STUDY DESIGNS

IN BIOMEDICAL RESEARCH

STUDY DESIGNS ON MACRO SCALE

Let start with a simple example with a very basic feature of most modern-day designs:

A Simple Example:

An experiment on the effect of Vitamin C on the prevention of colds could be simply conducted as follows. A number of n children (the sample size) are randomized; half were each give a 1,000-mg tablet of Vitamin C daily during the test period and form the "experimental group". The remaining half , who made up the "control group" received "placebo" – an identical tablet containing no Vitamin C – also on a daily basis. At the end, the "Number of colds per child" could be chosen as the outcome/response variable, and the means of the two groups are compared.

Randomization is a newer practice (1923) and has become the most basic feature of most modern-day designs; it helps to balance the characteristics we know as well as the characteristics we do not know or do not know how to quantify.

Gross Classification of Research

Research Designs could take different shapes and forms depending on 2 factors:

(1) Timing: past, present, or future;

(2) Focus of Research Question: Disease or Exposure

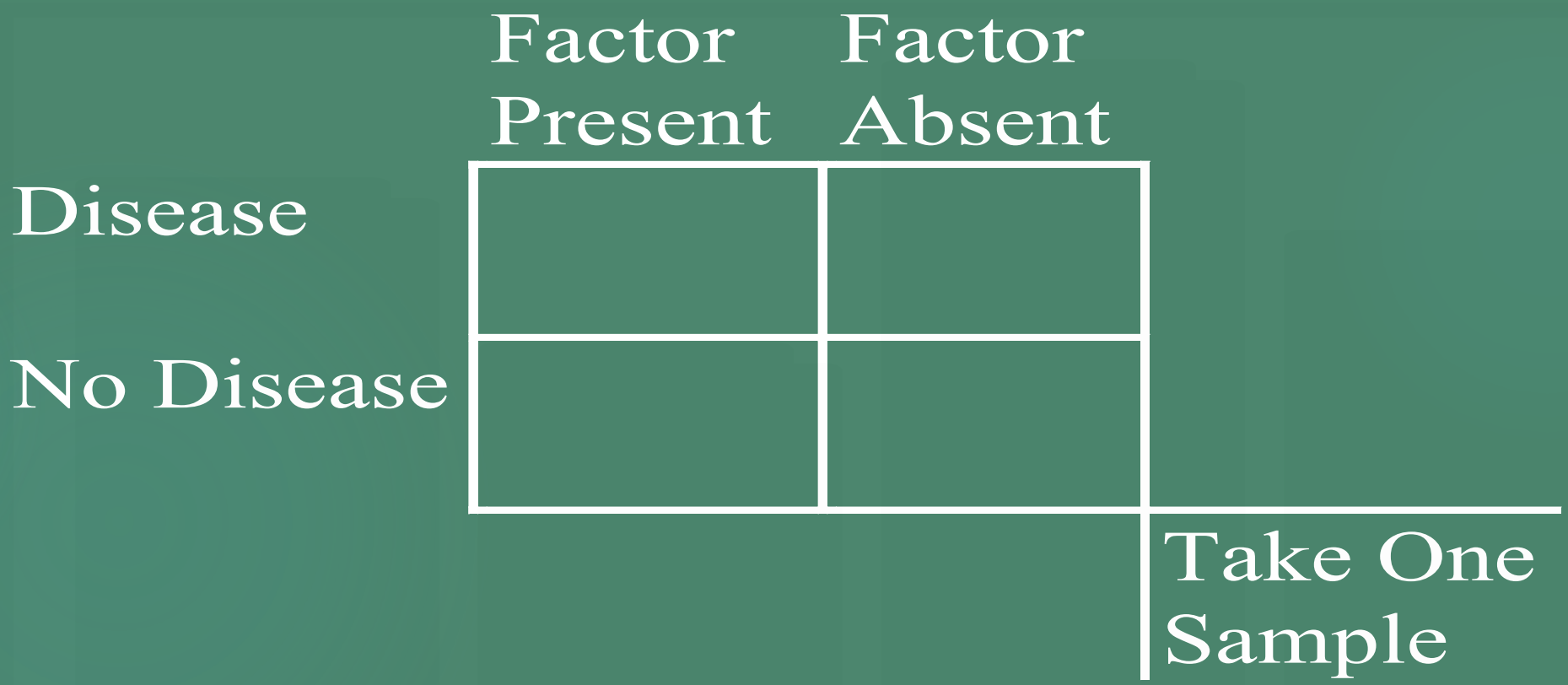
The combination of these two factors divides research designs into three categories:

