Clinical trials at a glance

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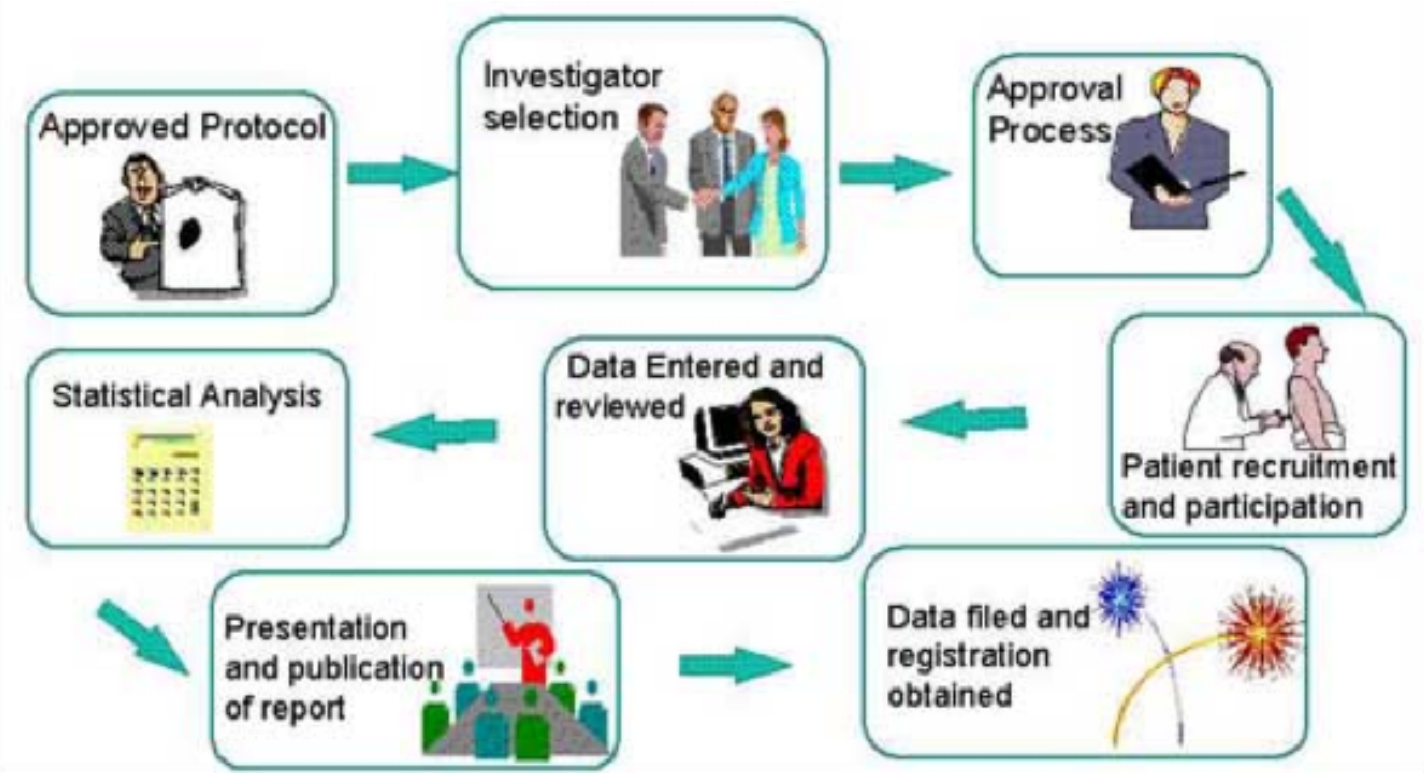
What is a Clinical Trial?

- A study to evaluate
  - Effectiveness of an intervention
  - Safety of new drugs
  - Dose defining
  - Drug formulation
  - Combination therapies
  - Effects on QoL

