Study Design

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Disclaimer

The views expressed in this talk are my own. They do not represent the position or policy of the NIH, DHHS, or US government

Overview

- Good study design is key to conduct of an ethical study.

Overview

- “Researchers have a fundamental obligation to plan, design, and conduct studies with honesty, truthfulness and integrity – values demonstrated by how researchers observe, record and interpret their work.” (Research Design, p.6)

Source: Presidential Commission for the Study of Bioethical Issues (2015)

Ethical Requirements

- Collaborative Partnerships
- Social or scientific value
- Scientific validity
- Fair subject selection
- Favorable risk-benefit ratio
- Independent review
- Informed consent
- Respect for participants

Source: Emanuel, Wendler and Grady (2008)

Study Design

- Basics
  - Observational Research
    - Descriptive
      - Retrospective or prospective
  - Experimental Research
    - Interventional
      - Usually prospective

Source: Presidential Commission for the Study of Bioethical Issues (2015)

Study Design

- Basics
  - Experimental Design
    - Manipulation
      - Changing at least one variable
    - Control
      - Prevent outside factors from influencing study outcome
    - Randomization
      - Random, unbiased selection and assignment of the research sample

Source: Presidential Commission for the Study of Bioethical Issues (2015)

Study Design

- Basics
  - Quasi Experimental Design
    - Manipulation
      - Changing at least one variable
    - Control
      - Prevent outside factors from influencing study outcome
    - ~~Randomization~~
      - ~~Random, unbiased selection and assignment of the research sample~~

Source: Presidential Commission for the Study of Bioethical Issues (2015)

Study Design

- Social Value
  - Does the Project have social value?
    - If **no**, study cannot go forward

Source: Emanuel, Wendler and Grady (2008)

Study Design

- Scientific Validity
  - Is the study design valid?
    - Sample size
      - Too small?
      - Too large?

Source: Presidential Commission for the Study of Bioethical Issues (2015)

Study Design

- Scientific Validity
  - Is the study design valid?
    - Is there *uncertainty* about potential benefit of the proposed intervention?
      - If **no**, study **cannot** go forward as designed
      - If **yes**, is randomized controlled trial (RCT) appropriate design
        - » Is randomization to a placebo acceptable?

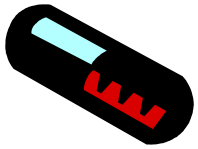
Source: Emanuel, Wendler and Grady (2008)

Study Design: RCT

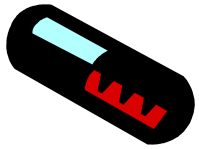
- Randomized Controlled Trial
  - Indifference among community of clinicians about which treatment superior
    - "Equipoise"
  - Controlled
    - Blinding
  - Randomized
    - Placebo or active control
      - Standard of Care

Placebo

- What is it?
  - Pill that looks just like the drug but doesn't contain any medicine.



Drug



Placebo

- Why is it included in study?
  - Want to find out if the real medicine works like they hope it does. Need to compare people who get the real medicine to those don't to see if the medicine works.

Placebo

- When is it ethically acceptable to include a placebo?
  - When no good standard treatment exists
  - If a standard treatment exists, then
    - When placebos are "additive"
      - Standard plus placebo vs. Standard plus new intervention
    - When the medical condition in question is not serious
    - When being off of standard medication for length of trial will not cause serious, irreversible harm

Placebo

- When is placebo ethically important? Why not just have ‘no intervention’ arm?
  - When outcome can be subjective (pain, emotion, endurance)
  - When risk behaviors may be affected by thinking one received experimental tx vs. nothing (e.g., HIV vaccines)
  - When follow up for data collection could be affected (need to keep getting pills so return)

WHO Guidance (2024)

https://iris.who.int/bitstream/handle/10665/378782/9789240097711-eng.pdf

Key scientific and ethical considerations for clinical trials

Reliably informative, ethical and efficient clinical trials need to address the following five key points which capture the necessary qualities of a well-planned, well-run and clinically relevant trial.

They should:

- be designed to produce scientifically-sound answers to relevant questions
- respect the rights and well-being of participants
- be collaborative and transparent
- be designed to be feasible for their context
- manage trial quality effectively and efficiently.

The methods and approaches needed to apply these qualities will differ in small or large ways from trial to trial, but their validity is universal.

