Clinical Trials – Not Just a Hail Mary

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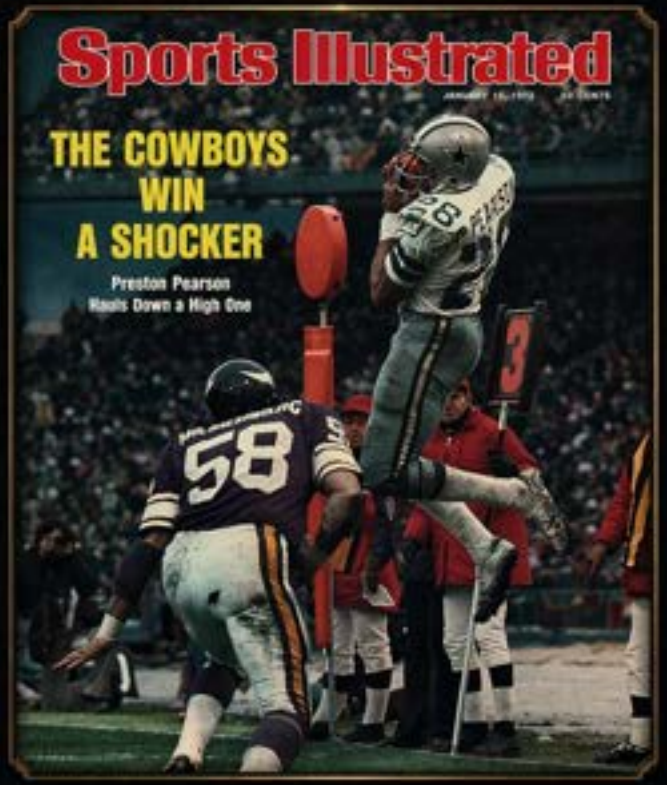
“I closed my eyes and said a Hail Mary.”



CLINICAL TRIALS:
NOT A LAST RESORT. A PLAN TO FIND THE TRUTH.

NOT A LAST RESORT

When all options are exhausted.

Uncertain. Reactive. Limited choices.

VS.

A PLAN

A deliberate path to generate evidence and improve outcomes.

SCIENCE
Build the foundation

PRECLINICAL
Generate evidence

PHASE I/II/III
Test in people systematically

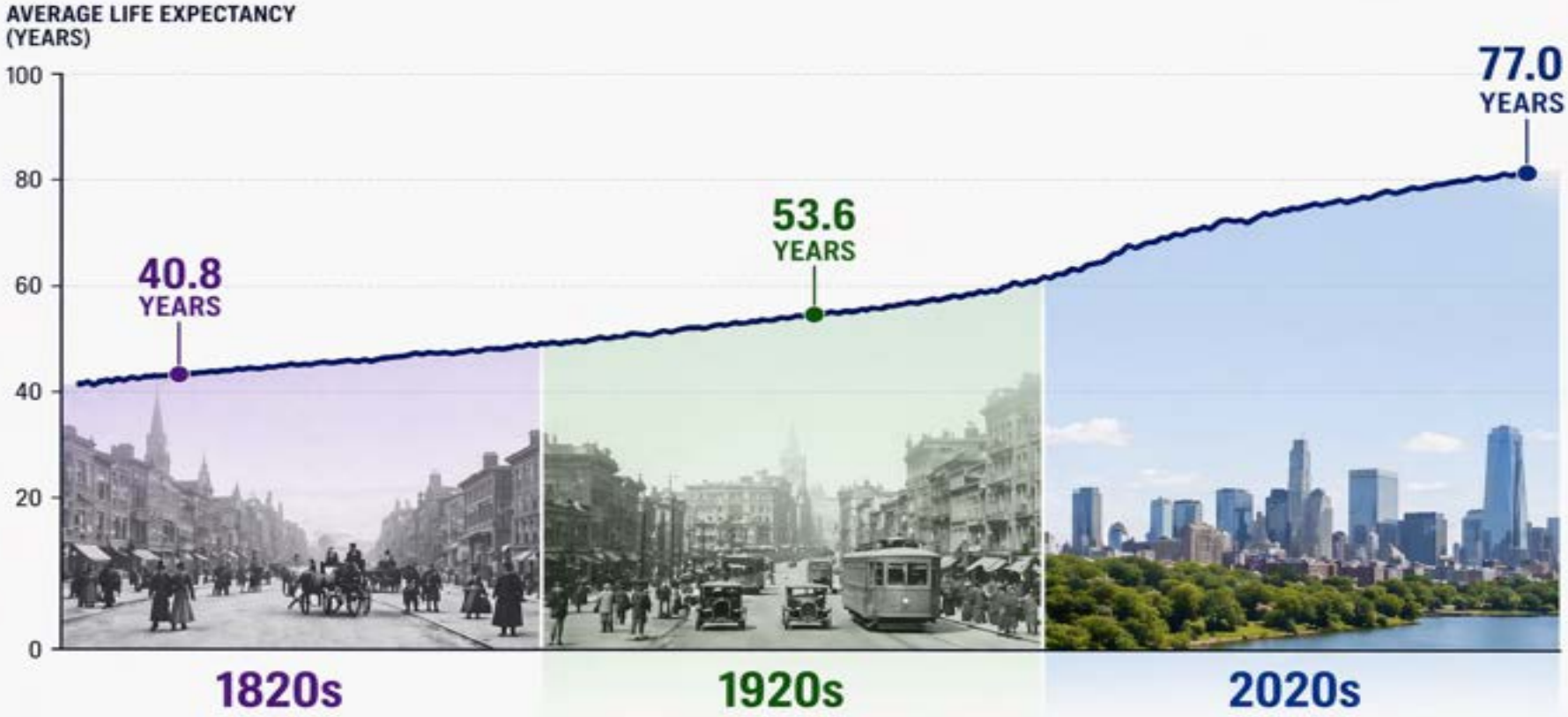
BETTER ANSWERS BETTER OUTCOMES
For patients

CLINICAL TRIALS ARE HOW WE TURN SCIENCE INTO CERTAINTY — FOR TODAY AND TOMORROW.

A PLAN TO FIND THE TRUTH.
A PROMISE TO PATIENTS.


AVERAGE LIFE EXPECTANCY
20,000
YEARS AGO
20–33 YEARS
average life expectancy
(20,000 BCE)

THE RISE IN LIFE EXPECTANCY IN THE U.S.



THE RISE IN LIFE EXPECTANCY IN THE U.S.

Science. Medicine. Innovation. Longer Lives.

1820s

- Limited medical knowledge
- High infectious disease
- Poor sanitation
- No antibiotics or vaccines

1920s

- Vaccines become widely available
- Advances in surgery and anesthesia
- Public health & sanitation improve
- Antibiotics (penicillin) introduced

2020s

- Genetic & biomedical advances
- Modern medicines & targeted therapies
- Advanced technology & diagnostics
- Better healthcare access & prevention

From ~40 years in the 1820s to ~54 years in the 1920s to ~77 years in the 2020s—science and innovation continue to add life to years.

Sources: National Center for Health Statistics, CDC | Our World in Data

THE QUALITY OF EVIDENCE: A HIERARCHY

Higher levels provide more reliable evidence and lower risk of bias.

HIGHER QUALITY
More reliable
Less bias

LOWER QUALITY
Less reliable
More bias

★ WHERE CLINICAL TRIALS STAND

Randomized Controlled Trials (RCTs) are the foundation for determining whether an intervention works and is safe.

- Minimize bias
- Allow causal inference
- Basis for guidelines and standard of care

BETTER EVIDENCE
BETTER DECISIONS
BETTER OUTCOMES

DAY TO DAY ANECDOTES LEAD TO BIAS

BIAS

a tendency or inclination, often unconscious, that influences our judgment and leads us to favor or support one thing over another, often in an unfair way.

HOW DO WE DEVELOP BIAS?

Bias isn't always intentional—it's shaped over time by our experiences, environment, and thinking habits.

1. EARLY INFLUENCES

From a young age, we absorb messages about the world.

- Family & upbringing
- Education & culture
- Media & society

2. FORMING MENTAL SHORTCUTS

To make sense of the world, our brain looks for patterns.

- We categorize
- We generalize
- We make assumptions

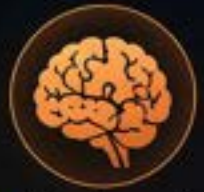
3. PERSONAL EXPERIENCES

Our experiences—especially emotional ones—leave a lasting imprint.

- Positive & negative experiences
- Memorable events
- Interactions with others

4. BIAS TAKES SHAPE

These patterns become automatic beliefs that influence how we see people and situations.



- We notice some things and ignore others
- We interpret through our lens
- We feel certain—often without full evidence

5. BIAS IN ACTION

Bias influences our choices, behavior, and decisions—often without us realizing it.

