

Design and Conduct of Clinical Trials: Past, Present and Future. New Innovative Technology Methods

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Clinical Trial: Definition

A prospective experiment comparing the effect and value of a test treatment to a control intervention in comparable groups of human subjects

Why are Clinical Trials Needed?

- SETTING – We want to know if an intervention produces given desirable results without having unwanted outcomes
 - A clinical trial is the most definitive way to determine if an intervention has a given effect
 - A clinical trial can also study if an intervention has unwanted effects
 - To ensure that if differences between treatment groups are found that these difference were from an intervention

Pre-Study Uncertainty of Intervention Effect

- Since control groups are denied an intervention, it is not ethical to test an intervention if you already know that it works
- How much uncertainty is legitimate? This is often a very controversial point for fatal diseases
- Persons dying of cancer don't want to be guinea-pigs in a study of a cure that probably works

HISTORY: A Study from the book of Daniel is often cited as the first controlled trial

- Daniel & 3 young men were among candidates (healthy, handsome, smart, wise)
- The king decreed that all were to eat the same diet as himself. As result, they were getting worse
- Daniel's group decided to eat only vegetables next 10 days
- The results were outstanding. They became palace advisors and their advice was found to be 10 times wiser than any of the other palace advisors

Past 200BC-1966

Critique of Daniel's study

- No demonstration of comparability of treatment groups (self-selected/no randomization)
- Very soft primary outcome (how'd they look)
- Softer secondary outcome (wisdom of advice)
- Unmasked (placebo effect in only the active treatment group)
- Small sample size

Past 200BC-1966

Scurvy: a big public health problem

- Vasco De Gama lost most of his crew to scurvy in his sentinel 1497 trip to *India*
- Sir John Hawkins, the Elizabethan pirate admiral, estimated that 20,000 men died of scurvy during his command year of service
- Between the years 1779 and 1794 one of every four British sailors came down with scurvy
- It killed a million seamen in 200 years

Past 200BC-1966

Lind's Scurvy experiment

- Lind took 12 patients with the scurvy on board the Salisbury at sea on the 20th of May, 1747
- All lay together in one place, same diet
- 2 of the worst patients were put under a course of seawater (control group)
- Underpowered? Design inadequate?

Past 200BC-1966

Landmark events for development of modern clinical trials

- 1747: Untreated comparison group (Lind scurvy)
- 1863: Placebo treatment (Gull & Sutton –mint water placebo for rheumatic fever)
- 1923: Randomization as a research tool (Fisher & Mackenzie – agricultural research)
- 1931: Call for clinical trials by the Medical Research Council of the UK
- 1944: Multicenter trial (Patulin Clinical Trial Committee – patulin for the common cold)
- 1966: Consent guideline
- 1993: Congressional mandate for inclusion of women and ethnic minorities in clinical research

Past 200BC-1966

Characteristics of many clinical trials

- Large sample size
- Multiple clinics to achieve recruitment goal
- The long period of patient recruitment and follow-up
- Follow-up period extends well beyond the close of patient recruitment

Present 1966-2020

Primary and Secondary Outcomes

- Primary Outcome –measures the event the trial is designed to prevent
 - regulatory agencies evaluate the trial based on the primary outcome
 - must be well defined to prevent multiple comparisons
- Secondary Outcome –use to see trends in an intervention's effect earlier in the trial
 - increase in the number of "events" observed
 - the decrease in both the number of patients needed in a study and the length of time those patients need to be followed

Present 1966-2020

Basic Study Designs

RANDOMIZED CONTROL

- One control arm
- One (or more) intervention arms
- Patients are prospectively randomly assigned to study arms by one of the following:
 - Standard randomization
 - Blocked randomization
 - Stratified randomization
 - Matching (extreme strata)

