Paper TT19

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

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ABSTRACT

A technically strong Data Management team defines pre-study uncertainty of intervention effect, soft primary outcomes, and inadequate cross-over/ parallel design of trials as the main failure for older studies. The team described a wonderful world of current statistical analysis for blocked, stratified randomization and extreme strata methods as primary selection criteria for current trial conduct. We describe benefits, drawbacks and biases effects of case-series, case-control, and cohort study design. Major Clinical Trials Innovation trends were defined as the following: the rise of patient-centric practices for pharmaceutical research; eHealth and data sharing increase in regulation and scrutiny; wearable technology and an assessment on their efficacy; strong facts of using artificial intelligence technology as the magic bullet for streamlining the clunky clinical trial process; cybersecurity for data protection This paper will discuss evolution of past, present and bright future of new innovative methods for the design and conduct of clinical trials.

INTRODUCTION

The purpose of this paper is to describe the benefits and drawbacks of different study designs and innovation trends. We will discuss the evolution of past, present and bright future of new advanced methods for the design and conduct of clinical trials.

WHY CLINICAL TRIAL IS NEEDED

We want to know if an intervention produces given desirable results without having unwanted outcomes. Clinical trial is the most definitive way to determine if an intervention has a given effect. Also, clinical trials can study if an intervention has unwanted effects. During trial conduct, we need to ensure that if differences between treatment groups are found that these differences 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
But 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 OF OLDER STUDIES AND MAIN FAILURE REASONS

STUDY FROM THE BOOK OF DANIEL

A study from the book of Daniel is often cited as the first controlled trial. Daniel and three young men were among the candidates. The main characteristics of those candidates are healthy, handsome, smart, and wise.

The king decreed that all were to eat the same diet as himself. As a result, they were getting worse. Because of this Daniel's group decided to eat only vegetables the next 10 days. As a fact results were outstanding. They became palace advisors and their advice was found to be 10 times wiser than any of the other palace advisors.

This study shows up a lot of drawbacks. Here are the main critique points of Daniel's study below:

- 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

SCURVY: A BIG PUBLIC HEALTH PROBLEM

Scurvy is a disease caused by severe and chronic vitamin C (ascorbic acid) deficiency. Most people think of scurvy as a disease of the past when sailors had to spend months at sea without access to fresh fruit and vegetables. While scurvy may be uncommon in modern society, it does still exist. In the 13th century, the crusaders frequently suffered from scurvy. 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. During the Age of Exploration(between 1500 and 1800), it has been assessed that scurvy killed at least two million seamen. In 1747James Lind formally demonstrated that scurvy could be treated by supplementing the diet with citrus fruit, in one of the first controlled clinical experiments reported in the history of medicine. Lind took 12 patients with the scurvy on board the Salisbury at sea on the 20th of May 1747. All patients lay together in one place and use the same diet. Two of the worst patients were put under a course of seawater (control group). Unfortunately, the experiment and its results had little impact due to the underpowered sample size and inadequate study design.

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 common cold
- 1966: Consent guideline
- 1993: Congressional mandate for inclusion of women and ethnic minorities in clinical research

CHARACTERISTICS OF MODERN CLINICAL TRIALS

Primary Outcome measures the event the trial is designed to prevent. Regulatory agencies evaluate the trial based on the primary outcome. 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. Secondary Outcome increase in the number of "events" observed and decrease in both the number of patients needed in a study and the length of time those patients need to be followed

BASIC STUDY DESIGNS

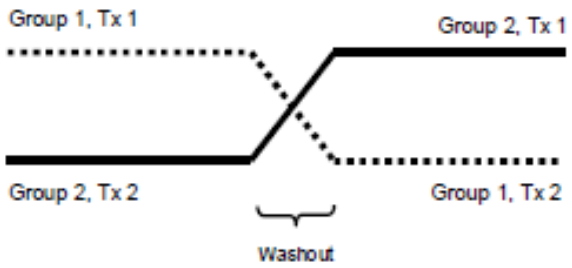
Randomized Control characteristics:

- 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 characteristics:

- 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 does not influence the outcome

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



PARALLEL- design refers to trial when all patients in each arm always get the same drug. If an 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

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

METHODS OF STATISTICAL ANALYSIS AND STUDY DESIGNS

There are two main statistical methods are used in data analysis. Descriptive statistics describe the relationship between variables in the sample population. Descriptive statistics summarize data from a sample using indexes such as the mean, median, mode or standard deviation. Inferential statistics draw conclusions from data that are subject to random variation (e.g., sampling variation or observational errors) and make inferences about the whole population.