- We make quicker decisions
- We treat people differently
- We reinforce our beliefs

6. BIAS BECOMES DEEPLY ROOTED

Over time, repeated use strengthens bias.

- Harder to question
- Feels like "common sense"
- Passed down to others

WHAT KEEPS BIAS GOING? THE REINFORCEMENT LOOP

Our bias influences what we notice... → ...which confirms our existing beliefs... → ...which shapes our decisions and actions... → ...which leads to outcomes that reinforce the bias. → And the cycle continues.

AWARENESS IS THE FIRST STEP.

By understanding how bias develops, we can interrupt the cycle, challenge our assumptions, and make more fair, open-minded, and informed decisions.

WE CAN BUILD BETTER HABITS.

Stay curious. Seek diverse perspectives. Question. Reflect. Grow.

HOW BIAS AFFECTS DECISION MAKING

Bias shapes our thinking at every step—leading to better outcomes or missed opportunities.

WE'RE EXPOSED TO INFORMATION

Data, experiences, conversations, and the world around us.

1

INFORMATION COMES IN

We take in far more information than we can consciously process.

2

BIAS FILTERS OUR THINKING

Mental shortcuts and biases influence what we notice, how we interpret it, and what we ignore.

EXAMPLES OF BIAS:

- Confirmation Bias
- Availability Bias
- Status Quo Bias
- Loss Aversion

3

PERCEPTION IS SHAPED

Our biased thinking creates a filtered view of reality—not the full picture.

4

DECISIONS ARE MADE

We choose based on our perception, often without realizing what influenced us.

BETTER DECISIONS BETTER OUTCOMES

More accurate choices, better results, positive impact.

POOR DECISIONS MISSED OPPORTUNITIES OR HARM

Errors, setbacks, wasted resources, negative impact.

IMPACTS OUR THINKING BY MAKING US...

- Focus on some information
- Discount or dismiss other information
- Overestimate what we know or predict

AWARENESS IS THE FIRST STEP

Recognizing bias helps us slow down, challenge our assumptions, and make more thoughtful, evidence-based decisions.

20 BIASES CLINICAL TRIALS WERE BUILT TO DEFEAT

Biases can make ineffective treatments look effective—or hide real harms. Clinical trials use rigorous design to find the truth.

BIAS	HOW TRIALS COMBAT IT
1. **SELECTION BIAS** — Groups differ in ways that affect outcomes.	Randomization, allocation concealment
2. **CONFOUNDING BIAS** — Another factor influences the result.	Randomization, stratification, multivariable analysis
3. **PERFORMANCE BIAS** — Different care or behavior because of group assignment.	Blinding, standardized care, equal co-interventions
4. **DETECTION / ASCERTAINMENT BIAS** — Outcomes measured or assessed differently.	Blinded assessors, central review, predefined endpoints
5. **ATTRITION BIAS** — Dropouts or missing data differ between groups.	Intent-to-treat analysis, betentien strategies, sensitivity analyses
6. **REPORTING BIAS** — Only selected outcomes are reported.	Trial registration, prespecified endpoints, CONSORT reporting
7. **PUBLICATION BIAS** — Positive studies get published; negative ones don't.	Registries, mandatory reporting, transparency, meta-analyses
8. **REGRESSION TO THE MEAN** — Extreme results improve naturally over time.	Control arm, randomization, repeated measurements
9. **PLACEBO EFFECT** — Improvement occurs because patients expect it.	Placebo control, blinding
10. **OBSERVER EXPECTANCY BIAS** — Investigators unintentionally rate outcomes more favorably.	Blinding (patients, clinicians, assessors), objective endpoints

BIAS	HOW TRIALS COMBAT IT
11. **ENTHUSIASM BIAS** — Excitement about a new treatment leads to overestimation.	Rigorous controlled trials, objective data, replication
12. **AVAILABILITY BIAS** — Dramatic anecdotes overshadow the totality of evidence.	Adequately powered, comparative trials, data over anecdotes
13. **SURVIVOR BIAS** — Only "success stories" are seen; failure stories are missed.	Consecutive enrollment, complete follow-up, report all outcomes
14. **MULTIPLICITY BIAS** — Many comparisons increase chance of false positives.	Predefined primary endpoint, alpha control, hiearchical testing
15. **SMALL SAMPLE / RANDOM ERROR** — Chance findings mistaken for real effects.	Sample size calculation, adequate power
16. **IMMORTAL TIME BIAS** — Time during which outcome cannot occur is misclassified.	Proper time-zero definition, time-dependent analysis
17. **LEAD-TIME BIAS** — Earlier detection appears to prolong survival without changing outcome.	Use outcomes that matter (e.g., overall survival), appropriate controls
18. **LENGTH-TIME BIAS** — Slower-progressing cases are more likely to be detected.	Randomization, minimize screening bias
19. **CROSSOVER CONTAMINATION** — Control group receives experimental treatment later.	Delay crossover, adjust analysis, sensitivity checks
20. **ASSESSMENT TIMING BIAS** — Differences in timing of assessments influence outcomes (e.g., PFS).	Standardized assessment schedule, blinded review

HOW TRIAL DESIGN FIGHTS BIAS

RANDOMIZATION
Balances known and unknown factors between groups.

BLINDING
Prevents knowledge of treatment from influencing behavior or judgment.

CONTROL GROUP
Provides a fair comparison to separate treatment effect from natural course, placebo, and regression to the mean.

PRESPECIFIED PLAN
Defines outcomes and analyses in advance to reduce selective reporting and data dredging.

ADEQUATE SIZE & FOLLOW-UP
Reduces random error and captures true benefits and harms.

TRANSPARENCY & REPORTING
Registries, full reporting, and data sharing reduce publication and selective reporting bias.

No trial eliminates all bias, but good trials minimize, measure, and transparently report it.

THE GOAL:
DECISIONS BASED ON EVIDENCE, NOT ILLUSION.

BETTER EVIDENCE. BETTER DECISIONS. BETTER OUTCOMES.
Clinical trials are our best defense against false hope and harmful mistakes.

AVAILABILITY BIAS: IVERMECTIN IN CANCER

We overestimate the importance of information that is easy to recall or see—while ignoring the full body of evidence.

WHAT'S EASY TO FIND

Videos and posts claiming ivermectin kills cancer cells in the lab.

Anecdotes and testimonials from people who say it helped them.

Small early studies or preprints that get a lot of attention.

Sensational headlines and social media sharing.

THE BIAS:
Because these examples are easy to recall, people overestimate ivermectin's effectiveness in cancer and underestimate the lack of strong evidence.

VS.

WHAT THE EVIDENCE SHOWS

Preclinical (lab) studies

Ivermectin shows anti-cancer activity in some cell lines and animal models.
These results do not reliably predict benefit in humans.

Clinical evidence in humans

- Very limited early-phase trials
- Small sample sizes
- Heterogeneous cancers and dosing
- No consistent or meaningful clinical benefit shown

Example Clinical Trials

Cancer Type	Phase	Result
Glioblastoma	I/II	No significant benefit
Colorectal	I/II	No significant benefit
Pancreatic	I/II	No significant benefit

High-quality evidence (what matters most)

No randomized controlled trials show ivermectin improves survival, tumor response, or quality of life in any cancer.

Major cancer and medical organizations

NCCN, ASCO, ESMO, and other expert bodies do NOT recommend ivermectin for cancer treatment outside of clinical trials.

KEY TAKEAWAY:
Don't be misled by what's easiest to remember.
Look at the quality and totality of the evidence.

BOTTOM LINE:
Ivermectin is NOT an effective cancer treatment.
Rely on rigorous clinical evidence, not anecdotes or what is most available.

BEWARE OF AVAILABILITY BIAS. SEEK EVIDENCE, NOT ANECDOTES.

SURVIVOR BIAS

WE SEE THE SURVIVORS, NOT THE INVISIBLE FAILURES.

EXAMPLE 1: WORLD WAR II PLANES

During WWII, analysts looked at bullet holes on planes that returned from missions.

WHAT THEY SAW

Bullet holes on returning planes

THE WRONG CONCLUSION.

Add armor where the holes are.

THE TRUTH

Survivor bias

THE RIGHT CONCLUSION:

Add armor where there are no holes — where planes were hit and didn't return.

FOCUS ON THE MISSING DATA, NOT JUST THE SURVIVORS.

EXAMPLE 2: FENBENDAZOLE IN CANCER

Online anecdotes and small, uncontrolled reports highlight dramatic stories.

WHAT WE SEE

People who report improvement after taking fenbendazole.

THE BIASED VIEW:

"It works!"
(We see only the survivors who speak up.)

WHAT WE DON'T SEE

Many who tried it and saw no benefit or experienced harm—who stay silent.