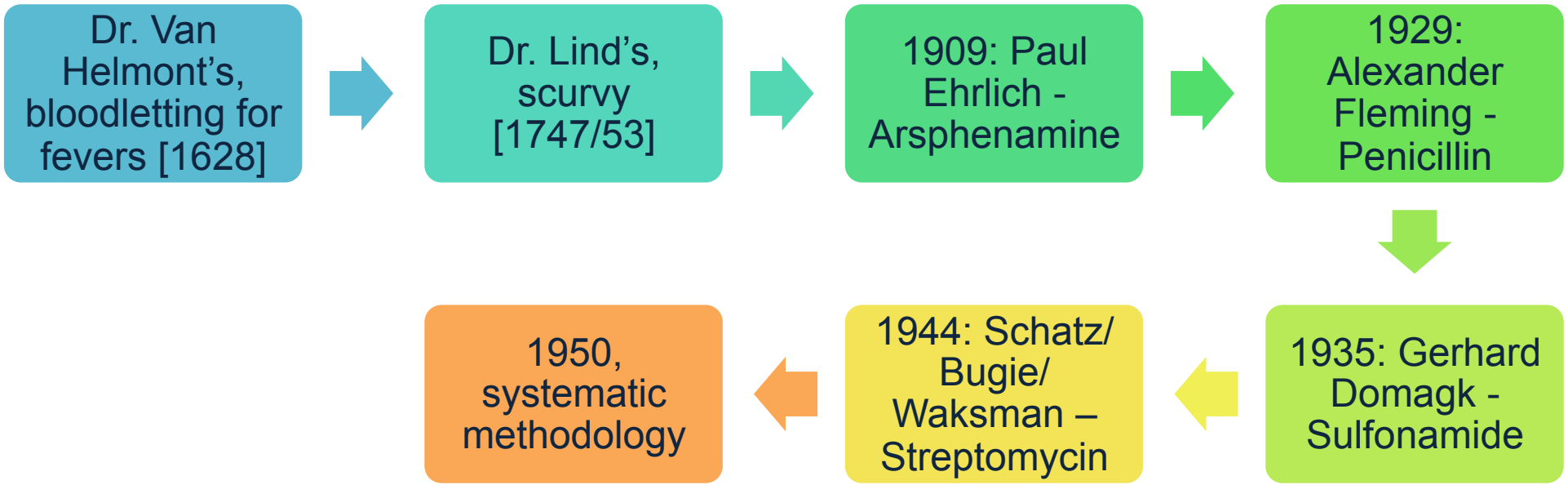
Clinical Trials in a Nut Shell



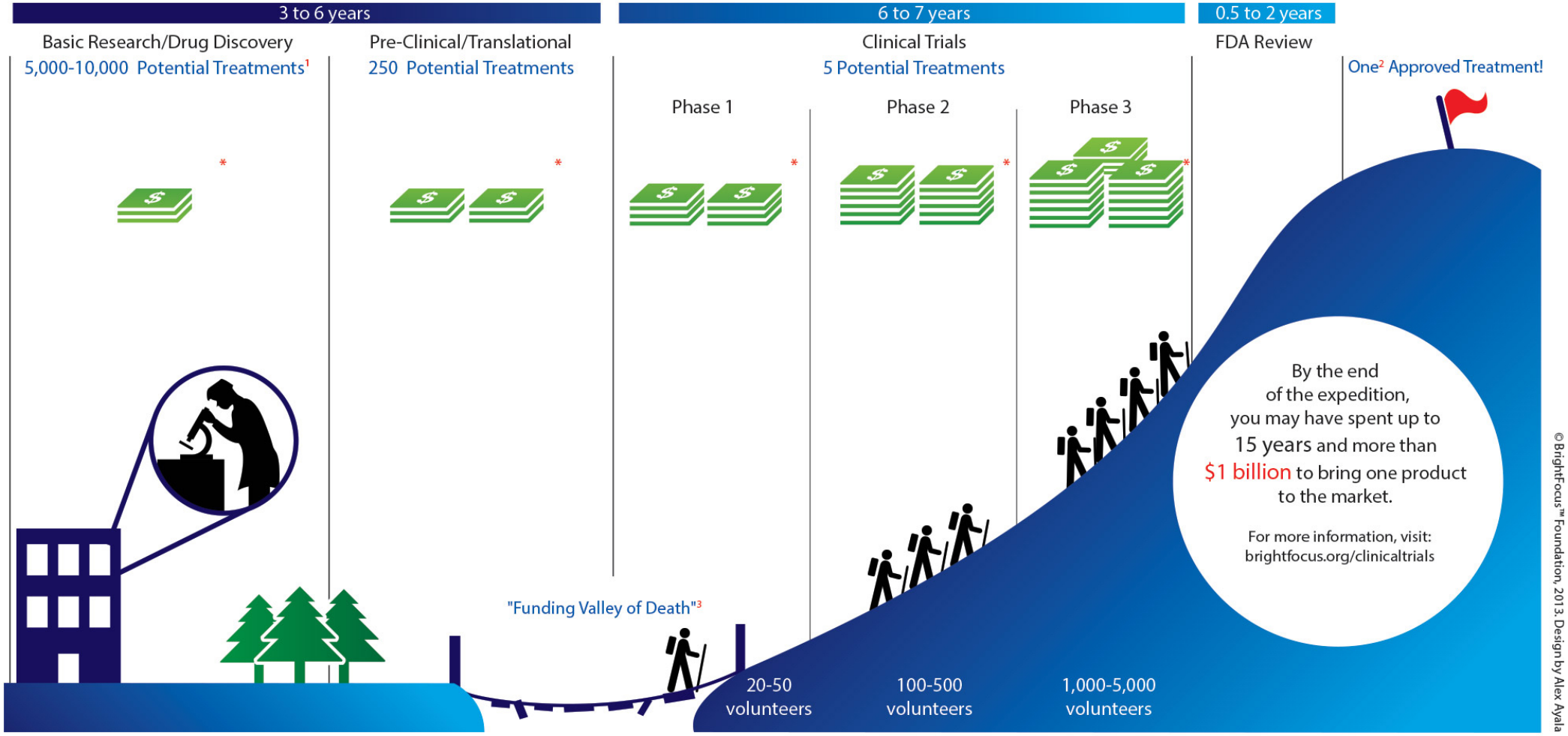
History

- Perhaps the first ever clinical trial was James Lind's demonstration in 1753 that citrus fruits cured scurvy.
- He compared the effects of various different acidic substances ranging from vinegar to cider, on groups of sailors
- Group who were given oranges and lemons recovered from scurvy after 6 days.

Historical highlights



How does a clinical trial start?



Basic concepts

- The protocol. Establishes the question – ideally has just one and this is the **primary end point**. Common failing is too many end points. The best designed trials keep it simple as this make a clear answer more likely and easier to acheive

- Secondary objectives; a few related, appropriate secondary questions are normal as long as they do not distract from the primary. Some might be exploratory.

- Trial is then designed around these. The protocol sets out how the question will be answered

