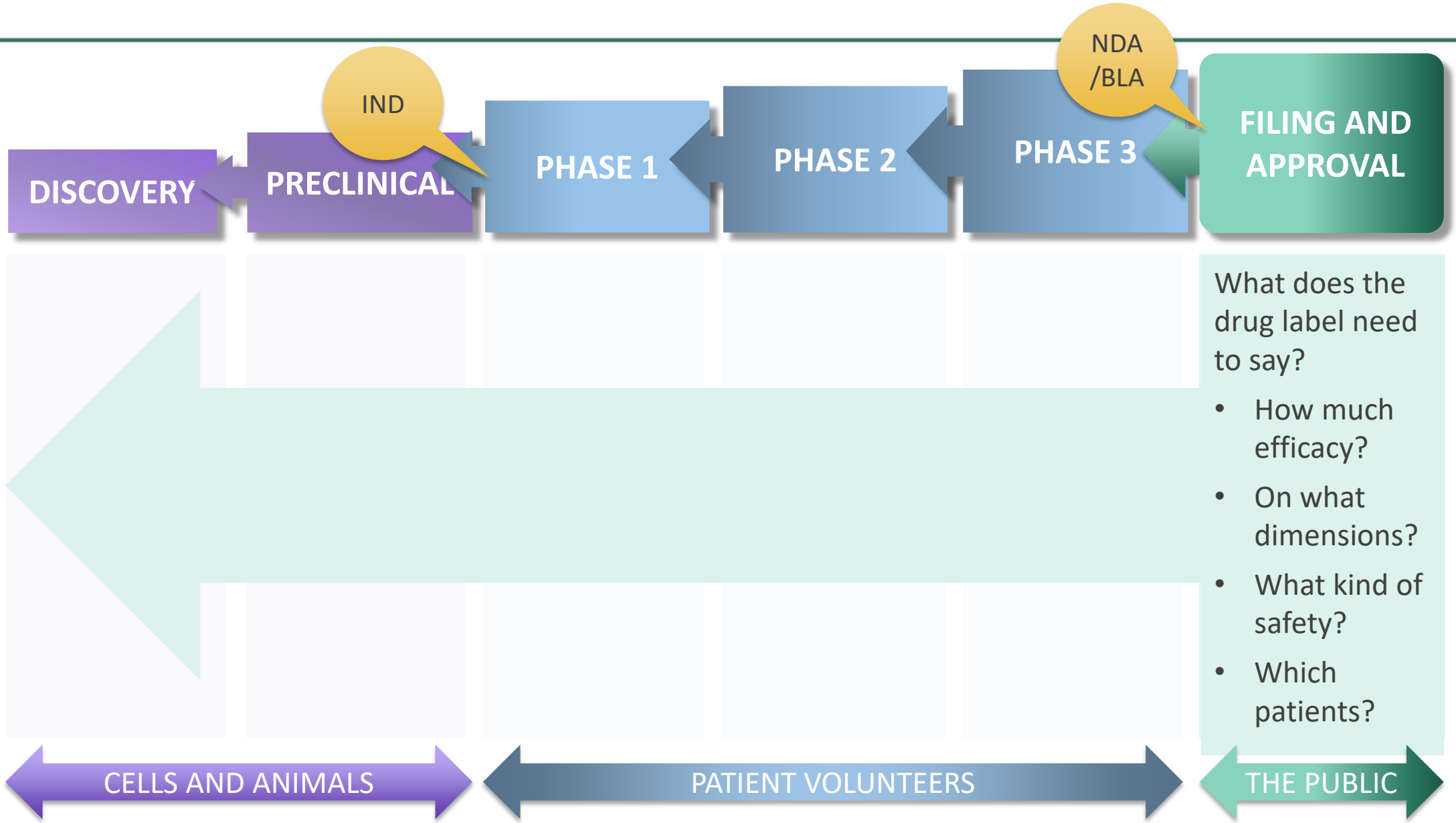
DISCOVERY/PRECLINICAL LIVER DISEASE PROGRAMS[1]

(Industry Pipeline, Total = 115)



1. BioCentury BCIQ database. Accessed Oct. 29, 2019.

Drug sponsors plan with the end in mind



What's a drug label?