THE FULL PICTURE:

No high-quality evidence of benefit.
Large, controlled studies are lacking.
Anecdotes ≠ evidence.

ANECDOTES ARE NOT EVIDENCE. LOOK FOR RIGOROUS, CONTROLLED STUDIES.

THE TAKEAWAY:

Survivor bias happens when we focus only on the successes we can see and ignore the unseen failures. Good decisions require the full picture.

APPLY IT:

- ☑ Question what's missing.
- ☑ Demand complete data.
- ☑ Rely on rigorous evidence, not anecdotes.

CONFIRMATION BIAS

We favor information that confirms what we already believe.

We notice and remember evidence that supports our beliefs and ignore or dismiss evidence that contradicts them.

EXAMPLE: IVERMECTIN IN CANCER

WHAT PEOPLE SEE

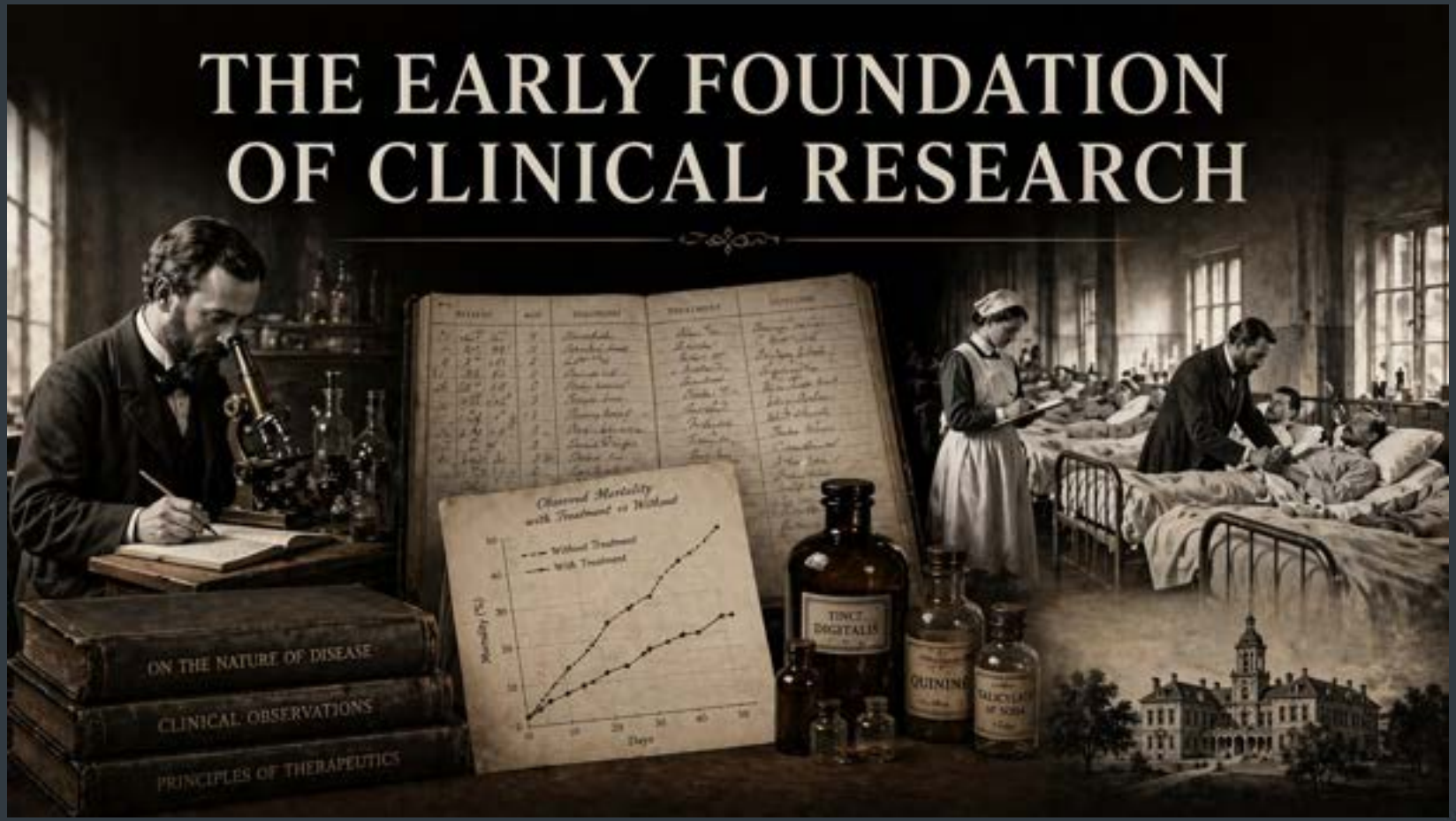
Small studies, case reports, and anecdotes suggesting benefit.

WHAT PEOPLE IGNORE

Large, high-quality trials showing no benefit or potential harm.

Confirmation bias can lead us to embrace ineffective or even harmful treatments—and delay real progress.

THE EARLY FOUNDATION OF CLINICAL RESEARCH



The earliest known treatise on clinical trial methodology

- **Ibn Sina (Avicenna)**, who wrote seven conditions for "The recognition of the strengths of the characteristics of medicines through experimentation" proposing the application of logic to drug testing.

- **Medieval Islamic scholars** contributed fundamental concepts, including the importance of experimental versus theoretical reasoning, the need for control groups, statistical approaches to interpreting results, and the distinction between human and animal trials.

James Lind's 1747 scurvy controlled trial

World's first prospective clinical trial with concurrent controls.

Aboard **HMS Salisbury**, Lind divided 12 sailors with scurvy into six groups of two, maintaining the same diet and environment for all but adding different treatments to each group: cider, sulfuric acid, vinegar, seawater, oranges and lemons, or nutmeg paste.

The **citrus group** showed dramatic improvement within six days.

JAMES LIND—CONQUEROR OF SCURVY

Surgeon to Britain's Royal Navy, James Lind in 1747 conducted clinical experiments proving citrus fruits would cure scurvy, decades later and saved. His recommendation and writings helped reform naval health practices.

THE FDA: PROTECTING THE PUBLIC FOR OVER A CENTURY

The FDA was created to protect the public from dangerous drugs, contaminated food, and fraudulent claims, with roots in 1906 and modern powers shaped in 1938.

"The object of the Pure Food and Drugs Act is to prohibit the manufacture, sale, or transportation of impure or misbranded foods, drugs, and liquors."

– Pure Food and Drugs Act, 1906

Harvey W. Wiley
Chief of the Bureau of Chemistry
A leader in the fight for pure food and safe medicines

1848
Drug Importation Act
Early law to stop the import of adulterated and misbranded drugs

1906
Pure Food and Drugs Act
Signed on June 30, 1906
The law gave the federal government the authority to regulate food and drugs and their labeling.

1927
Bureau of Chemistry Becomes Food, Drug, and Insecticide Administration (FDIA)
Expanded federal role to protect public health.

1930
Name Changed to Food and Drug Administration (FDA)
The FDA name is officially adopted.

1938
Federal Food, Drug, and Cosmetic Act
Strengthened the law after a deadly tragedy—requiring proof of safety before marketing.

THE ELIXIR SULFANILAMIDE TRAGEDY – 1937

A pharmaceutical company mixed sulfanilamide, an antibacterial drug, with diethylene glycol, a toxic industrial solvent.
More than 100 people, many of them children, died of kidney failure.


May 1, 1937 The New York Times.

DEATHS ARE CHARGED TO SULFANILAMIDE ELIXIR

Federal Inquiry Is Ordered as 15 States Report Victims Took Remedy.

THE RESULT: STRONGER PROTECTIONS

The Elixir Sulfanilamide tragedy shocked the nation and led Congress to pass the Federal Food, Drug, and Cosmetic Act in 1938.

The law required:

- Proof of safety before a drug can be sold
- Accurate labeling
- Government oversight of manufacturing

From 1906 to 1938, and continuing today, the FDA's mission remains the same:
PROTECTING THE PUBLIC HEALTH BY ENSURING THE SAFETY, EFFECTIVENESS, AND TRUTHFULNESS OF OUR NATION'S FOOD, MEDICINES, AND MEDICAL PRODUCTS.

WHAT IS NOT REGULATED BY THE FDA

These products do not require FDA approval for safety, efficacy, or quality

DIETARY SUPPLEMENTS

Vitamins, minerals, herbs, amino acids, enzymes, probiotics, etc.

PROTEIN & ENERGY PRODUCTS

Powders, shakes, pre-workout, mass gainers, performance supplements

CERTAIN TEAS & COFFFEES

Detox teas, herbal teas, specialty coffees

ESSENTIAL OILS & AROMATHERAPY

Essential oils, diffusers, roll-ons, blends

HOMEOPATHIC PRODUCTS

Remedies and dilutions

WELLNESS & LIFESTYLE PRODUCTS

Superfoods, fiber powders, cleanses, detox kits, beauty-from-within products

These products do not go through FDA premarket review.
Safety, effectiveness, and quality are not evaluated by the FDA.