CATEGORIES OF STUDY DESIGNS

How data will be collected? It's the complex issue of when to do what (combining the "timing" and the "focus"):

- Cross-section Design,
- Case-Control Design (retrospective),
- Cohort Design (prospective); Clinical Trials (one-arm, two-arm; open-label or randomized; double or triple blind)

Cross-Sectional Design



The cross-sectional designs are very popular in social/behavioral studies, e.g. teen surveys. As for health research data, since diseases are rare, there are very few cross-sectional designs conducted; fundamental designs are case-control and cohort.

Case-Control Design

	Factor Present	Factor Absent	
Disease			Sample 1: Cases
No Disease			Sample 2: Controls

These are "retrospective"; obtaining past data from cases and from controls (people without the disease). The research focus is the disease.

Retrospective Studies gather past data from selected cases (with disease) and controls (without disease) to determine differences, if any, in exposure to a suspected risk factor.

Advantages: Economical & Quick.

Major Limitations: Accuracy of exposure histories & Appropriateness of controls.

Cohort Design

These are "prospective"; obtaining future data (event/death) from "research arms" (Treatment and Placebo). The research focus is the exposure/treatment.

Prospective studies enroll two groups of subjects, say Treatment and Placebo in Clinical Trial; subjects are followed over time to obtain result (say, new SBP or occurrence of an event).

There are one-group prospective cohorts

TYPICAL CLINICAL TRIAL

Study Initiation

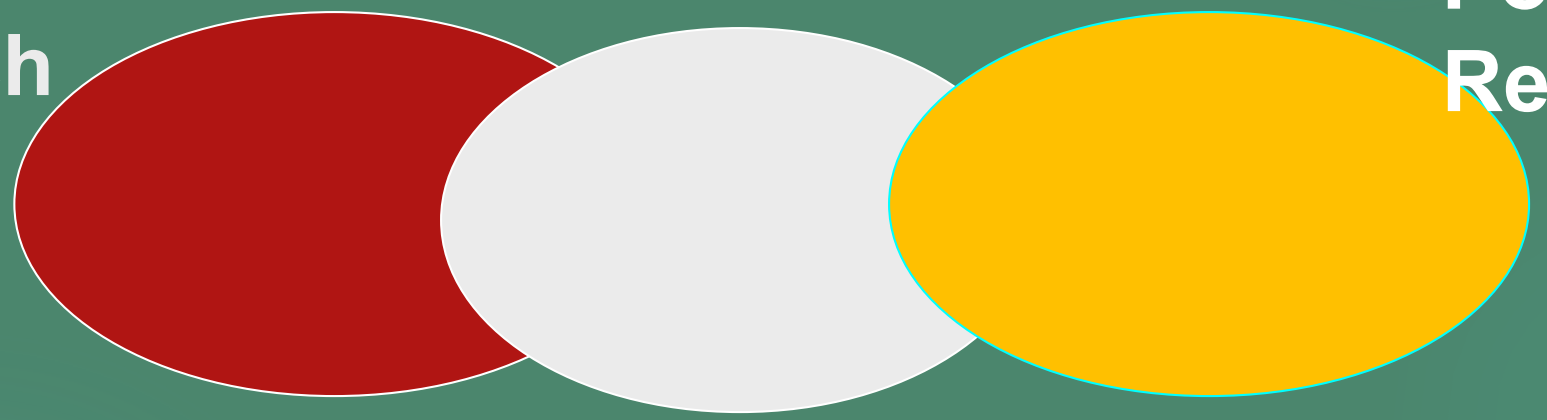
Study Termination

No subjects enrolled after π_1

Enrollment Period, e.g. three (3) years

Follow-up Period, e.g. two (2) years

OPERATION: Patients come sequentially; each is enrolled & randomized to receive one of two or several treatments, and followed for varying amount of time- between π_1 and $(\pi_2 - \pi_1)$.