Randomization allows to prevent the bias selection and assures against any accidental bias. It creates comparable groups and avoid the source of bias in treatment assignments during trial conduct. Randomization has been extensively used in majority human clinical trials and different biological experiments. Randomization also permits the use of probability theory to express the likelihood of chance as a basis for the difference of end outcome in a clinical trial.

The common types of randomization include standard, block, stratified and unequal randomization. The outcome could be binary and continuous, and each type is using a different statistical test for 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

OBSERVATIONAL STUDY DESIGNS

The major types of observational study designs used in the pharmaceutical industry, epidemiology, and medicine listed below:

1. Case Series
2. Cross-sectional study
3. Case-Control study (Matched Case-Control)
4. Cohort study (Nested Case-Control, Case-Cohort)

CASE-SERIES STUDY DESIGN

This is the 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. However, Case-Series studies have some limitations: cases may not be representative, outcome may be a chance finding and not characteristic of disease, cannot easily examine disease etiology, exposure reflects the underlying population, not the outcome since there is no control group without disease most of the risk measures cannot be obtained.
We need to be careful about jumping to conclusions from case series. For example, in one study 95% of patients at "New Brunswick Psychiatric Hospital" went to church as a child. Does going to the church as a child cause psychiatric problems? We can't make this conclusion …. maybe 95% of everyone in the New Brunswick area went to church as a child. Case-series are usually the first type of study conducted for a newly emergent disease.

CROSS-SECTIONAL STUDIES

Cross-sectional studies take a random sample of a population of interest at a given time point or short interval. Current and previous exposures and outcomes of Interest are then measured at that timepoint.
Common statistical measures of cross-sectional studies: point prevalence, interval prevalence, prevalent lifetime, expected time or duration, odds ratios (except for logistic regression), examine characteristics associated with condition or disease by comparing cases to noncases. It is important to derive a sampling "frame", choose a sampling strategy and maximize a response rate for conducting the cross-sectional study.
Main types of sampling for cross-sectional studies:

- *Simple random*--everyone has the same probability of being chosen
- *Stratified random*—if the most variance is between strata, gives lower sampling variance
- *Systematic*—used commonly in clinical research, akin to stratified random sample if the list is ordered
- *Cluster*

Nonresponse in sampling for cross-sectional studies could be minimized by smaller sample size allows more intensive recruitment, collect data on non-responders ff possible, and intensively recruit a sub-sample of non-responders
ADVANTAGES OF CROSS-SECTIONAL STUDIES

- Can simultaneously look at several exposures and diseases
- The best type of study to establish prevalence's and attributable risk
- If follow up on the subject is continued, 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 study designs
- Can be addressed to specific populations of interest

STATISTICAL DISADVANTAGES OF CROSS-SECTIONAL STUDIES

- Unsuitable for rare or short duration diseases
- High refusal rate may make accurate prevalence estimates impossible
- No data on the temporal relationship between risk factors and disease development
- Obviously can't be used when death is the outcome (everyone must be alive to be in a cross-sectional sample)
- Cross-Sectional studies can also have survivor length sampling bias

Cross-sectional studies are often used for "economic purposes" to qualify and compare absolute risk, attributable risk and the association.

CASE-CONTROL STUDIES

Case-control study compares two groups of people: those with the condition or disease under study (named cases) and a very similar group of patients who don't have these types of disease or condition (named controls). If a disease is a rare, a cross-sectional study design cannot be chosen. For example, in a study of epilepsy we sampled even 1,000 people at most there would be very few cases. This necessitates having to: first - obtain a sample of cases in order to ensure that there are enough

cases, and next – separately obtain a sample of controls in order to make comparisons. In this situation cases are randomly chosen persons with the disease or outcome of interest, and controls are randomly chosen "comparable" persons without the disease or outcome of interest.