One of the most important TEA test in history of statistics

Ronald Fisher [Statistician]

Tea

Milk

Fisher pours tea for Blanche, putting milk first.

'20's: Agricultural Research Station North of London and Ronald Fisher, a statistician is to have tea with botanists Blanche Bristol and William Roach

Blanche Bristol [Botanist]

William Roach [Botanist]

Ronald Fisher [Statistician]

'20's: Agricultural Research Station North of London and Ronald Fisher, a statistician is to have tea with botanists Blanche Bristol and William Roach

Blanche Bristol [Botanist]

William Roach [Botanist]

Tea

Fisher pours tea for Blanche, putting **milk first.**

Milk

But Bristol stops him, saying she prefers to pour the **tea first.**

Believing the order of pouring should make no difference,

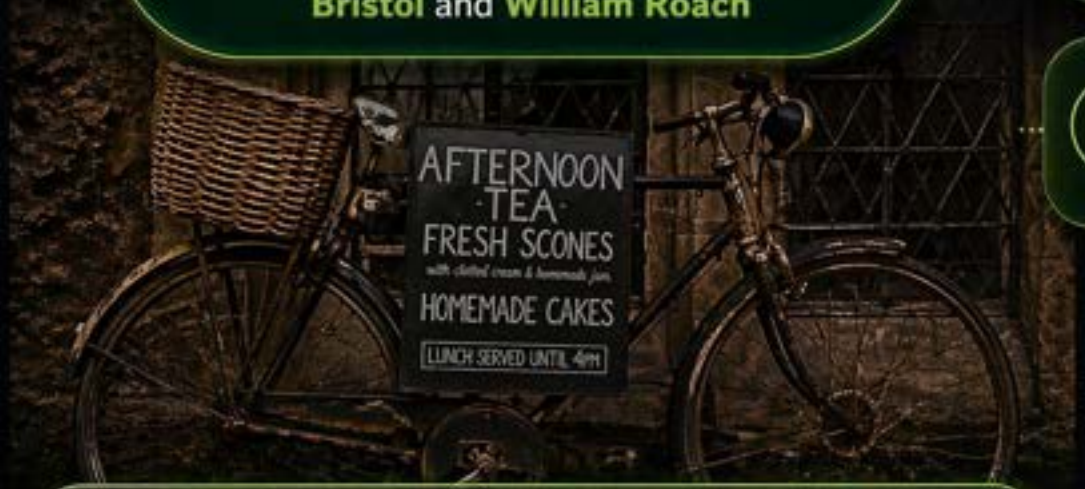
Fisher was skeptical

Ronald Fisher [Statistician]

'20's: Agricultural Research Station North of London and Ronald Fisher, a statistician is to have tea with botanists **Blanche Bristol** and **William Roach**

Blanche Bristol [Botanist]

William Roach [Botanist]



Null hypothesis was – the lady could not tell the difference between the teas and it was **just guessing**

Ronald Fisher [Statistician]

Milk

Tea

FOUR

Tea

Milk

FOUR

Milk

Tea

1:70

0.014

'20's: Agricultural Research Station North of London and Ronald Fisher, a statistician is to have tea with botanists **Blanche Bristol** and **William Roach**

Blanche Bristol [Botanist]

William Roach [Botanist]

Null hypothesis was – the lady could not tell the difference between the teas and it was **just guessing**

P<0.05

In a clinical trial of a cancer therapy, if one has a finding at the **p<0.05** level, the same or a greater magnitude of benefit is expected to be achieved at least **95 of every 100 times** the trial is repeated.

1955: THE FIRST RANDOMIZED CLINICAL TRIAL IN THE U.S.

In the United States, the first randomized clinical trial at the National Cancer Institute commenced in 1955 for acute leukemia treatment, establishing the phase I-II-III trial structure still used today.

- Pioneered by the NCI Clinical Center under Dr. E. Donnall Thomas
- Tested new therapies systematically and fairly (randomization)
- Generated reliable evidence to improve patient outcomes
- Laid the foundation for the modern clinical trial framework (Phase I–II–III)

THE PHASE I–II–III TRIAL STRUCTURE ESTABLISHED AND STILL USED TODAY

PHASE I

Safety & Dose

- 20–80 participants
- Evaluate safety, side effects
- Determine safe dose range

PHASE II

Efficacy & Side Effects

- 100–300 participants
- Evaluate effectiveness
- Further assess safety

PHASE III

Confirm & Compare

- 300–3,000+ participants
- Confirm effectiveness
- Monitor side effects
- Compare to standard treatment

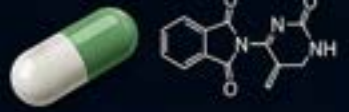
The 1955 NCI trial for acute leukemia was a landmark moment that transformed cancer care and created the gold standard for evaluating new therapies.

1955

WHY THE U.S. FDA DID NOT APPROVE THALIDOMIDE— AND HELPED PREVENT THOUSANDS OF BIRTH DEFECTS

A story of scientific skepticism, demanding evidence, and one reviewer's courage that changed drug safety forever.

WHAT WAS THALIDOMIDE?



Marketed in the late 1950s as a **"miracle"** sedative and anti-nausea drug for anxiety, insomnia and morning sickness.

THE MAIN REASON: ONE FDA REVIEWER SAID "NO"

FRANCES OLDHAM KELSEY, MD
FDA Medical Officer

In 1960–1961, she refused to approve thalidomide in the U.S. because the **safety data were inadequate.**

> "I was not satisfied that the available data established that the drug was safe for use in the American public."

WHAT HAPPENED NEXT

While approval was delayed in the U.S., thalidomide was widely used in Europe, Asia, Africa and Australia.

It was later linked to thousands of severe birth defects, especially:
phocomelia (severely shortened or absent limbs), as well as defects of the ears, eyes, heart, and internal organs, fetal loss, and infant deaths.

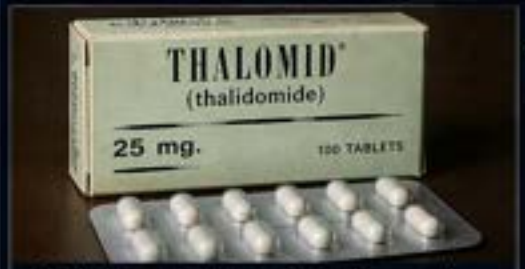
Because thalidomide never received standard U.S. approval before the danger was known, the United States had far fewer affected pregnancies than many other countries.

THALIDOMIDE-ASSOCIATED PHOCOMELIA

Thousands of children were born with devastating, preventable birth defects.

WHAT DR. KELSEY NOTICED

1. **INSUFFICIENT EVIDENCE OF SAFETY**
   The data submitted were incomplete and not rigorous enough to prove safety.
2. **CONCERN ABOUT NERVE TOXICITY**
   Reports of peripheral neuropathy in adults suggested the drug was not as harmless as advertised.
3. **SHE DEMANDED BETTER EVIDENCE**
   She repeatedly requested stronger data instead of bowing to pressure for quick approval.



Thalidomide was advertised as safe and widely promoted before its devastating effects were recognized.

A TRAGEDY THAT CHANGED DRUG REGULATION

The thalidomide disaster led to the 1962 Kefauver–Harris Amendments, transforming U.S. drug regulation.

- Proof of efficacy as well as safety
- Better informed consent in research
- Stronger adverse-event reporting
- More rigorous clinical trial standards
- Greater FDA authority to protect the public

SIMPLE TRUTH

The FDA did not "magically know" thalidomide caused birth defects beforehand. **Skeptical review, insistence on evidence, and refusal to rush approval prevented widespread U.S. exposure** before the danger was recognized.

ONE REVIEWER. MILLIONS PROTECTED.

Frances Kelsey's courage helped save countless children from preventable harm.

A LASTING LEGACY

Thalidomide's tragedy became a turning point in drug safety—protecting generations to come through stronger science, stronger laws, and a culture of questioning assumptions.

★ BIAS AND ASSUMPTIONS CAN BE DANGEROUS. **EVIDENCE AND SKEPTICISM SAVE LIVES.** ★

TWO LANDMARK MILESTONES IN RESEARCH ETHICS & PROTECTIONS

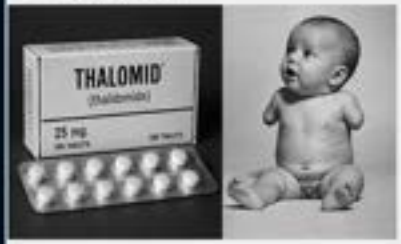
Stronger Science. Stronger Safeguards. Greater Trust.