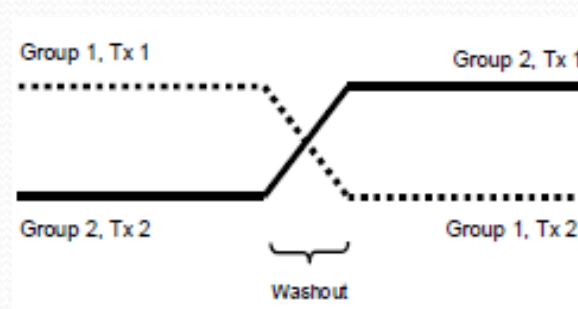
NON-RANDOMIZED CONTROL

- One control arm
- One (or more) intervention arms
- Patients are prospectively assigned to study arms by non-random or pseudo-random process by convenience treatment settings:
 - Treatment settings do not influence the outcome

Present 1966-2020

Basic Study Designs (cont.)

- CROSS-OVER –this is special type of design in which it's possible to give person different drugs over different time period



PARALLEL- design refer to trial when all patients in each arm always get the same drug

If the outcome is a sudden and permanent condition, parallel designs must be used
(for example, if the outcome is death)

ADVANTAGE OF CROSS-OVER vs. PARALLEL DESIGN

- Variance reduction by matching patients
- Study requires fewer patients

DISADVANTAGE OF CROSS-OVER vs. PARALLEL DESIGN

- Cross-over design is much more complicated logically
- Harder to mask
- Takes longer to complete

Present 1966-2020

Basic Study Designs (cont.)

GROUP RANDOMIZATION – interventions are randomized to groups rather than to persons

WHEN USED: Behavioral interventions in one of the following:

- The intervention must be delivered to a group as a whole
- Individuals in the same group interact with each other and “contaminate” each other’s outcome

Examples:

- Smoking cessation study
- Weight loss program study
- Virginity pledge study

Present 1966-2020

Methods of Statistical Analysis

RANDOMIZATION	OUTCOME	
	BINARY	CONTINUOUS
Standard Unadjusted With Covariates	Exact Test Logistic Regression	T-test Linear Models
Blocked Unadjusted With Covariates	Exact Test Logistic Regression	T-test Linear Models
Stratified* Unadjusted With Covariates	Exact Test Logistic Regression*	T-test Linear Models*
Matched* Unadjusted With Covariates	McNemar's Test Conditional Logistic Regression	Paired T-test Linear Model of Differences

Present 1966-2020

Case-Series studies

- A simplest observational study design that selects persons with the disease of interest and does descriptive statistics on them.
- The main advantage of case-series studies: they are inexpensive and relatively quick, Informs patients and physicians about natural history and prognostic factors, helpful in hypothesis formation.
- Limitations: cases may not be representative, the outcome may be a chance finding and not characteristic of the disease, cannot easily examine the disease, since there is no control group without disease

CROSS-SECTIONAL STUDIES

Cross-sectional studies take a random sample of a population of interest at a given time point or interval.

ADVANTAGES OF CROSS-SECTIONAL STUDIES

- Can simultaneously look at several exposures/diseases
- The best type of study to establish prevalence's
- Can be extended into Cohort Studies
- Can be conducted over a short time period
- Should be able to get a better response rate than other

DISADVANTAGES OF CROSS-SECTIONAL STUDIES

- Unsuitable for rare or short duration diseases
- High refusal rate
- No data on relationship between risk factors & disease
- Obviously can't be used when death is the outcome
- Cross-Sectional can have survivor length sampling bias

CASE-CONTROL STUDIES

The case-control study compares 2 groups of people: with the condition or disease (cases) and those who don't have these types of disease or condition (controls)

ADVANTAGES OF CASE-CONTROL STUDIES

- Inexpensive
- Relatively short
- Can look at multiple exposures for the disease
- Can sometimes collect data from existing records
- No risk (except for privacy issues and minor discomfort) to subjects

DISADVANTAGES OF CASE-CONTROL STUDIES

- Hard to select appropriate cases (Survival Bias, Berksonian bias, etc.)
- Hard to select appropriate controls
- Data collected can be biased (Recall bias, Interviewer Bias)
- Temporal problem sometimes hard to establish whether “exposure” or “outcome” came first
- Can only look at one outcome or disease. Cases only have one disease (i.e. epilepsy)