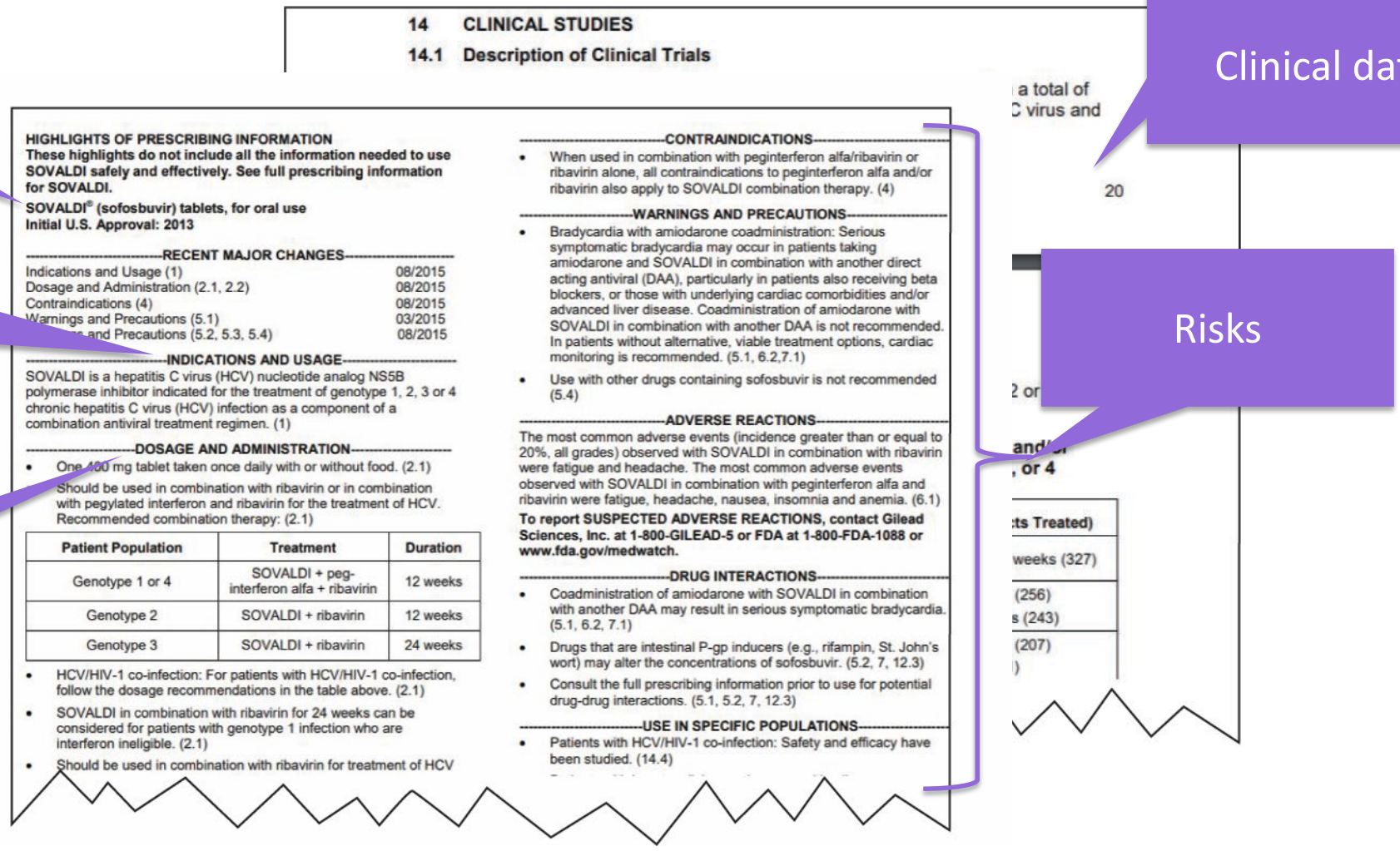
Drug name

Approved uses

Doses and route of administration

Clinical data

Risks



14 CLINICAL STUDIES

14.1 Description of Clinical Trials

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SOVALDI safely and effectively. See full prescribing information for SOVALDI.