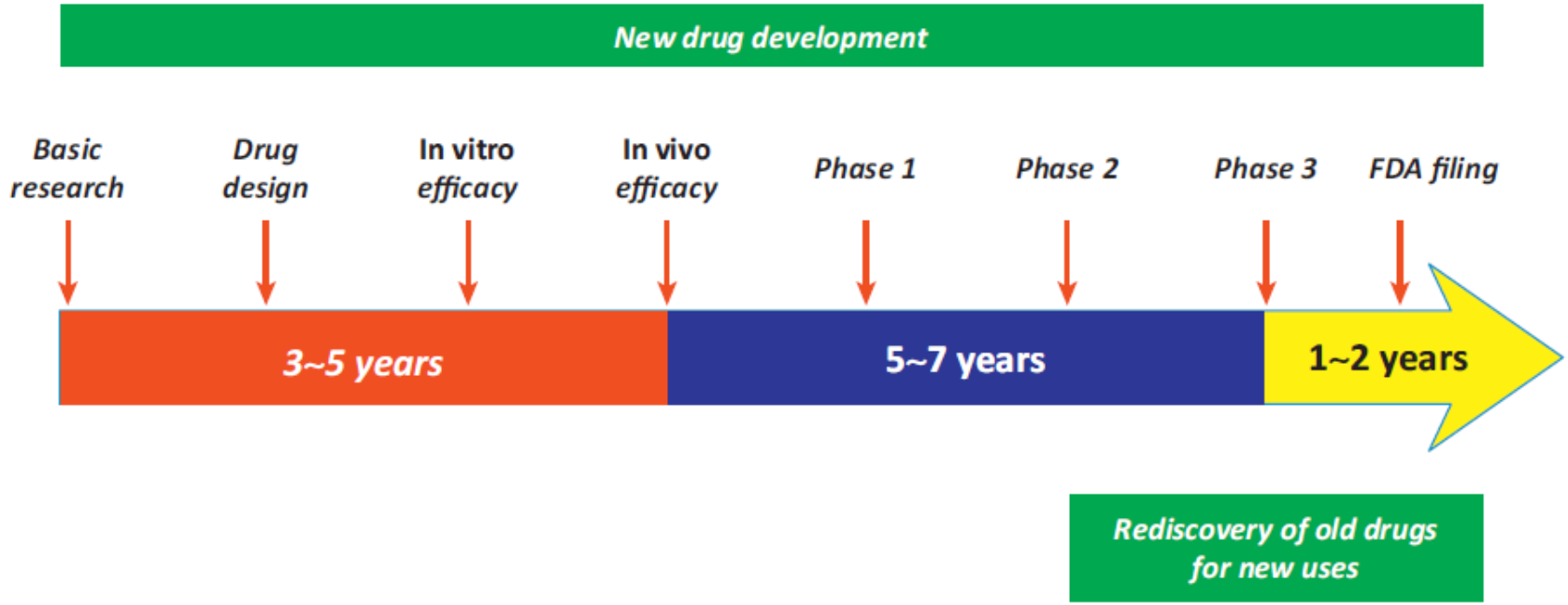
Protocol’s title

- Single centre, placebo controlled etc etc
- Who is conducting the trial, who is sponsoring it, where is it to be conducted and on whom will you be conducting the research
- What are you testing? Is it safe, have the tests been validated? Why is this research needed.