Briefly, Translational Research is the component of basic science that interacts with clinical research or with population research.

Translational research is scientific research that helps to make findings from basic science useful for practical applications that enhance human health and well-being. It is practiced in the medical, behavioral, and social sciences. For example, in medicine it is used to "translate" findings in basic research quickly into medical practice and meaningful health outcomes.

Applying knowledge from basic science is a major stumbling block in science, partially due to the compartmentalization within science. Hence, translational research is seen as a key component to finding practical applications, especially within medicine. The term itself often fails to distinguish itself from research that is not scientific (e.g., market research), which are considered outside its scope.

The traditional categorization of research identifies just two categories: basic research (also labeled fundamental or pure research) and applied research. Basic research takes a long time – often decades – to be applied in any practical context. Basic research often leads to breakthroughs or paradigm-shifts in practice. On the other hand, applied research can have an impact in practice in a relatively short time, but often represents only an incremental improvement to current processes rather than delivering radical breakthroughs.

With its focus on multi-disciplinary collaboration, translational research has the potential to advance applied science. This has been attempted particularly in medicine with *translational medicine*, research that aims to move "from bench to bedside" or from laboratory experiments through clinical trials to point-of-care patient applications.

Translational research refers to two distinct domains: *T1 research*, the "bench-to-bedside" enterprise of translating knowledge from the basic sciences into the development of new treatments; and *T2 research*, translating the findings from clinical trials into everyday practice, e.g. Public Health interventions.

The cultural separation between different scientific fields makes it difficult to establish the multidisciplinary and multi-skilled teams that are necessary to be successful in translational research. Other challenges arise in the traditional incentives which reward individual principal investigators over the types of multi-disciplinary teams that are necessary for translational research. Also, journal publication norms often require tight control of experimental conditions, and these are difficult to achieve in real-world contexts.

To flourish, translational research requires a knowledge-driven ecosystem, in which constituents generate, contribute, manage and analyze data available from all parts of the landscape. The goal is a continuous feedback loop to accelerate the translation of data into knowledge. Collaboration, data sharing, data integration and standards are very important. Only by seamlessly structuring and integrating these data types will the complex and underlying causes and outcomes of illness be revealed, and effective prevention, early detection and personalized treatments be realized.

Natural History of Research: When to do What?

It often starts with some common/ typical, health-oriented curiosity (e.g. What is the average fish consumption in American diet?) leading to a descriptive/observational research study. For example, a "survey" (cross-sectional) which requires minimal statistical supports – mostly descriptive. Major tool is a questionnaire.

Then it would be followed by an analytic/observational study for some more scientific/statistical curiosity (e.g. Is there an association between fish intake and risk of myocardial infarction?). More statistical supports here: Correlation & Regression.

This could take the form of a "Case-Control" investigation focusing on myocardial infarction, a "disease".

Then concluded with a randomized, controlled clinical trial to establish the case for interventions (e.g. Does treatments with fish oil capsules reduce total cardiovascular mortality?)

Sometimes, an one-arm, early-phase trial or trials could precede this if treatment or intervention is more experimental – say, with possible side effects.

A Historic Timeline of Clinical Trials

Clinical trials are structured, supervised studies where the safety and efficacy of a new drug or therapy are tested in an effort to develop new treatments that will help those afflicted with the targeted condition. Clinical trials have a long and rich history; the first clinical trial documented in the Old Testament dates back to 605 BC. Since this first trial, the industry has progressed immensely, refining the process of clinical trials and furthering the methods of protection for the patients involved.