SOVALDI® (sofosbuvir) tablets, for oral use
Initial U.S. Approval: 2013

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	08/2015
Dosage and Administration (2.1, 2.2)	08/2015
Contraindications (4)	08/2015
Warnings and Precautions (5.1)	03/2015
and Precautions (5.2, 5.3, 5.4)	08/2015

----------INDICATIONS AND USAGE----------

SOVALDI is a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor indicated for the treatment of genotype 1, 2, 3 or 4 chronic hepatitis C virus (HCV) infection as a component of a combination antiviral treatment regimen. (1)

----------DOSAGE AND ADMINISTRATION----------

- One 400 mg tablet taken once daily with or without food. (2.1)
- Should be used in combination with ribavirin or in combination with pegylated interferon and ribavirin for the treatment of HCV. Recommended combination therapy: (2.1)

Patient Population	Treatment	Duration
Genotype 1 or 4	SOVALDI + peg-interferon alfa + ribavirin	12 weeks
Genotype 2	SOVALDI + ribavirin	12 weeks
Genotype 3	SOVALDI + ribavirin	24 weeks

- HCV/HIV-1 co-infection: For patients with HCV/HIV-1 co-infection, follow the dosage recommendations in the table above. (2.1)
- SOVALDI in combination with ribavirin for 24 weeks can be considered for patients with genotype 1 infection who are interferon ineligible. (2.1)
- Should be used in combination with ribavirin for treatment of HCV

----------CONTRAINDICATIONS----------

- When used in combination with peginterferon alfa/ribavirin or ribavirin alone, all contraindications to peginterferon alfa and/or ribavirin also apply to SOVALDI combination therapy. (4)

----------WARNINGS AND PRECAUTIONS----------

- Bradycardia with amiodarone coadministration: Serious symptomatic bradycardia may occur in patients taking amiodarone and SOVALDI in combination with another direct acting antiviral (DAA), particularly in patients also receiving beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone with SOVALDI in combination with another DAA is not recommended. In patients without alternative, viable treatment options, cardiac monitoring is recommended. (5.1, 6.2,7.1)
- Use with other drugs containing sofosbuvir is not recommended (5.4)

----------ADVERSE REACTIONS----------

The most common adverse events (incidence greater than or equal to 20%, all grades) observed with SOVALDI in combination with ribavirin were fatigue and headache. The most common adverse events observed with SOVALDI in combination with peginterferon alfa and ribavirin were fatigue, headache, nausea, insomnia and anemia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Coadministration of amiodarone with SOVALDI in combination with another DAA may result in serious symptomatic bradycardia. (5.1, 6.2, 7.1)
- Drugs that are intestinal P-gp inducers (e.g., rifampin, St. John's wort) may alter the concentrations of sofosbuvir. (5.2, 7, 12.3)
- Consult the full prescribing information prior to use for potential drug-drug interactions. (5.1, 5.2, 7, 12.3)

----------USE IN SPECIFIC POPULATIONS----------

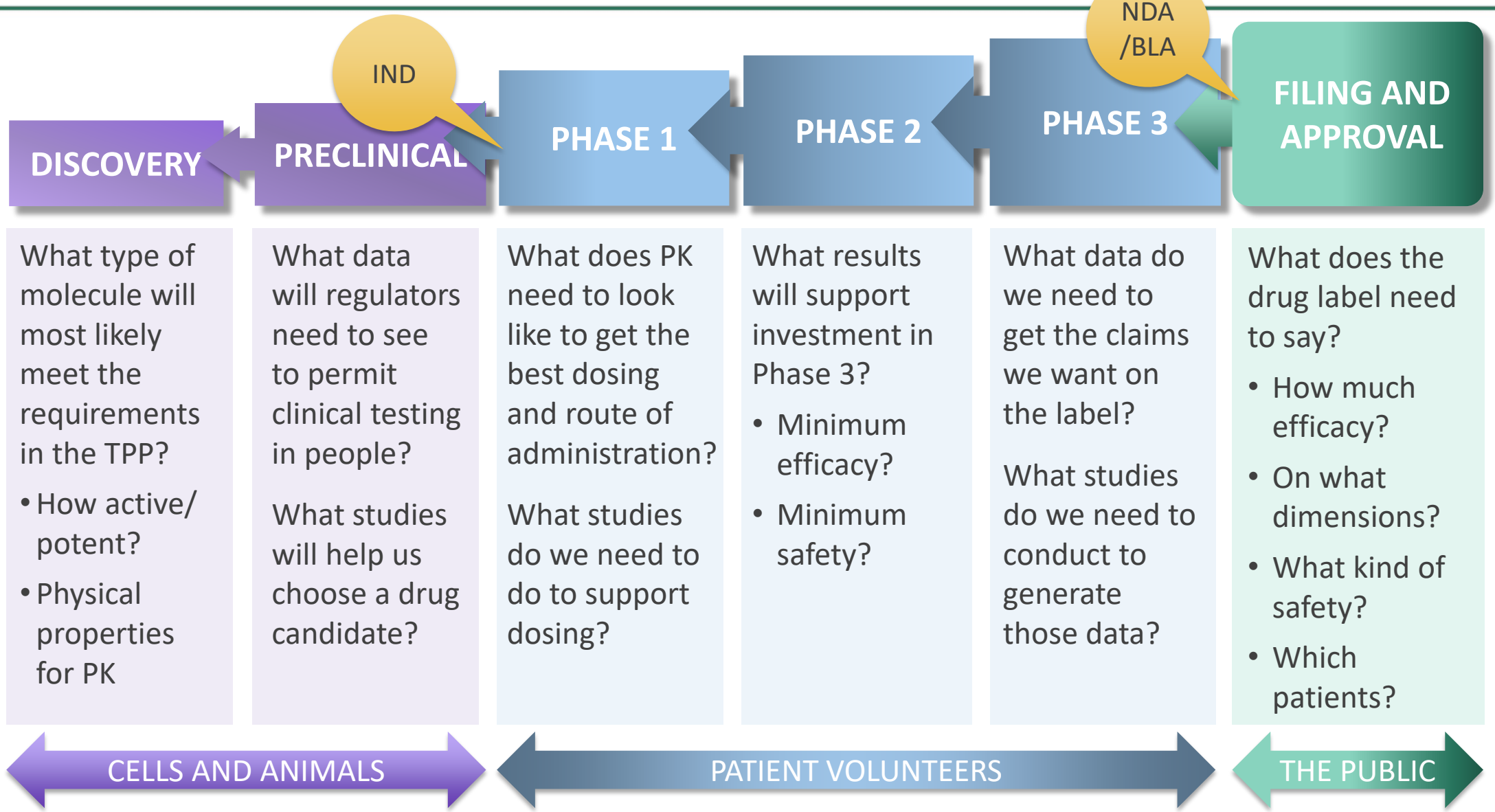
- Patients with HCV/HIV-1 co-infection: Safety and efficacy have been studied. (14.4)