- What are the risks, what are the procedures, how will data be collected. How did you calculate how many patients you will need.

Research Protocol: Roadmap

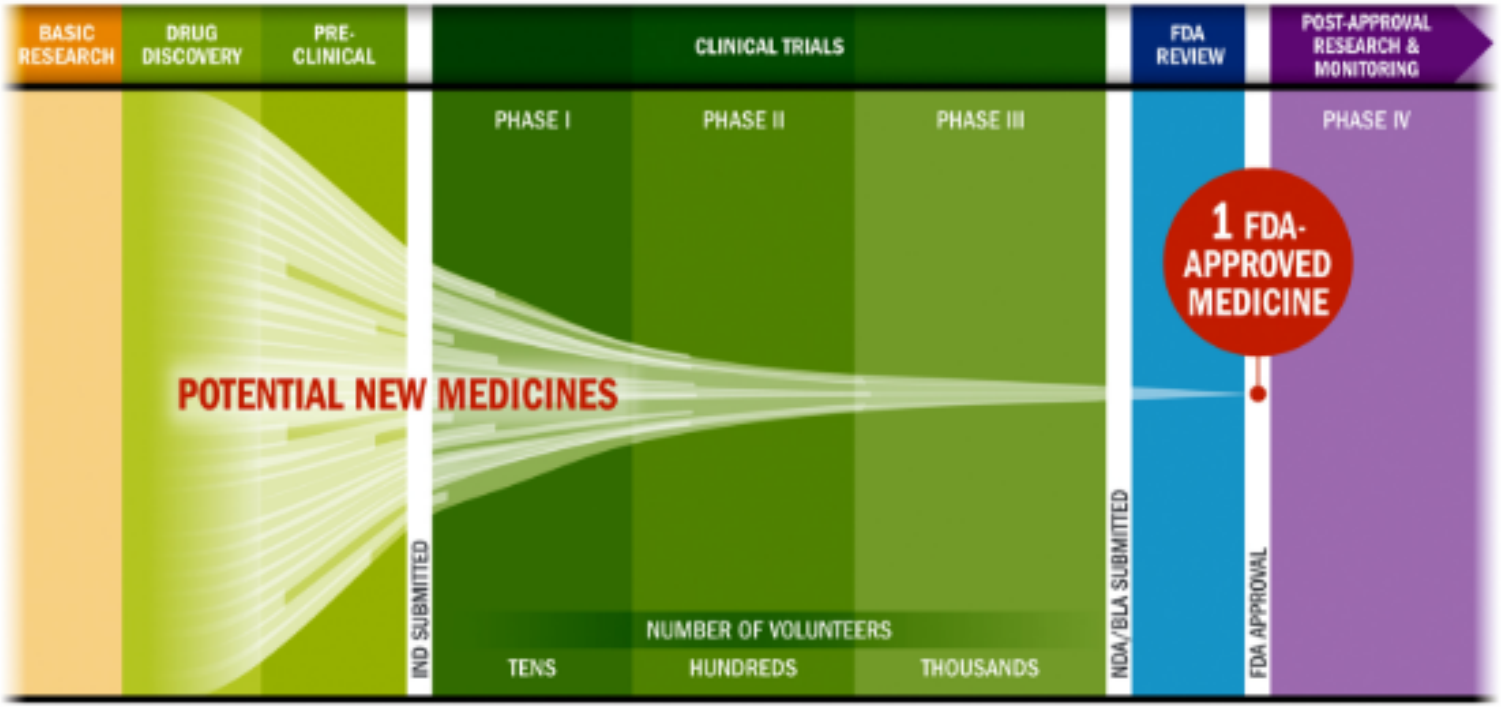
- Detailed Research Plan that Includes:
  - Objectives
  - Background and Rationale
  - Subject Selection Criteria
  - Treatment Plan
  - Study Procedures
  - Response Evaluation Criteria
  - Statistical Section