1962 KEEFAUVER–HARRIS AMENDMENTS

Strengthening the Safety & Effectiveness of Drugs

WHY IT WAS NEEDED

The thalidomide tragedy and other drug disasters revealed the danger of weak or incomplete drug regulation.



THE IMPACT

The amendments transformed drug development and regulation—making patients safer and clinical evidence more reliable.

KEY PROVISIONS

- Proof of **EFFICACY** required
  Not just safety—drugs must be shown to work.
- Well-controlled **CLINICAL TRIALS**
  Adequate and well-controlled investigations are required.
- Informed **CONSENT** in research
  Subjects must be informed and agree to participate.
- Stronger **ADVERSE EVENT REPORTING**
  Mandated reporting of side effects and drug risks.
- More **FDA AUTHORITY**
  Inspections, record access, and enforcement powers were expanded.

RESULT: Safer medications, stronger evidence standards, and greater public protection.

THE BELMONT REPORT (1979)

Ethical Principles for Research with Human Subjects

WHY IT WAS NEEDED

History of unethical research—such as the Tuskegee Study, WWII atrocities, and other abuses—showed the need for fundamental ethical principles to protect people.

THE IMPACT

These principles became the foundation for human research protections, IRB review, federal regulations, and ethical standards worldwide.

THREE CORE PRINCIPLES

RESPECT FOR PERSONS

- Recognize autonomy and individual rights
- Informed consent
- Additional protections for vulnerable people

BENEFICENCE

- Do no harm
- Maximize possible benefits
- Minimize possible risks
- Favorable risk–benefit balance

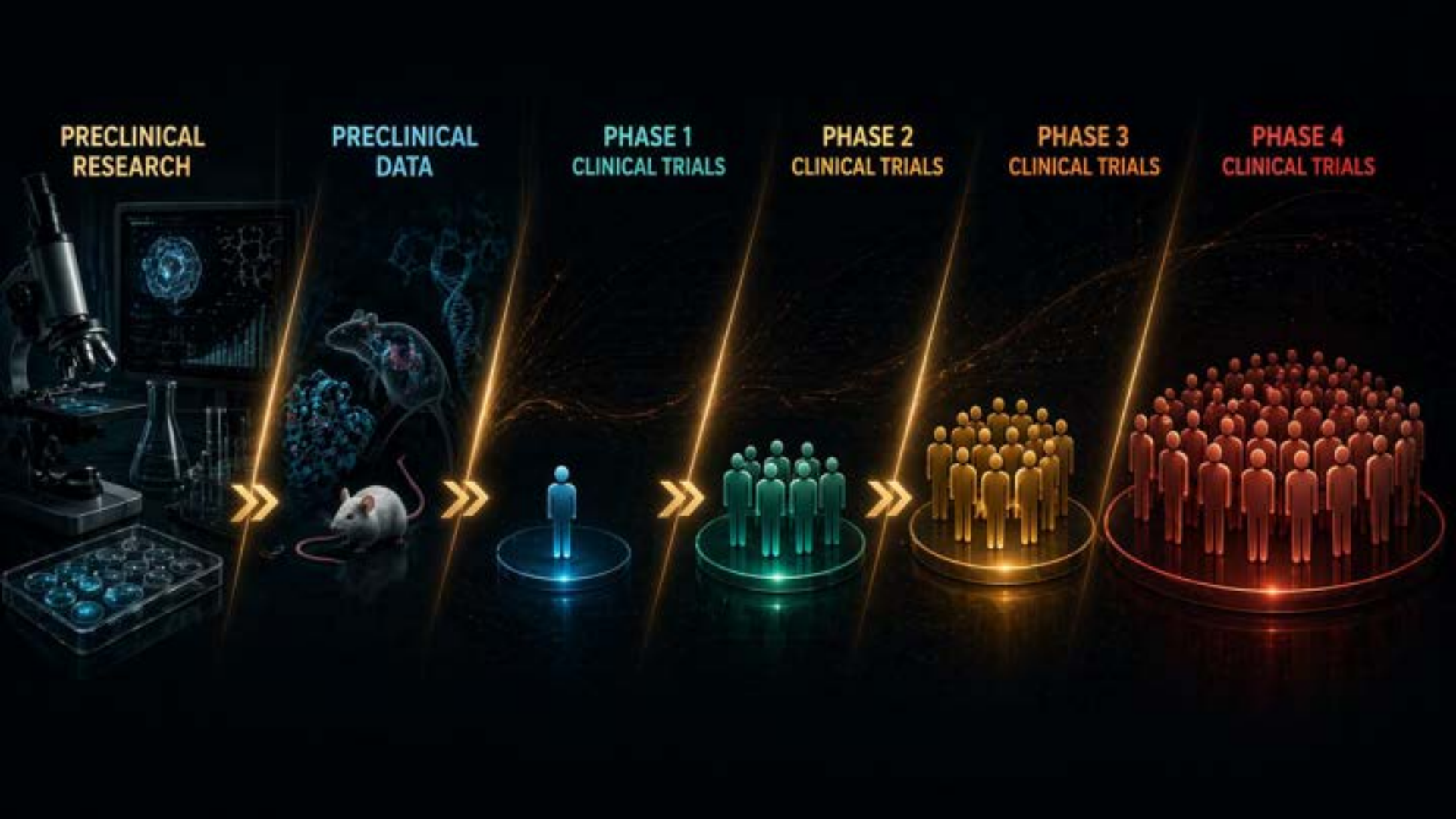
JUSTICE

- Fair and equitable selection of participants
- Avoid exploitation of vulnerable or disadvantaged groups
- Share the burdens and benefits of research fairly

RESULT: Ethical research that respects people, promotes fairness, and builds public trust.

BETTER LAWS. STRONGER ETHICS. SAFER RESEARCH. BETTER HEALTH FOR ALL.

Science advances when people are protected. Ethics strengthens every discovery.


PRECLINICAL RESEARCH
PRECLINICAL DATA
PHASE 1 CLINICAL TRIALS
PHASE 2 CLINICAL TRIALS
PHASE 3 CLINICAL TRIALS
PHASE 4 CLINICAL TRIALS

PRECLINICAL DATA: IMMUNE CHECKPOINT INHIBITORS (ICI)

GOAL:

Demonstrate that blocking immune checkpoints can restore anti-tumor immunity safely and effectively.

KEY PRECLINICAL DATA GENERATED

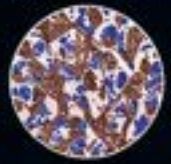
MECHANISM OF ACTION

Blocking PD-1/PD-L1 releases the brake on T cells, restoring their ability to kill tumor cells.

ANTI-TUMOR ACTIVITY (IN VIVO)

Tumor growth inhibition or regression in multiple cancer models.

BIOMARKER INSIGHTS

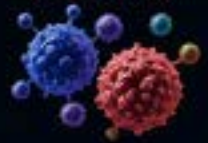


↑ PD-L1 expression
↑ T cell infiltration
Association with response.

SAFETY (TOXICOLOGY)

Favorable safety profile in rodents and non-rodents at clinically relevant doses.

COMBINATION RATIONALE (EXPLORATORY)



Enhanced anti-tumor activity when combined with other therapies in preclinical models.

ANIMALS & MODELS USED

MICE
Most commonly used for genetic models and tumor xenografts.

RATS
Used in toxicity and pharmacology studies.

DOGS
Used in safety and antibody pharmacology (as needed).

HUMANIZED MICE
Used to evaluate human immune system/tumor interactions.

KEY PRECLINICAL MILESTONES

1990s
PD-1 and PD-L1 discovered

Early 2000s
Preclinical proof of concept

Mid 2000s
Robust anti-tumor activity in models

Late 2000s
Safety, biomarkers and combination rationale

2011+
Ready for first-in-human trials

NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE 2018

James P. Allison
Discovered CTLA-4

Tasuku Honjo
Discovered PD-1

For their discovery of cancer therapy by inhibition of negative immune regulation.

PHASE I TRIAL: IMMUNE CHECKPOINT INHIBITORS (ICI)

GOAL

Evaluate safety, tolerability, identify dose-limiting toxicities (DLTs), and determine the recommended Phase II dose (RP2D).

PHASE I TRIAL DESIGN

KEY EVALUATIONS

SAFETY & TOLERABILITY

- Adverse events
- Dose-limiting toxicities

PHARMACOKINETICS (PK)

- Drug exposure
- Half-life

PHARMACODYNAMICS (PD)

- Target engagement
- Immune activation

IMMUNOGENICITY

- Anti-drug antibodies
- Neutralizing antibodies

PRELIMINARY ANTI-TUMOR ACTIVITY

- Objective response
- Duration of response

TYPICAL PHASE I TRIAL MILESTONES

ICI EXAMPLES

Anti–PD–1
Nivolumab
Pembrolizumab

Anti–PD–L1
Atezolizumab
Avelumab

Anti–CTLA–4
Ipilimumab
Tremelimumab

TYPICAL PATIENT POPULATION

- Advanced or metastatic solid tumors
- Limited standard treatment options
- Heavily pretreated patients

PHASE II TRIAL: IMMUNE CHECKPOINT INHIBITORS (ICI)

Evaluate anti-tumor activity and further assess safety to confirm efficacy signal and optimize dosing.