Target product profile

DRUG X

Indication	To treat or prevent a disease or condition, or an important manifestation of a disease or condition -OR- To relieve symptoms associated with a disease or syndrome
Target population	Age, severity of illness, prior treatment, other illnesses (co-morbidities)
Treatment duration	Days, weeks, months, for life
Route of administration	Oral, IV, subcutaneous injection, topical, inhaled
Dosage form	Tablets, capsules, syrup, premixed
Dosage	How much and how often
Efficacy	How much improvement, on what specific measures, compared with what specific alternative
Safety	What side effects or risks are acceptable

Planning with the end in mind



Considerations for engagement

INGREDIENTS FOR SUCCESSFUL PARTNERSHIPS

GOALS AND EXPECTATIONS	Are goals and expectations clear? Designed for mutual benefit? Agreed to up front?
ROLES AND RESPONSIBILITIES	Will you be involved in every step, or only some? Will you have input into key decisions? Do you represent yourself only, or your patient community?
MEANINGFULNESS	Do the goals and expectations support your objectives? Is it clear how your input will be used? Is it early enough for your input to count? Is there a plan for two-way communication?
CONFLICTS OF INTEREST	How will you handle real or perceived conflicts of interest? How will your partner?

PATIENTS' ACADEMY FOR RESEARCH ADVOCACY

Questions and follow-up

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APPENDIX—Glossary of clinical and regulatory terms

Biologic – a drug made of molecules that are produced by a living organism, e.g., antibodies and other proteins

BLA, Biologics License Application –the application a drug sponsor submits to FDA to seek approval of a drug candidate that is a biologic

Clinical trial – research studies that test whether drugs are safe and how they work in people who are either healthy volunteers or patients

Drug sponsor – the developer of a drug, usually but not always a pharmaceutical company

DSMB, Data Safety Monitoring Board – a scientific committee that monitors data from an ongoing clinical trial to determine whether the study should continue

Endpoint – a measure of efficacy in a research study

FDA, Food and Drug Administration – the U.S. regulator that oversees clinical testing and drug approvals

IND, Investigational New Drug – the application a drug sponsor submits to FDA to seek permission to begin clinical studies in people

Informed consent – the practice of giving a potential volunteer all the facts about a clinical trial and getting their consent to participate before they join the study

IRB, Institutional Review Board – a committee of doctors, statisticians, and community members who review clinical trial protocols to ensure they are medically, ethically, and legally acceptable

In vitro research – laboratory studies on cells or molecules outside the body

In vivo research – laboratory studies on living animals

Label – a medication package insert approved by FDA that describes the drug, how it is used, how it works, and what is known about its safety and efficacy