COHORT STUDIES

A cohort is a group of people (with similar characteristics/ experiences)

ADVANTAGES OF COHORT STUDIES

- Can best establish if the exposure or the outcome came first
- Since data is collected prospectively before outcome there is less recall and interviewer bias
- Since selection is not made based on disease, can study multiple outcomes
- Gives more control over how variables and data are collected

DISADVANTAGES OF COHORT STUDIES

- Requires large numbers for rare diseases
- Follow up can also be very long so historical cohorts are used
- Expensive to conduct
- The loss to follow up (people move, quit, etc.)
- Can be made irrelevant before it finishes by future findings
- They are typically unsuitable for identifying the causes of a sudden outbreak of disease. A case-control study can give quicker results
- They can only offer clues about the causes of disease

The first step to becoming patient-centric is making instruments to capture real patient & their knowledge

- Patients will be united in the groups that make critical decisions in the organization.
- Companies will seek to understand what a better-quality outcome means for patients
- Companies must engage with patients and learn from the patient in the networks

Present-Future

The second step is to translate the patient and their involvements into internal programs, and learnings that will advance offerings

- Finding ways to fit in this data into the day-to-day operations is a revolution challenge
- Data can only be used to drive improved outcomes
- push the boundaries where you have chosen to differentiate

Present-Future

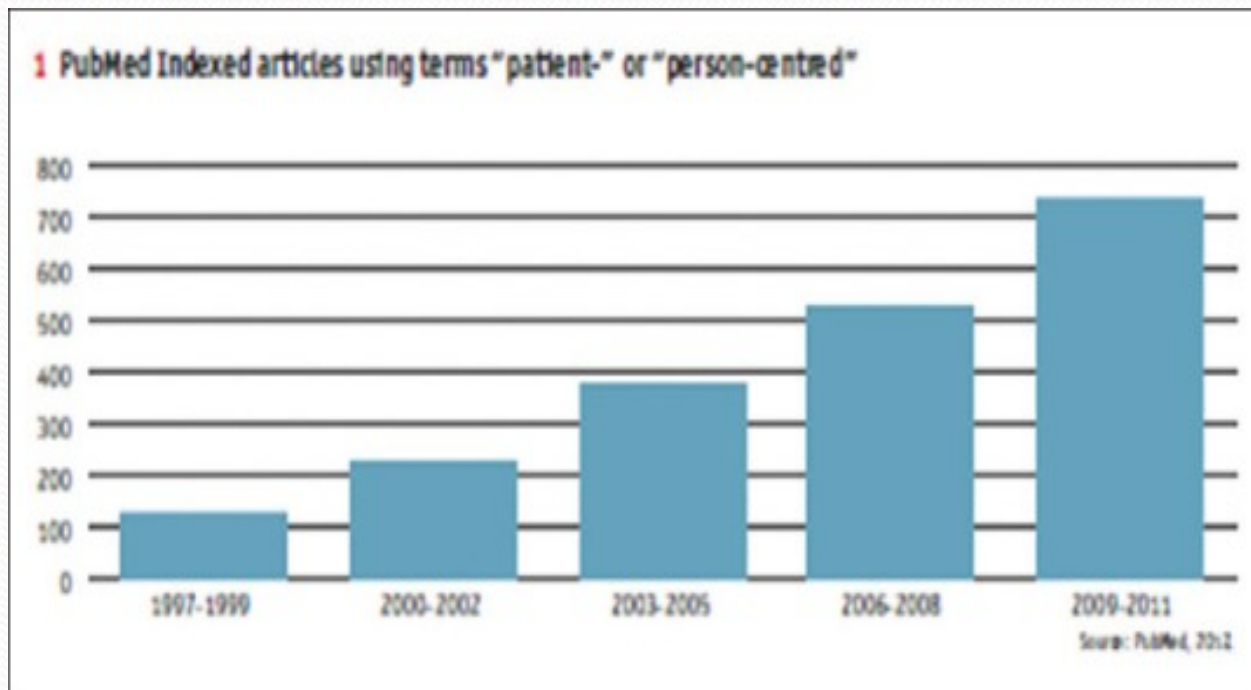
PATIENT-CENTRIC PRACTICES FOR RESEARCH: MODEL FOR FUTURE

The final step is to use the knowledge from the prior two steps to enhance input mechanisms and apply the information to improve outcomes.