GOAL

Evaluate anti-tumor activity and further assess safety to confirm efficacy signal and optimize dosing.

PHASE II TRIAL DESIGN

Select patient population (specific cancer type) → ICI administered at selected dose and schedule → Assess tumor response (RECIST) and biomarkers → Continue safety monitoring → Confirm efficacy signal and refine dose/regimen

KEY EVALUATIONS

EFFICACY (PRIMARY)

- Objective Response Rate (ORR)
- Durable responses

EFFICACY (SECONDARY)

- Progression-Free Survival (PFS)
- Overall Survival (OS)

BIOMARKER ANALYSIS

- PD-L1 expression
- Tumor mutational burden
- Immune cell infiltration

SAFETY

- Adverse events
- Immune-related adverse events (irAEs)

DOSE & REGIMEN OPTIMIZATION

- Identify optimal dose
- Evaluate alternative schedules (if needed)

TYPICAL PHASE II TRIAL MILESTONES

ENROLLMENT — Enroll selected patient cohort

TREATMENT — Administer ICI and monitor patients

INTERIM ANALYSIS — Assess response rate and safety

CONFIRM SIGNAL — Confirm anti-tumor activity

DECISION POINT — Proceed to Phase III if criteria met

ICI EXAMPLES

Anti-PD-1
Nivolumab
Pembrolizumab

Anti-PD-L1
Atezolizumab
Avelumab

Anti-CTLA-4
Ipilimumab
Tremelimumab

TYPICAL PATIENT POPULATION

- Specific cancer type of interest
- Measurable disease (RECIST)
- Prior therapy allowed (as per protocol)

ULTIMATE GOAL

Demonstrate meaningful anti-tumor activity and an acceptable safety profile to justify advancement to Phase III trials.

PHASE III TRIAL: IMMUNE CHECKPOINT INHIBITORS (ICI)

Confirm efficacy and safety, compare with standard of care, and support regulatory approval.

GOAL

Confirm superior efficacy and acceptable safety of ICI vs standard of care and demonstrate clinical benefit for regulatory approval.

PHASE III TRIAL DESIGN

1. Randomize large patient population (multiple countries, multicenter)
2. ICI + standard of care vs standard of care (or comparator)
3. Evaluate primary endpoint (e.g., OS or PFS) and key secondary endpoints
4. Ongoing safety monitoring and quality assurance
5. Data analysis and regulatory submission

KEY EVALUATIONS

EFFICACY (PRIMARY)

- Overall Survival (OS) or Progression-Free Survival (PFS)
- Superiority or non-inferiority vs comparator

SECONDARY ENDPOINTS

- Objective Response Rate (ORR)
- Duration of Response (DoR)
- Disease Control Rate (DCR)
- Quality of Life (QoL)

BIOMARKER ANALYSIS

- PD-L1 expression
- Tumor mutational burden
- Other predictive biomarkers

SAFETY

- Adverse events (irAEs)
- Long-term safety
- Benefit-risk assessment

GLOBAL & REGULATORY

- Diverse patient population
- Standardized protocols
- Supports regulatory approval and global guidelines

TYPICAL PHASE III TRIAL MILESTONES

1. **TRIAL INITIATION** — Protocol finalization and site activation
2. **PATIENT ENROLLMENT** — Enroll large, diverse patient population
3. **TREATMENT & FOLLOW-UP** — Treat per protocol and collect outcome data
4. **DATA ANALYSIS** — Interim analyses and final efficacy analysis
5. **SUBMISSION** — Regulatory submission and label decision

ICI EXAMPLES

Anti-PD-1
- Nivolumab
- Pembrolizumab

Anti-PD-L1
- Atezolizumab
- Avelumab
- Durvalumab

Anti-CTLA-4
- Ipilimumab
- Tremelimumab

TYPICAL PATIENT POPULATION

- Advanced or metastatic cancer
- Selected based on disease type and biomarker status
- Prior lines of therapy allowed per protocol

ULTIMATE GOAL

Establish ICI as a new standard of care that improves survival, quality of life, and long-term outcomes for patients with cancer.

How many years does it take for ICI pathway to molecule discovery to first FDA approval?

Estimated average timelines based on publicly reported data for immune checkpoint inhibitor (ICI) therapies

KEY ICI TARGET DISCOVERIES

PD-1
Discovered in
1992

CTLA-4
Discovered in
1992

1. TARGET IDENTIFICATION & VALIDATION	2. LEAD DISCOVERY & PRECLINICAL	3. IND-ENABLING & IND SUBMISSION	4. CLINICAL DEVELOPMENT	5. NDA/BLA SUBMISSION & REVIEW	6. FDA APPROVAL
Basic research to validate ICI targets (e.g., PD-1, PD-L1, CTLA-4)	Lead identification, optimization and preclinical testing	IND-enabling studies and regulatory submission	Phase 1, 2, and 3 clinical trials	Regulatory review by FDA	First FDA approval
2 – 4 years (1992 – 1996)	**2 – 3 years** (1996 – 1999)	**1 – 2 years** (1999 – 2001)	**6 – 8 years** (2001 – 2009)	**0.5 – 2 years** (2009 – 2011)	(2011)

Total estimated time from target identification to first FDA approval

~11 – 19 years

(Average ~14 – 15 years)

EXAMPLE MILESTONE
Ipilimumab (anti–CTLA-4)
First FDA approval: March 25, 2011

- Analysis of 9 approved ICI therapies (2011–2023) showed a median of **~14.5 years** from target identification to FDA approval.
- Timelines vary based on target novelty, clinical development strategy, trial design, and regulatory pathways.

References:

1. Rask-Andersen M, Almen MS, Schiöth HB. Trends in the exploitation of novel drug targets. Nature Reviews Drug Discovery. 2011;10(8):579-590. doi:10.1038/nrd3478
2. Wang Y, et al. Development timelines and success rates of immune checkpoint inhibitors. Journal for ImmunoTherapy of Cancer. 2023;11(11):e005876. doi:10.1136/jitc-2022-005876

Note: Time ranges reflect averages from publicly disclosed data on FDA-approved ICIs including ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, cemiplimab, dostarlimab, and retifanlimab.

How many molecules fail vs get FDA approved

~10,000
molecules fail

Drug Discovery
to FDA Approval

~10
molecules get
FDA approved

Success rate:
~0.1%
(1 in ~10,000)

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1. Wouters OJ, McKee M, Luyten J. Estimated research and development investment needed to bring a new medicine to market, 2009–2018. JAMA. 2020;323(9):844–853.
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CLINICAL TRIALS

AN INTEGRAL PART OF ONCOLOGY CARE

DISCUSS
Explore all treatment options

CONSIDER
Clinical trials as a treatment option

ADVANCE
Access innovative therapies and contribute to science

CARE
Close monitoring and personalized support

IMPACT
Better outcomes for today and tomorrow

CLINICAL TRIALS ARE SAFE, ETHICAL, AND RIGOROUSLY REGULATED.
Your care. Your choice. Our future.

Advancing cancer care together.

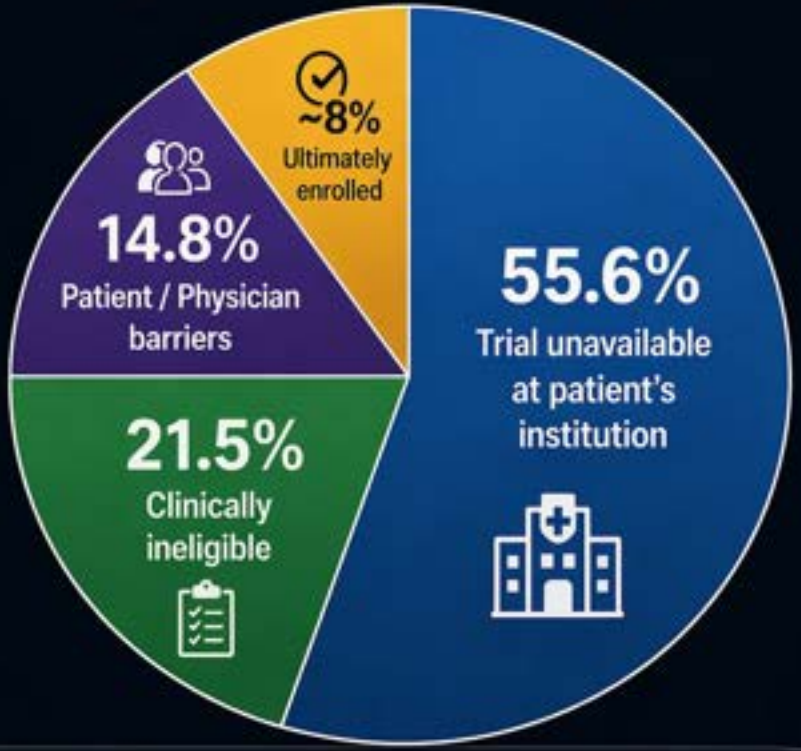
TODAY'S DECISIONS. TOMORROW'S BREAKTHROUGHS.
CLINICAL TRIALS ARE HOW WE MOVE FORWARD TOGETHER.