POTENTIAL EPIDEMIOLOGIC BIASES FOR CASE-CONTROL STUDIES

- Recall Bias – people are often asked about exposures in the past
- Interviewer Bias – If the interviewer knows who the cases are he can be biased when writing down the answers to questions. It is better if interviewers don't know who cases and controls are, but often this is impossible to do
- Selection Biases – It is very hard in practice to obtain cases and controls and one is often forced to select these from different sources introducing potential biases. since cases and controls are selected separately differential biases in the selection processes can occur

Berksonian Selection Bias is a type of selection bias when often cases and/or controls are Identified in hospitals, registries, etc. But doing so we selectively includes cases that have other problems besides the one of interest. For example, maybe epileptic children cases were identified using records from hospitals that treat large numbers of alcoholics, while children's controls were obtained from a General Population Census. Sometimes multiple control groups are used for this reason i.e. take a second control group of children of patients at hospitals. Survival Selection Bias is like cross-sectional studies. If cases are taken from death registries we selectively get those with poor survival. If cases must be alive to be identified we selectively get long survivors.

ADVANTAGES OF CASE-CONTROL STUDIES

- inexpensive
- Relatively short
- Can look at multiple exposures for the disease, i.e. mother's alcohol vs epilepsy, mother's smoking vs epilepsy, premature birth vs epilepsy…
- Can sometimes collect data from existing records (i.e. hospitals, registries, etc.), but often due to patient privacy concerns this is not legal to do in the United States
- Since case and control groups can be made comparable in size (i.e. 200 cases and 200 controls) is more powerful than an equivalent size cross-sectional study. Unless cases are limited in number or more expensive to recruit, in general power is maximized with equal numbers of cases and controls
- 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 (Sometimes Similar Selection Biases as Cases)
- Data collected can be biased (Recall bias, Interviewer Bias)
- Temporal Problem Sometimes hard to Establish whether "exposure" or "outcome" came fist
- Can only look at One Outcome or Disease. Cases only have one disease (i.e. epilepsy)
- Cannot use Case-Control studies to measure the incidence or prevalence of disease. Cases are over-selected, and it is almost always impossible to know by how much
- Harder to validate information … and often a lot of data is missing. Information from Case-Control studies is from what happened in the past … often a long time ago

COHORT STUDIES

Cohort is defined as a group of people (usually with similar characteristics or experiences) that go forward together over time. Cohort studies recruit people that do not yet have the outcome of Interest yet and follow them forward in time to ascertain the development of that outcome. The cohort study design classifies people exposed to a specific factor and a comparison group that was not exposed to that factor. These studies measure and compare the incidence of disease in the two groups. A higher incidence of disease in the exposed group suggests a correlation between such factors and the outcome of studying disease. This design is generally a very good choice when dealing with an outbreak in a comparatively small, well-defined source population, mainly if the disease being studied was common. They can be prospective studies and gather data going forward, or retrospective cohort studies, which look at the data which was already collected. Such research can help to identify social factors that influence people's health.

The cohort study design is the best available scientific method for measure the effects of some suspected risk factors. In prospective cohort study, researchers raise a question and form a hypothesis about what might be a disease factor. Then they observe a group of patients, named as a cohort, over a certain period and this may take a few years. They collect data relevant to disease. In such a way they goal to detect all changes in patient health linked to a possible risk factor which was identified. For instance, research requires participates to record specific lifestyle details during study conduct. Then they analyze all correlations between lifestyle factors and disease.

COHORT STUDIES COMPARE TO OTHER STUDY DESIGN

Randomized controlled trials are considered the best, most rigorous way of examining interventional medicine, such as new drugs, but it is not possible to use them to exam for the causes of disease. Cohort studies are observational studies. The investigators observe what happens without intervening. In experimental studies, such as randomized controlled trials, the researchers intervene, for example, by giving participants a new drug and assessing the outcomes.