605-562 BC

The Old Testament outlines how King Nebuchadnezzar II ordered the children of royal blood to eat only meat and wine for three years. Daniel requested that he and three other children be allowed to eat only bread and water. Daniel and the three children were noticeably healthier and more vivacious than those who were relegated to the wine and meat diet.

1537

A Renaissance surgeon, Ambroise Pare, unintentionally carried out a clinical trial when he ran out of the standard treatment of boiling oil for open wounds. He mixed egg yolk, turpentine and oil of rose and soon noticed that the wounds treated with this mixture healed well as compared to those wounds that became swollen and infected with the standard treatment.

1747

James Lind conducted **the “first” controlled clinical trial** on a group of sailors suffering from scurvy. He placed them all on the same diet, but fed one group additional items such as cider and vinegar and fed the other group lemon juice. The group who had the lemon juice supplement recovered from scurvy in just six days.

1863

Placebos are first used in clinical trials. Placebos are non-effective medical treatments given to control groups to compare the results with those from the new drug.

1923

Randomization is introduced to clinical trials. Randomization involves participants randomly receiving one of the treatments, one being a placebo and one being the new drug. Blind clinical trials, where neither group knows which treatment they are receiving, also emerged in the 20th century

1944

Multicenter clinical trials are introduced, where multiple studies are conducted at various sites all using the same protocol to provide wider testing and more data.

1947

The Nuremberg Code is developed which outlines 10 basic statements for the protection of human participants in clinical trials.

1964

The Declaration of Helsinki is developed which outlines ethical codes for physicians and protection of participants in clinical trials all over the world.

1988

The U.S. FDA is provided more authority & accountability over the approval of new drugs and treatments.

1990

The International Conference on Harmonization (ICH) was assembled to help eliminate differences in drug development requirements for three global pharmaceutical markets: The EU, Japan and U.S. The ICH initiatives promote increased efficiency in the development of new drugs, improving their availability to patients & the public.

2000

A Common Technical Document (CTD) is developed. The CTD acts as a standard dossier used in Europe, Japan and the U.S. for proposing data gathered in clinical trials to respective governing authorities.

2009

The Family Smoking Prevention and Tobacco Control Act was signed into law by President Obama; the Act gives the Food and Drug Administration (FDA) the power to regulate the tobacco industry.

For Clinical Trials since 1950, we go over the landmark trial of the Salk Polio Vaccine, perhaps the largest and best known trial in the U.S., and outline the current organizational landscape of clinical trials: Cancer Chemotherapies, Treatments of Acute Myocardial Infarction, and the Role of Pharmaceutical Industry.

THE SALK POLIO VACCINE

In 1954, 1.8 million young children in the United States participated in the largest field trial ever undertaken to assess the effectiveness of the Salk vaccine in preventing paralysis or death from poliomyelitis.
A common approach would have been to introduce the vaccine into certain areas and compare subsequent polio incidence with unvaccinated areas; a common practice even in today's marketing research. The problem is that polio tends to occur in epidemics which can affect some cities and not others so that geographical differences could not necessarily be attributed to the vaccine.

For the next plausible step, it was proposed that each area participating in the trial should be offer vaccination to all second-grade children and use unvaccinated first and third graders as a control group. This part involved over 1 million children. Comparison would be performed within each area, to obtain “treatment effect”, and results pooled across participating areas.

Problems with this “observed control approach” were that:

(1) Only volunteers in the participating areas were vaccinated and these children tended to be from the wealthier and more high educated background. Samples were biased.

(2) Evaluating physicians would be aware which children had been vaccinated and such knowledge could, in theory, influence their diagnoses. Trial was not blinded.

To overcome those anticipated problems, a randomized double-blind placebo-controlled trial. This part involved 0.8 million volunteer children. These volunteers were randomly assigned to placebo or vaccine in a way such that neither the child, his or her family, nor the evaluating physicians were aware of whether the child had the vaccine. Identities were only revealed after the trial and evaluations ended.