New Drug Development



Gupta S. Trends in Pharm Sci. 2013

Bringing a drug to market



- 5 in 5000 enter human testing; 1 in 5 approved
- 1/500
- 14 years
- Expensive
  - 2 billion
- Failure rate >95%

Clinical Trials

- Several shortcomings
  - Large sample size
  - Long study duration
  - Lack of power to evaluate efficacy
    - Overall or in important subgroups
  - Cost.

"Human clinical trials start in six months. Sooner if we run out of mice."

Bhatt D. N Engl J Med 2016;375:65-74.

Different aimes of Clinical Trials

Treatment

- Test new approaches

Prevention

- Approaches to prevent it

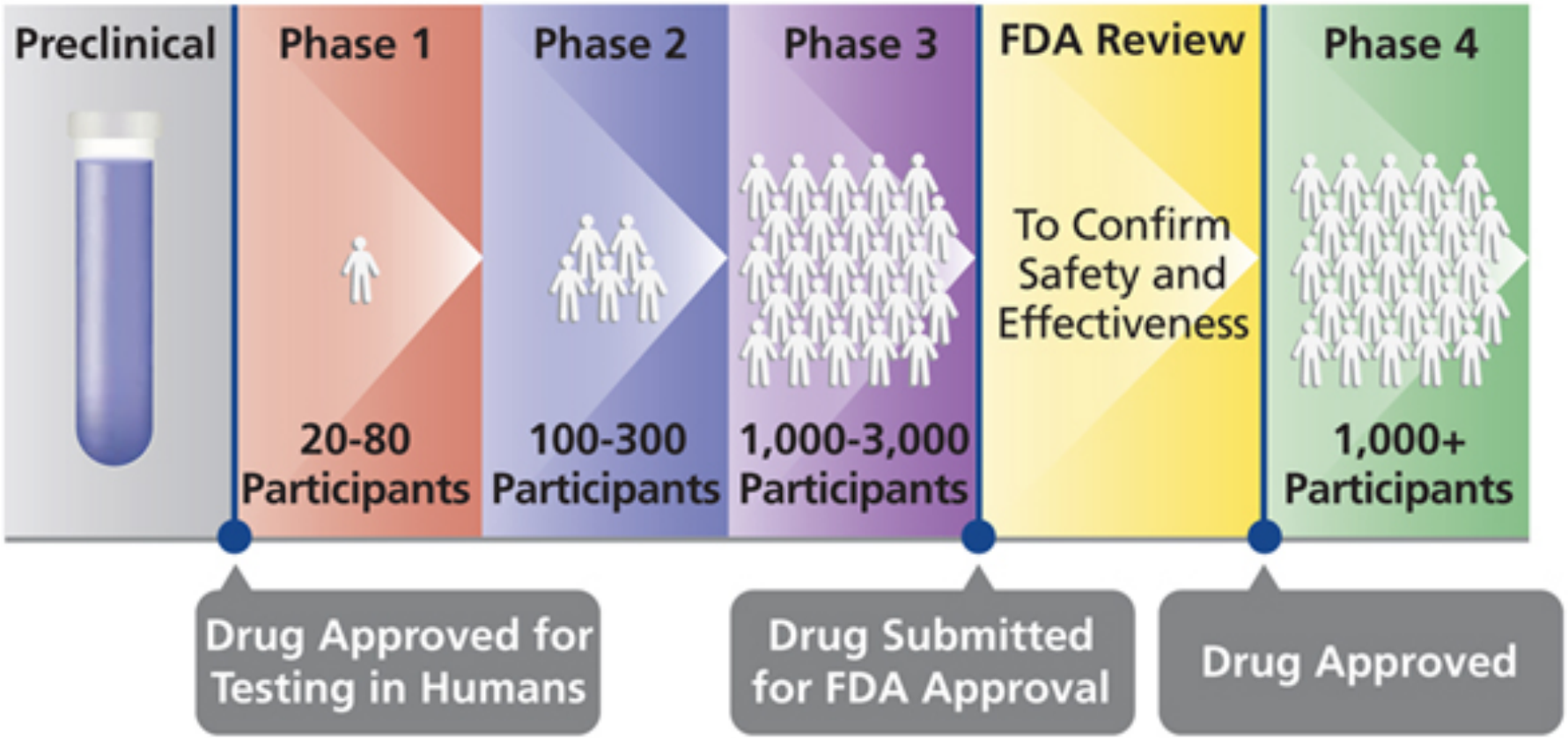
Early detection/screening

- Find new strategies

Diagnostic

- Identification

Phases of Drug Development



What is *Randomization?*

- **Researchers assign patients by chance to either a group taking the new diagnostic or treatment agent. Similar to “flipping a coin”.**