- Be tactical to warrant that everyone is rowing in the same direction and is constantly repeated of the importance of patient-centrism to the company
- Monitoring progress across quantifiable goals and metrics will help to improve performance.
- Crowdsourcing: has been used since long as a powerful tool to engage the masses in other industries.
- Focus on patient education, engagement using technology

PATIENT-CENTRIC PRACTICES FOR RESEARCH: MODEL FOR FUTURE

The graph depicts a six-fold increase in the last 12 years related to the term “patient-centered



- 29 billion connected and wearable devices across the world by the end of next year
- Bluetooth headset sales growing from 150 million in 2017 to a forecast of 206 million by 2021.
- Here is a breakdown of numbers of devices projected to be sold in four years for wearables by category:
- 206 million – Bluetooth headset
- 81 million – Smartwatch
- 67 million – Head-mounted display
- 64 million – Wristband
- 59 million – Other fitness monitors
- 22 million – Sports watch
- 6 million – Body-worn camera

WEARABLE TECHNOLOGY AND AN ASSESSMENT ON THEIR EFFICACY

- Companies are looking to digital solutions to minimize costs and improve efficiency
- Patients must travel to a physical location, such as a hospital or GP surgery. Wearable devices linked to mobile apps remove this issue instantaneously
- Ability to have immediate access to patient data allows trial designers to quickly identify anomalies and trends
- While this wealth of data offers more opportunity for pharma to better understand individual patients and to better prepare therapeutically, it also poses a substantial data management challenge

e-HEALTH AND DATA SHARING

- The increasing focus on transparency of clinical trials for patients has been matched by a commitment to the security of information. eHealth and data sharing the increase in regulation and scrutiny.
- Business associates are discovering how to improve patient care by engaging in health data exchange but are also concerned with how they keep that data secure
- Federal regulations do allow for information to be exchanged in certain circumstances, including the ability to access patients own data

Present-Future

e-HEALTH AND DATA SHARING

Benefits of data sharing	Disadvantage of data sharing
Cost Saving, reduces paper costs	Expensive
Speed, electronic data transfer ensures more accuracy and data stability	Too many standards, multiple standards can often limit how many devices can be connected to the network
Accuracy	Initial setup is time consuming
Business efficiency, eliminates computational repetition, redundancies, and errors	System electronic protection
Security	Proper backup
Environment friendly	Electronic data interchange can limit the types of partnership

Artificial intelligence in pharma refers to the use of automated algorithms to complete tasks that usually rely on human intelligence. Over the last few years, the use of artificial intelligence in the pharma industry and biotech industry has redefined how scientists investigate new drugs, tackle the disease, and more.