When looking for the causes of disease, it would be practically unethical to deliberately expose participants to a suspected risk factor, as would be the case in a randomized controlled trial. Such a prospective cohort study is observational rather than interventional.

For drug testing, randomized controlled trials are the best option. Humans are used to test the safety and potential benefit of a treatment.

While the harms of treatment sometimes outweigh the benefits, this form of testing is considered acceptable because the drug has already been tested many times and the investigators are sure that it is safe enough to attempt.

In addition, patients agree to join the trial, sometimes because it is a good chance the drug will improve their health.

Cohort studies are better than case-control studies because they are usually prospective. Case studies are limited because they are usually retrospective and involve a smaller number of participants.

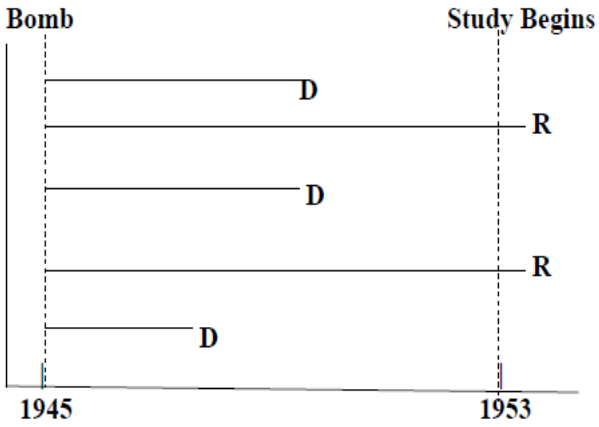
TYPES OF COHORT STUDIES

An extended cross-sectional cohort just recruits a cross-section from the general population or a specific risk group and follows them forward number of participants. For example, the MACS study recruited about 2,000 men infected with HIV in 1988 and has continued to follow them over time. While multiple outcomes were studied the focus was on AIDS. There is usually no "single comparison exposure" in mind for when an extended cross-sectional study" is planned.

Exposure Comparison Cohorts is when **t**wo (or more) specific exposure groups are recruited and the idea is to compare if future outcomes are different. For example, men with enlarged prostates divide on 2 groups: 350 treated by surgery and 350 treated by drugs. Does survival differ by group? This differs from the previous design in that there are "quotas" for each exposure group. For 2 exposure groups, it is usually optimal to have 50% of subjects in each. This Differs from a Clinical Trial in that subjects are choosing the treatment on their own.

Historical Cohort Study. Sometimes Cohorts can be Identified from Information on exposure or event in the past and followed forward to the present and then beyond. For example, the cohort study of survivors of the Nagasaki atomic bomb in Japan did not begin until 8 years after the bomb was dropped. The main question is how does a "Historical Cohort Study Differ from a Case-Control Study? In Case-control study they recruit people based on whether they had the outcome and find out next whether they had an earlier exposure. During the Historical Cohost study, they recruit people without an outcome at an earlier date based on exposure or data is available at that earlier date and follow them forward to see if the outcome occurs later.

If a Historical Cohort Study requires the person to be alive at the future date when it is started, this leads to a length sampling bias known as truncation. Historical Cohort Study of atomic bomb survivors recruited in 1953 is a perfect example.



Anyone who dies < 8 years after being exposed to the radiation will not be recruited. Unadjusted Estimates of Survival time from this study will be too large. This study will not be able to identify factors associated with rapid death after radiation exposure

ADVANTAGES OF COHORT STUDIES

- Can best establish if the exposure or the outcome came first (especially if people are recruited prior to exposure and some become exposed later)
- 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 including quality control

DISADVANTAGES OF COHORT STUDIES

- Requires large numbers for rare diseases
- Follow up can also be very long so historical cohorts are sometimes used
- Expensive to conduct
- 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, rather than definitive proof of links between risk factors and health. This is true of any observational medical research

In general, there is a guide for general sequence of observational studies for a given exposure/disease. Case series and cross-sectional studies are done first. If these studies find evidence to go further, case-control studies are done then. If issues of bias or timing in case-control studies exist then cohort studies done. Cohort studies also done to more fully study outcomes.