Model – a cell line, tissue sample, or animal used to study disease biology or screen drug candidates

NDA, New Drug Application – the application a drug sponsor submits to FDA to seek approval of drug candidate that is a small molecule

PK, pharmacokinetics – the way a drug is absorbed, distributed, metabolized and eliminated by the body

Protocol – a detailed written plan for a clinical trial that describes every aspect of study design and conduct

Regulator – a government organization that oversees clinical testing and drug approvals

R&D, research and development – the activity of discovering and testing a drug to show that it can treat disease

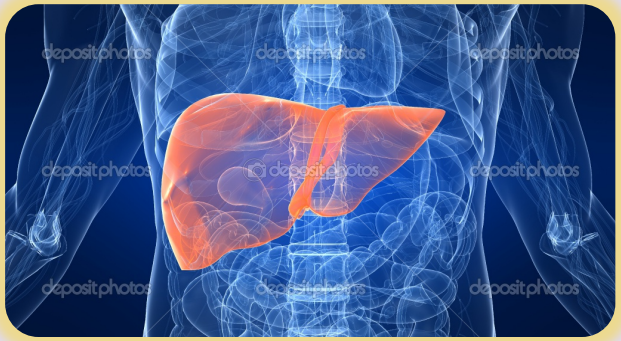
Small molecule drug – a drug that is made of molecules that are chemical compound

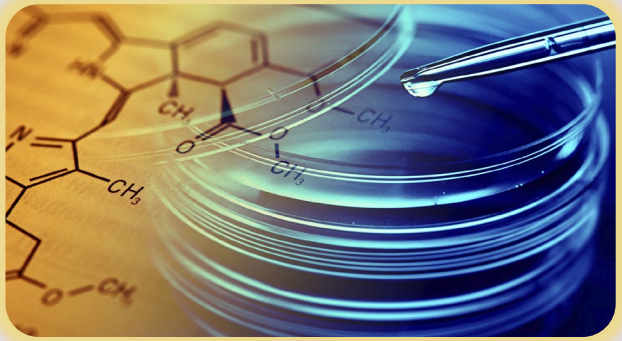
Target – a molecule or cell that a drug binds to or interacts with to stop, start or change a process that does not work correctly in a disease

TPP, target product profile – a detailed description of the ideal characteristics of a new drug candidate that is used to guide R&D

APPENDIX—Before drug ‘R&D’ begins

BASIC AND TRANSLATIONAL RESEARCH





WHAT

- What happens in this disease, biologically?
- What molecules and cells are involved?
- Could these molecules or cells be drug targets?

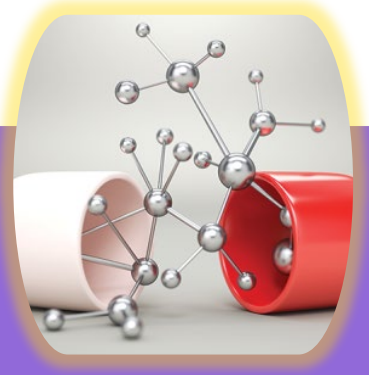
HOW

- Lab tests (assays) in cell lines or samples of blood/tissue (biospecimens) from patients
- Studies in animal models of the disease

WHO

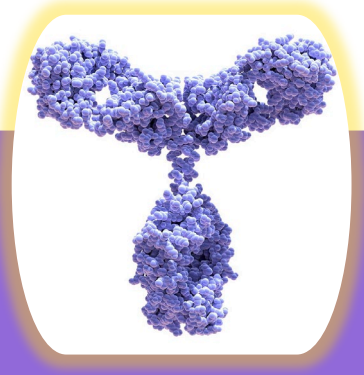
- Usually researchers in academia, government, medical research centers

APPENDIX—Types of drugs and how they work



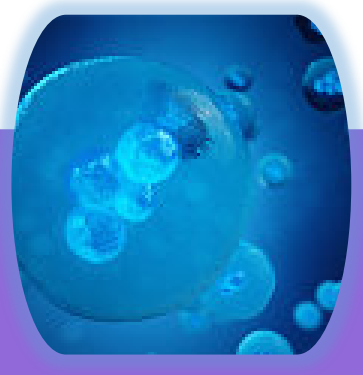
SMALL MOLECULE

A chemical compound



BIOLOGIC

A molecule produced by a living organism



GENE & CELL THERAPIES

Cells, genes, and/or viruses

Stop, start, or change a biological process that doesn't work correctly in disease

Bind to molecules in our bodies called targets

Kill or modify cells