Present-Future

ARTIFICIAL INTELLIGENCE TECHNOLOGY

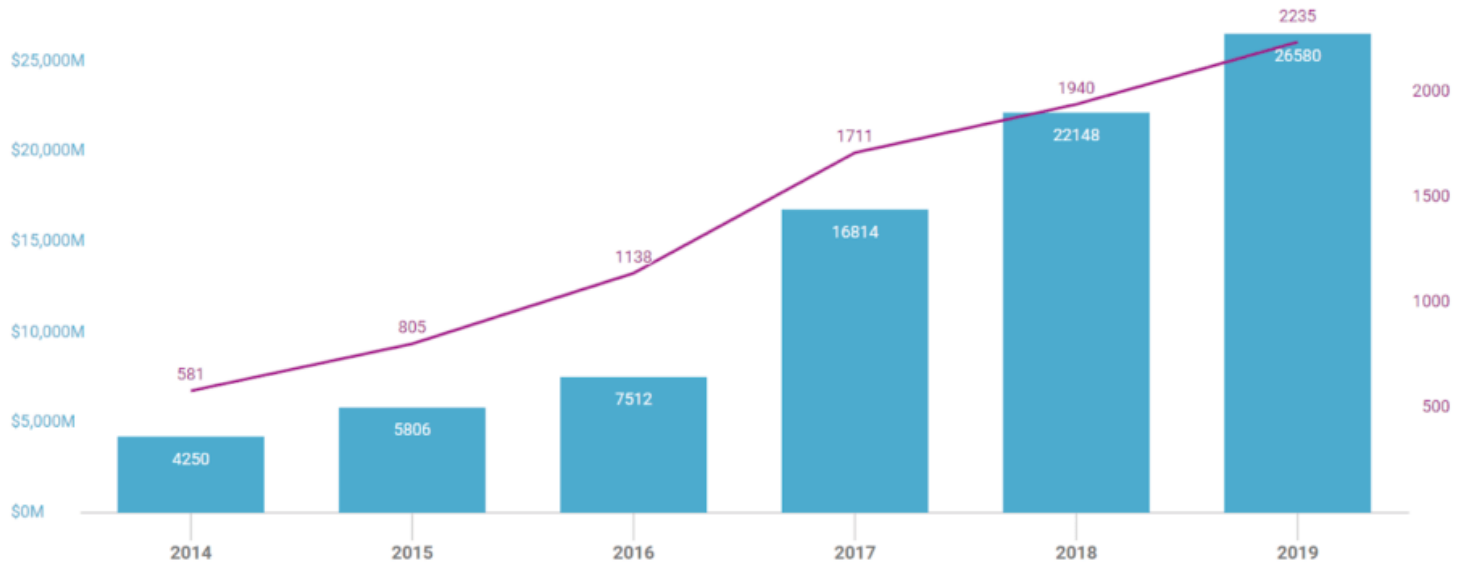
STARTUP FUNDING

2019 sees record funding to AI startups at \$26.6B

2014 - 2019 (swipe right to see full data)

Amount of funding (\$M)

Number of deals



Created with: **CBINSIGHTS**

Source: CB Insights

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PHARMACEUTICAL COMPANIES
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ARTIFICIAL INTELLIGENCE TECHNOLOGY

Artificial intelligence can potentially boost the success rate of clinical trials by:

- Efficiently measuring biomarkers that reflect the effectiveness of drugs
- Identifying patient subpopulations best suited for specific drugs. Only 30 % of all phase II compounds advance to phase III, and every third phase III trials fail because the trial lacks enough patients or the right kinds of patients.
- Start-ups, large organizations, and governments are all exploring and driving the use of AI for improving clinical trial

CYBERSECURITY FOR DATA PROTECTION

The main three reasons that cybersecurity is of the highest importance in clinical research:

- **Patient privacy:** Electronic health records are full of patient data.
- **Intellectual property:** The data gathered in clinical trials decide the competitive potential of the drug, device, diagnostic tool, or vaccine on trial, and as such is considered sensitive intellectual property
- **Company reputation:** After cyber-attack and data were compromised and it difficult for companies to win favor among sponsors.

CONCLUSION

- The future promises to be exciting, with statistics getting used for real-world evidence, expansion of biosimilars, mining of adverse event data, and an essential function in the development of new drugs.
- Clinical trial reporting has also been regularly developing globalization is also having significant effects on the development of clinical research.
- One final concern is that with the increasing complication of pharmaceutical research, translational research has also become more and more complex. Regulatory changes have also been vital in improving the safety of clinical research.
- However, in the era of globalization, new ethical challenges rise and require more training programs.

TA areas of Janssen Trials

Janssen conducts the 6 priority therapeutic areas

- **Cardio & Metabolism**
- **Immunology**
- **Infectious Diseases & Vaccines**
- **Oncology**
- **Neuroscience**
- **Pulmonary Hypertension**