- **Randomization helps avoid bias.**

- **The assigned groups are often referred to as “arms”.**

Example: Patient #1 is assigned to Arm A of the trial, which involves the new modality or treatment. Patient #2 is assigned to Arm B, which is the standard modality or treatment.

What is a Blinded Study?

- In a single blinded study, the patient does not know which arm of the protocol they have been assigned to.

- This approach avoids bias because when people know what they are taking, it might change the way they react.

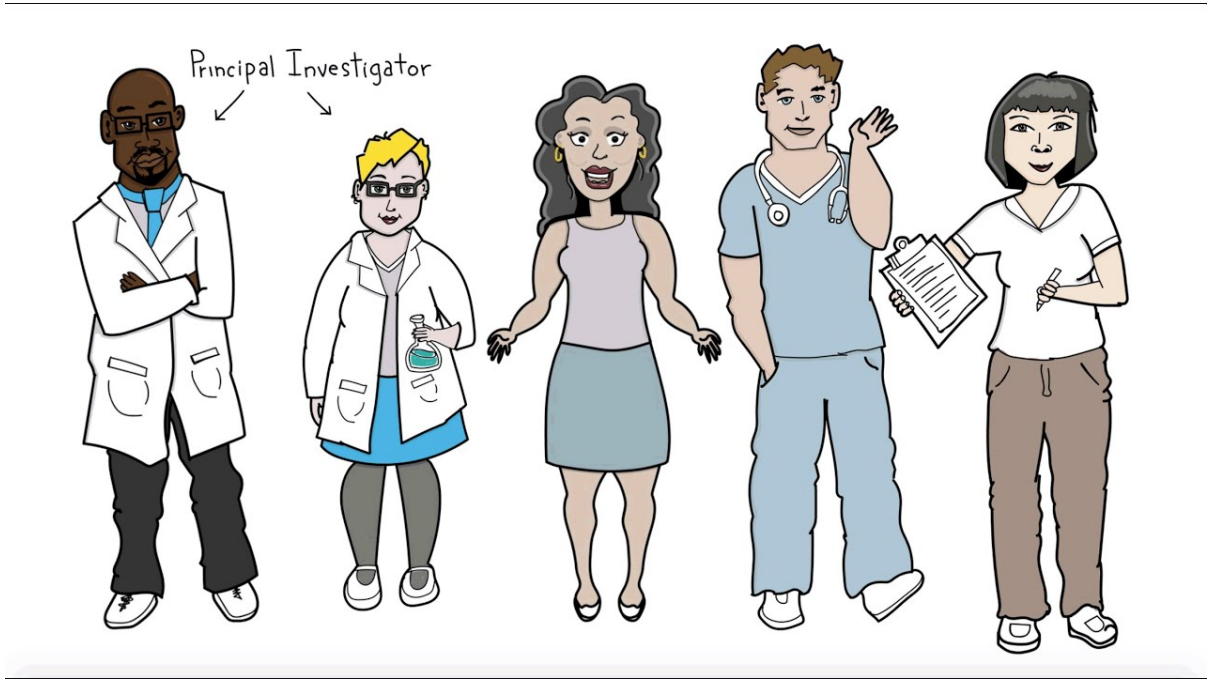
Example: Patients who know that they are assigned to the "new treatment" group might expect it to work better and report hopeful signs because they want to believe they are getting well. This could bias the study by making results look better than they are.