The results of the randomized placebo-controlled part of the trial were very convincing: the overall polio incidence in the vaccinated group was half of the Placebo group, and the incidence of paralytic polio was over 70% less; there we
re only 4 deaths and they were all in the Placebo group.

Results from the observed-control part of the trial also supported the findings from the randomized placebo-control part of the trial. However, there was also evidence that children in the participating areas who were invited but declined to participate had lower incidence than the non-vaccinated controls. This means the non-randomized observed control part of the trial could not by itself have provided such unequivocal evidence of the vaccine's value.

CHILDREN CANCER THERAPIES

In 1954, the National Cancer Institute (NCI) organized the first randomized trial in acute lymphocytic leukemia (ALL); it involved 5 centers and 56 patients. The successful organization of this trial led to the formation of two “collaborative groups” for leukemia which are still operative today under the names (1) Children’s Cancer Study Group, and (2) Cancer and Leukemia Group B. Funding for Cancer Research has steadily increased, and many similar but smaller groups have been formed.

ADULT CANCER THERAPIES

The original Eastern Solid Tumor Group with participating institution has expanded and renamed the Eastern Cooperative Oncology Group (ECOG) in 1971 with 15 centers. Since then, this group has contributed to the development of many drug combinations particularly in breast cancer and lymphomas. Inspired by successes of ECOG, many other similar but smaller groups have been formed, and funding, mostly from NCI, have steadily increased.

Through ECOG and other chemotherapy groups, scope has been broaden over the years, so that many trials now use drugs as a front line weapon to be combined with conventional surgery and/or radio-therapy for primary diseases, e.g. breast cancer, melanoma, colorectal cancer, and brain cancer.

The development of new drugs and combinations continues; trials nowadays are more efficient, better organized, and have greater prospect of patient benefit and survival than in early years.

ACUTE MYOCARDIAL INFARCTION

In the complex area of the treatment and management of patients after acute myocardial infarction, there are two main types of drug therapy, anticoagulants and platelet-active drugs.

The potential benefit of anticoagulants was first realized in the ‘40 and was endorsed by the American Heart Association as long ago as 1948. There still remains today considerable divergence of opinion regarding their value; this uncertainty has partly resulted from the doubtful quality of early trials. T the same period of time, there has developed considerable interest in the role of plalet-active drug such as aspirin. By 1980, there was already 6 large randomized trials comparing aspirin with placebo involving over 10,000 patients. The quality of these trials has been high but their interpretation is not easy.

I believe that interests in these two types of drug remain high.

THE PHARMACEUTICAL INDUSTRY

Since about 1938 there was a requirement in the United States that animal research, particularly on drug toxicity, be formally documented. But, before the Second World War, there were no formal requirements for clinical trials before a drug could be freely marketed. It was required, however, since 1962 that “adequate and well controlled trials” be conducted. In 1988, the U.S. FDA is provided more authority & accountability over the approval of new drugs and treatments.

Since then, the FDA has continually expanded and elaborated on the precise sort of clinical trial evidence needed for different types of drugs. These FDA Guidelines form a sound model which is followed in principle by many other countries.

There are more clinical trials currently taking place than ever before. The majority of these clinical trial efforts are for the evaluation of new drug developments and, because of their increasing enormous costs, are mostly supported directly or indirectly by the pharmaceutical industry.

The pharmaceutical Manufacturers Association (PMA) has about 150 members of which there are between 20 and 30 major U.S. companies which are research-intensive.

A typical one of these larger companies would have 20-50 pharmaceutical products currently undergoing clinical trials prior to marketing. Each product might require 10 to 80 different trials in different phases, averaging about 25 involving around 3000 patients.

The FDA requires that each new drug has an IND (Investigate New Drug) application approved before clinical trials may be undertaken.

Suggested Readings:

Search and learn about the history, the structure, and major functions of the FDA