RIGOROUS SAFETY

SCIENTIFIC INTEGRITY

PATIENT FOCUSED

Why do patients say "NO"?

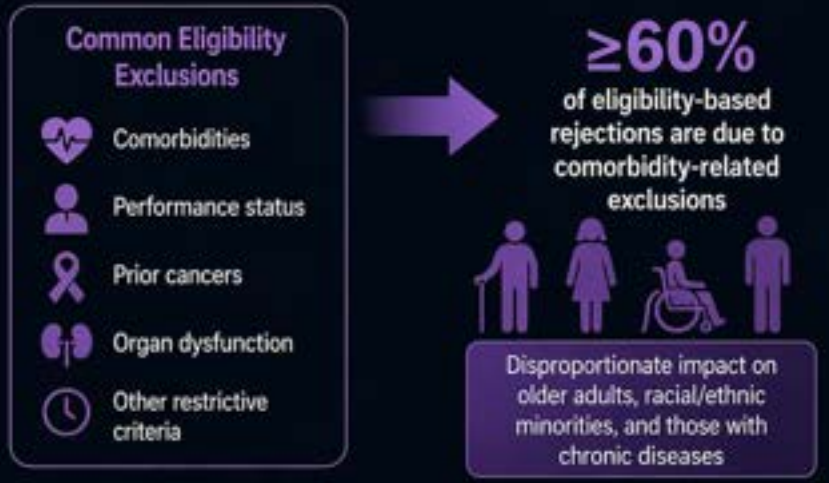


Reference: [1] Reasons for refusing oncology clinical trial participation are multifactorial, spanning structural/systemic barriers, protocol-related concerns, patient-related fears and misconceptions, and physician-related factors. A systematic review and meta-analysis found that a trial was unavailable at the patient's institution 55.6% of the time, 21.5% were clinically ineligible, and 14.8% did not enroll due to patient/physician barriers — meaning only about 8% ultimately enrolled.

Structural and Systemic Barriers

Trial unavailability at the treating institution is the single largest barrier, affecting over half of all patients. Community settings have lower enrollment rates (~7%) compared with academic centers (~16%). [1]

Restrictive eligibility criteria — comorbidities, performance status, prior cancers, and organ dysfunction disproportionately exclude older adults, racial/ethnic minorities, and patients with chronic diseases. **Comorbidity-related exclusions account for at least 60% of eligibility-based rejections.** [1,3,4]



References:

1. Systematic Review and Meta-Analysis of the Magnitude of Structural, Clinical, and Physician and Patient Barriers to Cancer Clinical Trial Participation. *Journal of the National Cancer Institute*. 2019. Unger JM, Vaidya R, Hershman DL, Minasian LM, Fleury ME.
2. Clinical Trial Enrollment, Ineligibility, and Reasons for Decline in Older vs Younger Patients With Cancer in the National Cancer Institute Community Oncology Research Program. *JAMA Network Open*. 2022. Sedrak MS, Ji J, Tiwari A, et al.
3. Association of Patient Comorbid Conditions With Cancer Clinical Trial Participation. *JAMA Oncology*. 2019. Unger JM, Hershman DL, Fleury ME, Vaidya R.
4. An Examination of Factors Associated With Disparities in Clinical Trial Eligibility Guided by the Socioecological Model. Cancer. 2025. Zhao Y, Amorrortu RP, Hicks JK, et al.

Patient-Related Reasons for Declining

THREE MAJOR THEMES IDENTIFIED BY PATIENTS WHO DECLINED

FEAR

- Fear of the unknown
- Concerns about side effects
- Skepticism about experimental drug effectiveness
- Worry about potential costs

MISTRUST

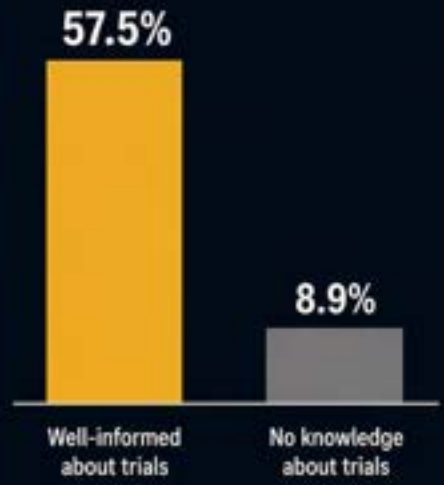
- Distrust of medical research
- Historical injustices (e.g., Tuskegee)
- Skepticism toward pharmaceutical companies

LOGISTICAL BURDENS

- Travel constraints
- Time commitment
- Financial concerns
- Existing health challenges

MOST FREQUENTLY CITED PATIENT-LEVEL REASONS FOR DECLINING (QUANTITATIVE DATA ACROSS MULTIPLE STUDIES)

INSUFFICIENT UNDERSTANDING OF CLINICAL TRIALS IS A MAJOR CONTRIBUTOR



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- Clinical Trial Discussion and Participation in a Breast Cancer Cohort by Race and Ethnicity. *JAMA Network Open*. 2025.
- Barriers to Participation in Clinical Trials of Cancer: A Meta-Analysis and Systematic Review of Patient-Reported Factors. *The Lancet. Oncology*. 2006.
- "Why I Said No": Trial-Eligible Patient Perspectives on Declining Breast Cancer Clinical Trial Participation. *JCO Oncology Practice*. 2025.
- Breaking through barriers: Unraveling challenges in clinical trial participation among oncologic patients in a developing country. JCO. 2024.
- Assessing Patient Perspectives on Enrollment in Lymphoma Clinical Trials. *Cancer*. 2026.
- Oncologic Patients' Misconceptions May Impede Enrollment Into Clinical Trials: A Cross-Sectional Study. *BMC Med Res Methodol*. 2022.
- Use of a Clinical Trial Screening Tool to Enhance Patient Accrual.

PHYSICIAN-RELATED BARRIERS

Physician attitudes toward a trial and failure to discuss trials with patients are significant barriers.

2%

of eligible patients were not offered participation because the physician declined to offer it. (Screening tool study)

Strained doctor-patient relationships and communication issues were noted as barriers in

95%

of respondents.

71.5%

of patients stated they would join a trial if their own oncologist were the investigator.

88%

reported their physician's advice would most influence their decision.

Patients were more likely to participate if the physician/ team member was of similar race/ ethnicity.

REFERENCES

Barriers to Participation in Clinical Trials of Cancer: A Meta-Analysis and Systematic Review of Patient-Reported Factors. *The Lancet. Oncology*. 2006.
Mills EJ, Seely D, Rachlis B, et al.

Breaking through barriers: Unraveling challenges in clinical trial participation among oncologic patients in a developing country. *JCO*. 2024.
Bushatsky E, Cândido A, Quispe D, et al.

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Oncologic Patients' Misconceptions May Impede Enrollment Into Clinical Trials: A Cross-Sectional Study. *BMC Med Res Methodol*. 2022.
Asher N, Raphael A, Wolf I, et al.

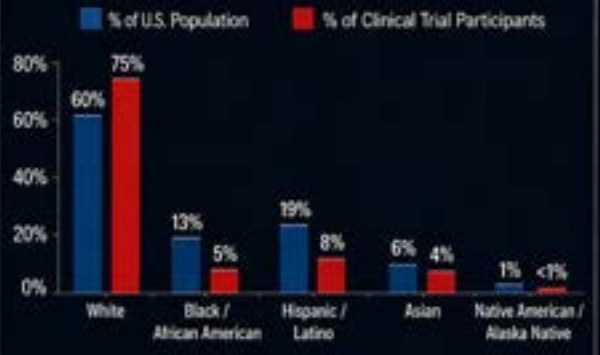
Use of a Clinical Trial Screening Tool to Enhance Patient Accrual. *Cancer*. 2021.
St Germain DC, McCaskill-Stevens W.

DISPARITY IN CLINICAL TRIAL ENROLLMENT IN THE UNITED STATES

Participation is unequal across race, ethnicity, and geography.