Blinded Trials *cont…*

- **Double blinded studies are those studies where neither the patient or the research physician know whether the patient is receiving the actual study drug or standard drug.**
- **When no standard is available, some studies compare new drugs with placebo drugs.**
- **All patients are informed of the possibility of being assigned to the placebo arm of a study**
- **Patients are "unblinded" only if it becomes medically necessary prior to the end of the study.**

Fig. 3 **A double-blind placebo-controlled clinical trial for CAM therapies.**

Team members



Human Research is Highly Regulated

- Code of Federal Regulations (CFR)
  - Title 21- Food and Drugs
    - Part 50 Informed Consent
    - Part 56 IRB
    - Part 312 IND
    - Part 314 NDA
    - Part 600, 6001 Biologics
    - Part 812, 813, 814 Medical Devices
  - Title 45- Public Welfare
    - Part 46 (subparts B, C, D) DHHS, Protection of Human subjects

What About International Regulation?

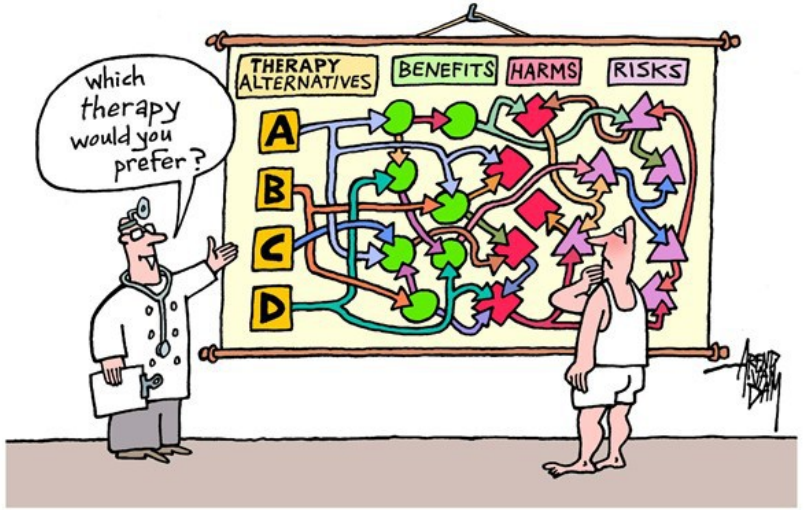
- E6 Good Clinical Practice (GCP): Consolidated Guidance
  - International ethical and scientific quality standard for designing, conducting, recording and reporting trial results.

Why is Human Research Highly Regulated?

- Past transgressions lead to the need for laws that protect the rights and welfare of human subjects.
  - Nuremberg Doctors Trial of 1946 (Nuremberg Code)
  - Thalidomide Tragedy (Kefauver-Harris Amendment)
  - Tuskegee Experiments (Belmont Report)
  - Human Radiation Experiments
  - Gene Transfer Experiment

Informed Consent

- Learning the key facts about a trial before deciding whether to participate.
  - Research study purpose
  - Risks/Benefits
  - Alternative treatments
  - Confidentiality of records
  - Medical treatment available if injury occurs
  - Whom to contact for answers to questions
  - Statement that participation is voluntary