WHO (2024)

Ethical Principles: Study Design

- Independent review
  - Peer review
- Design executed as described in approved protocol
  - Oversight
- Study findings must be reported completely and promptly
  - During trial
  - After trial

Source: Joffe and Troug (2008)

Types of Trials

- Clinical Trials
  - Phase 1
  - Phase 2
  - Phase 3
  - Phase 4

100

Phase 1

70

Phase 2

23

Phase 3

6-7

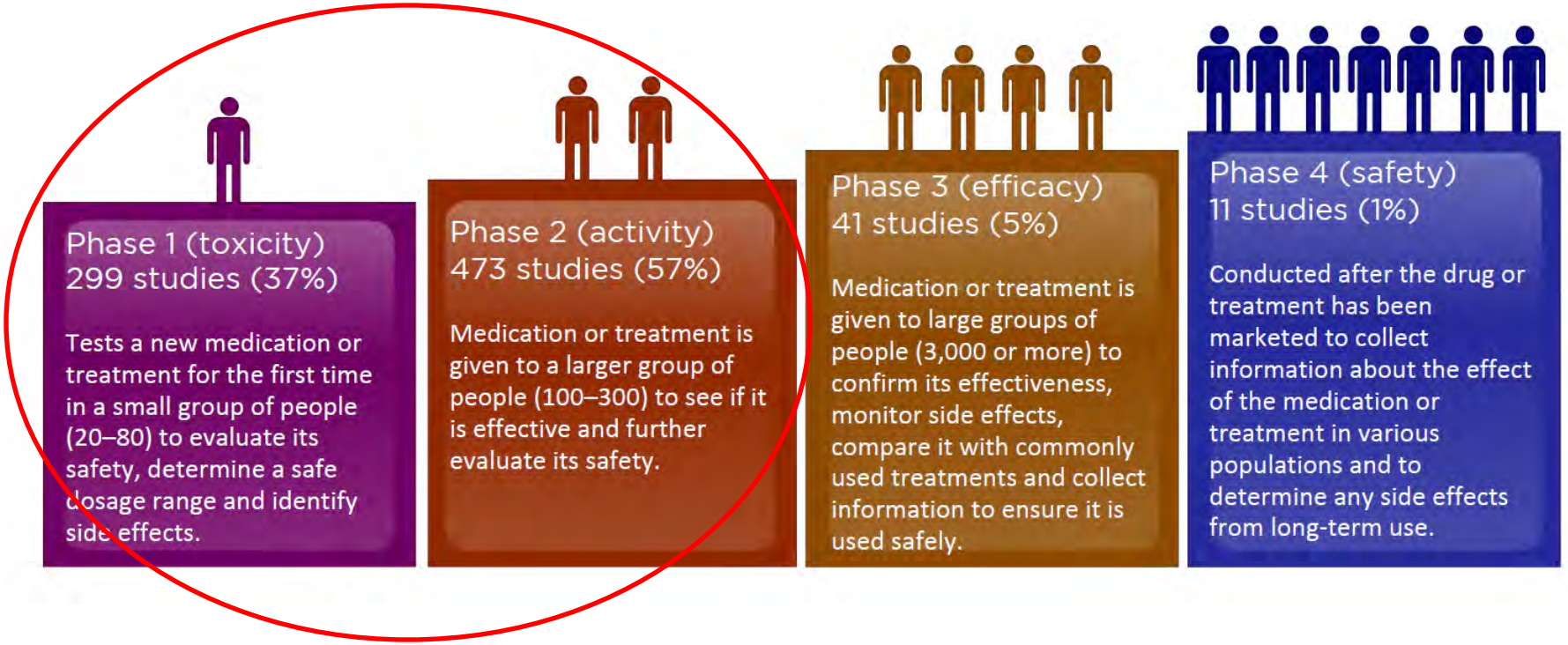
Phase 4/Market

For every 100 Phase I Trials testing novel interventions, 6-7 make it To FDA approval for marketing.

Source: FDA (2022)

2023	
Phase I	304 (38%)
Phase II	453 (56%
Phase III	41 (5%)
Phase IV	10 (1%)
Total	808 (100%)

95% of trials conducted at the NIH Clinical Center early phase trials.



Source: NIH Clinical Center Data Report (2021;2023)

Types of Trials: Clinical

- Clinical Trials
  - Phase 1 (n=20-80)
    - First in human trial
    - Safety
    - Dosage
      - Maximum Tolerated Dose (MTD)

Source: Friedman, Furberg and DeMets (1998)

Types of Trials: Clinical

- Clinical Trials
  - Phase 2 (n=20-300)
    - First dose, one lower than MTD
    - Assess biologic effect
    - Adverse events

Source: Friedman, Furberg and DeMets (1998)

Types of Trials: Clinical

- Clinical Trials
  - Phase 3 (n=300-3000+)
    - Based on results of Phase II
    - Effectiveness
    - Safety
    - Risk/benefit for adoption in clinical practice

Source: Friedman, Furberg and DeMets (1998)

Types of Trials: Clinical

- Clinical Trials
  - Phase 4
    - Post marketing trial
    - Long term safety
      - Celebrex
      - Avandia

Source: Friedman, Furberg and DeMets (1998)

Oversight: DMC

- Oversight
  - Data Monitoring Committees (DMCs)
    - Protect subjects from previously unknown adverse events
    - Avoid unnecessarily prolonged exposure to an inferior treatment
      - Interim analysis
      - Stopping rules

Summary

- Good study design is key to conduct of an ethical study.