DISPARITY BY RACE & ETHNICITY

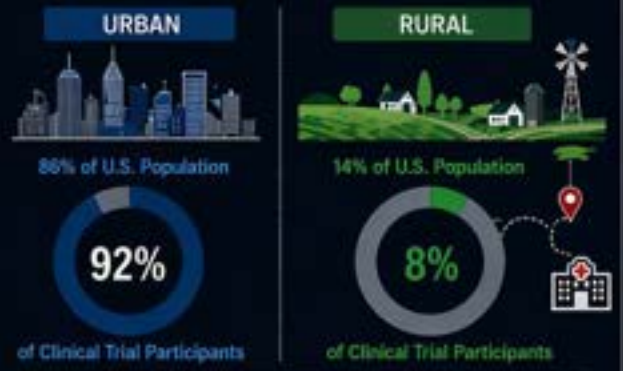
Percent of U.S. Population vs. Percent of Clinical Trial Participants



Racial and ethnic minorities are consistently underrepresented in clinical trials across therapeutic areas.

DISPARITY BY GEOGRAPHY: URBAN VS. RURAL

Percent of U.S. Population vs. Percent of Clinical Trial Participants



People living in rural areas are significantly underrepresented in clinical trials.

BARRIERS TO RURAL PARTICIPATION

- **LONG TRAVEL DISTANCE** — Greater distance to trial sites and specialty centers
- **FEWER TRIAL SITES** — Limited availability of clinical trial sites in rural areas
- **TRANSPORTATION BURDEN** — Limited public transportation and high travel costs
- **SPECIALIST SHORTAGE** — Fewer specialists and research providers
- **FINANCIAL & TIME BURDEN** — Time off work, lodging, and out-of-pocket costs
- **DIGITAL ACCESS BARRIERS** — Limited broadband access for telehealth and digital trial participation

Underrepresentation limits generalizability of results and may impact safety and effectiveness for all patients.

Missed opportunities for innovation and advances that benefit diverse populations.

Health disparities persist when trial access is unequal.

TRIAL ACCESS IS NOT ONLY UNEQUAL BY RACE AND ETHNICITY—IT IS ALSO UNEQUAL BY GEOGRAPHY.

EQUITY IN TRIAL ACCESS MEANS RACE, ETHNICITY, AND GEOGRAPHY MUST ALL BE ADDRESSED.

REFERENCES

1. U.S. Food & Drug Administration (FDA). Enhancing the Diversity of Clinical Trial Populations — Eligibility Criteria, Enrollment Practices, and Trial Designs Guidance for Industry. April 2020. https://www.fda.gov/media/142498/download
2. Tufts Center for the Study of Drug Development. 2023 Tufts CSDD Clinical Trials Landscape. https://csdd.tufts.edu
3. National Academies of Sciences, Engineering, and Medicine. Improving Representation in Clinical Trials and Research: Building Research Equity for Women and Underrepresented Groups. The National Academies Press; 2022.
4. National Library of Medicine. Assessing Clinical Trial Diversity. 2022. https://www.nlm.nih.gov/research/umls/assessing-clinical-trial-diversity.html

GET INVOLVED
AT UNMC
COMMUNITY OUTREACH AND ENGAGEMENT

Cancer patients, cancer survivors, caregivers, and community organization representatives can contribute their insights to help shape and support ongoing cancer research.

FLEXIBLE PARTICIPATION FOR COMMUNITY MEMBERS

- Community members can decide how much time they would like to commit.
- The amount of involvement can vary depending on the research or project.
- Clinical Trial Community Scientists receive training in research ethics and responsible conduct.
- They are compensated for their participation in select research projects.

QUESTIONS OR WANT TO LEARN MORE?

For any questions or to learn more about how to get involved, please contact Melissa Baron, Clinical Integration Coordinator at the Fred & Pamela Buffett Cancer Center Office of Community Outreach and Engagement.

402.559.5639
mbaron@unmc.edu

CLINICAL TRIAL COMMUNITY SCIENTIST PROGRAM

A powerful way community members can get involved and help shape cancer research at every stage.

- **Give feedback** and share insights on research protocols and study design.
- **Provide feedback** on recruitment strategies and materials for clinical trials to ensure they are clear, culturally appropriate, and easy to understand.
- **Offer letters** of support and other advocacy for research studies.
- **Receive training** in research ethics and responsible conduct.
- **Be compensated** for your time and expertise on select research projects.

YOUR VOICE. OUR RESEARCH. BETTER OUTCOMES TOGETHER.

OTHER WAYS TO GET INVOLVED

Some groups have historically had fewer opportunities to take part in clinical trials. Women and people from racial and ethnic minority communities are underrepresented, but this is changing as researchers and community members work together.

By addressing barriers such as cost, transportation, and access to information, and by building trust through strong communication, communities can play a key role in shaping clinical trials.

- Serve as advocates for cancer care and increase representation in clinical trials.
- Educate communities on clinical trials to help them make informed decisions.
- Join outreach events that share information about clinical trials.
- Join the Fred & Pamela Buffett Cancer Center Clinical Trial Community Scientist program.

UNMC
BREAKTHROUGHS FOR LIFE

CLINICAL TRIALS ARE NOT A HAIL MARY—THEY'RE A PLAN

A HAIL MARY HOPES FOR A MIRACLE. A CLINICAL TRIAL SEEKS RELIABLE ANSWERS.

A HAIL MARY

High risk. High uncertainty. No plan.

- ✗ Low chance of success
- ✗ Unpredictable outcome
- ✗ No data to guide the decision
- ✗ High risk of harm
- ✗ If it works, you can't be sure why
- ✗ One-off attempt

VS.

A CLINICAL TRIAL

Planned. Systematic. Designed to learn and protect.

- ✓ Built on prior research and evidence
- ✓ Carefully designed and monitored
- ✓ Controls and comparisons reduce bias
- ✓ Risks are measured and managed
- ✓ Results are interpretable and trustworthy
- ✓ Knowledge gained helps future patients

The goal is not just to try a treatment—it's to find out if it truly works, for whom, and at what cost.

HOW CLINICAL TRIALS TURN UNCERTAINTY INTO EVIDENCE

1. PRECLINICAL RESEARCH

Laboratory and animal studies identify potential benefits and possible risks.

2. PHASE 1 SAFETY FIRST

Small group of people. Focus on safety, dose, and side effects.

3. PHASE 2 LOOKS PROMISING?

Larger group. Looks at effectiveness and continues safety assessment.

4. PHASE 3 CONFIRM AND COMPARE

Large, diverse groups. Compares to standard treatment or placebo to confirm benefit and monitor risks.

5. REVIEW & APPROVAL

Regulators review all evidence to decide if benefits outweigh risks for approved use.

6. POST-MARKET MONITORING

Ongoing surveillance ensures long-term safety and real-world effectiveness.

WHY THIS MATTERS

PROTECTS PATIENTS
Risks are identified early and monitored closely.

REDUCES FALSE HOPE
Separates real benefit from wishful thinking or placebo effect.

INFORMS DECISIONS
Doctors and patients can choose treatments based on solid evidence.

BUILDS TRUST
Transparent results—good or bad—help science move forward.

THE BOTTOM LINE

A HAIL MARY HOPES FOR THE BEST.
A CLINICAL TRIAL WORKS TO FIND OUT WHAT'S TRUE.

Clinical trials are not about giving up hope—they're about replacing uncertainty with evidence so we can deliver therapies that are safe, effective, and truly improve lives.

SCIENCE DOESN'T RELY ON MIRACLES. IT RELIES ON METHOD.

Better evidence. Better decisions. Better outcomes.

PATIENT RESOURCES

PATIENT RESOURCES

THANK YOU

CLINICAL TRIALS—
NOT JUST A HAIL MARY

EVIDENCE. NOT LUCK. BETTER DECISIONS. BETTER OUTCOMES.

American Cancer Society (ACS) information on Clinical trials

PRE ACT Interactive videos

RIGOROUS DESIGN — Minimizes bias

RANDOMIZATION — Balances the unknowns

CONTROLS & COMPARISON — Reveal what truly works

DATA & ANALYSIS — Turn information into insight

BETTER DECISIONS — For patients. For the future.

UNMC BREAKTHROUGHS FOR LIFE

Harshraj Leuva, MD

hleuva@unmc.edu

CANCER CLINICAL TRIAL PATIENT RESOURCES

Cancer.Net

American Cancer Society information on Clinical trials

Pre-Act

Interactive videos which has been validated to Improve understanding of clinical trials and Willingness to participate.

ClinicalTrials.gov

Any clinical trial that is open needs to be registered here but can be a bit complex to find a trial for a patient.

MyTrialist

Trial matching help and little more simpler way to look for clinical trials.

Scan QR codes