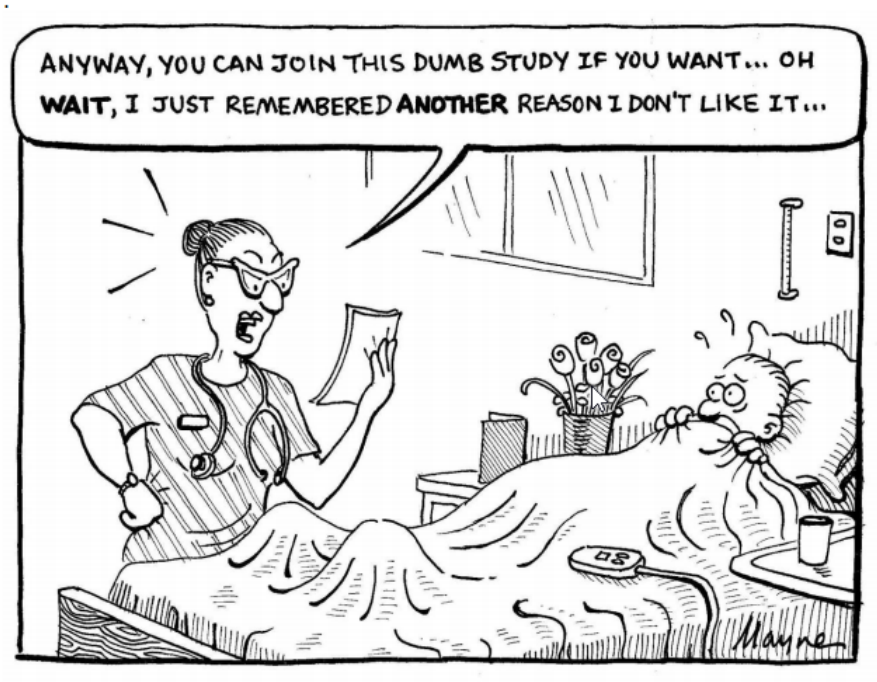
informed consent

Institutional Review Board (IRB)

- All clinical trials must be approved and monitored by an IRB.
- IRB is an independent committee of physicians, nurses, statisticians, community advocates and others.
- The function of the IRB is to ensure that a clinical trial is ethical and the rights welfare of study participants are protected.

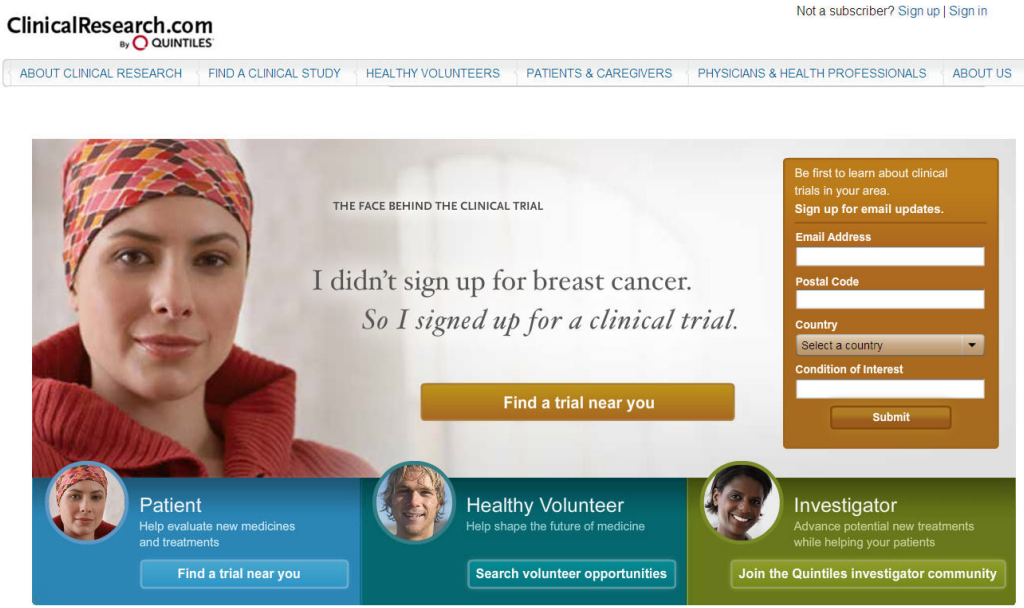
Patient Recruitment Challenge

- Poor patient recruitment is the number one reason that trials fail.
- Only 3 to 5 percent of newly diagnosed adult cancer patients participate in a clinical trial.
- Reasons for this relatively low number are many.



Recruitment Strategies

- Physician trust and contact
- Study staff contact
- Speaking to community groups
- Newspaper and radio Ads
- Internet websites
- Physician referrals



Subject Data Collection

- Data is collected on case report forms (CRF)
- Much of clinical data is taken from the subjects medical record (source documents)
- Pharmaceutical and device trials, data is verified by multiple players

Serious Adverse Events

- Events that results in any of the following:
  - Death or life-threatening
  - Hospitalization or prolonged hospitalization
  - Persistent or significant disability/incapacity
  - Congenital anomaly/birth defect
- Events that are serious, unexpected, and related or possibly related to participation in the research must be reported to the Sponsor, FDA and IRB in a timely manner.

The transformation is pretty bad, but the worst part is filling out the paperwork for the adverse events.

Clinical Trial Result

- Ideal:
  - Unambiguous conclusion regarding the clinical outcome of the test treatment/device.

- Always strive for the ideal, but in most cases have to settle for the best comprise.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Any questions?