PATIENT-CENTRIC PRACTICES FOR PHARMACEUTICAL RESEARCH: MODEL FOR FUTURE

Pharmaceutical companies have begun to recognize that patient-centrism is the right thing to do for their customers, and it is a smart business decision. Customer's feedback helps to analyze challenges earlier, formalized structures allow ideas to flow through organizations, and crowdsourcing helps to ensure patients understand the meaning of "better outcomes" and how they look like.

The first step to becoming patient-centric is making instruments to capture real patient and their knowledge. This is true considering what the patient meets.

- **Create formalized mechanisms for input:** Patients will be united in the groups that make critical decisions in the organization.
- **Utilize individualized data to expand the narrative:** Companies will seek to understand what a better-quality outcome means for patients on a more individualized level. They must recognize how to collect and frame the patient and their needs and experiences.
- **Strengthen patient advocacy partnerships:** The industry's best companies have deep roots in advocacy groups in order to create a two-way street for all necessary information.
- **Meet patients:** Companies must engage with patients and learn from the patient in the networks they select. Modern technology allows companies to analyze and aggregate enormous amounts of data. Attempting to "bring the patient to them" is to become truly patient-centric.
- **Benefits of "digital patients"**. Companies are offering a ready repository of patients who have enrolled in different trials to pharma companies keen on conducting trials-driving cost and effort saving. For example, "Digital Patient Unit" program with over three million patients helps to use real-world patients for the faster testing of inclusion/exclusion criteria

The second step is to translate the patient and their involvement into internal programs, and learnings that will advance offerings and drive improved outcomes. The key is to focus on solving the problems of each patient.

- **Institutionalize structures and processes to utilize data:** All business functions should be plugged into the data described above, not just those that are traditionally customer-facing. Finding ways to fit in this data into the day-to-day operations is a revolution challenge, but it's required for companies to lead in patient-centricity. For example, the pharmaceutical companies utiliza the information gained in the design of future clinical trials so that endpoints and objectives are aligned with the interests of the patient.
- **Communicate, and integrate:** Data can only be used to drive improved outcomes if it is suitably spread throughout an organization. Manufacturers must create structures to disseminate information and integrate patient-centrism as a role for every level in the company. This should be revisited and reinforced frequently (e.g. quarterly and monthly reviews, team meetings, etc.).
- **Guarantee the seats at the table have weight:** The first step was creating a seat at the table for patients. Pharma companies have tried this before. To make it stick, balances need to be developed to guarantee that the patient role

isn't eclipsed by the traditional decision-makers. Pharma organizations will create a role with a direct line to the CEO with the remit to further elevate the perspective of the patient

- **Hyper-focus where capabilities are differentiating:** The most critical place to seek patient input is where capabilities are distinctive. As services develop to be more homogenous, patient-centrism is important to push the boundaries where you have chosen to differentiate. Change in the DNA of the business can be the most challenging to enact but can also yield the greatest rewards.

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

- **Create the patient-centric C-Suite:** Just like every other transformation it all starts with a public, shared, and specific vision from the top. The C-suite of a successful company must be patient-obsessed regardless of their functional role. This not only communicates the desired behavior to the organization but also helps to ensure that top leaders do not make business decisions that run counter to your commitment to the patient (ruining trust).
- **Create employee-patient stewardship:** 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, and in their role. Integrate this deep into performance metrics and people practices. For example – every employee who joins LEO pharma meets a patient as part of induction.
- **Create and utilize patient-centrism KPIs:** Monitoring progress across quantifiable goals and metrics will help to improve performance. These should become as critical as quality or financial metrics in an organization. The key is asking the right questions to track, then determining how each business function should ladder up to improve patient-centricity. It is also low hanging fruit and a great way to get started.
- **Form partnerships with social and economic value:** Lastly, organizations are more valuable with the information and internal structures to put it to use. Take learnings and form better partnerships. It becomes a virtuous cycle, as pharma can better tool actions with patient needs and shared goals can be realized. Partner types include advisory boards, digital health, pharmacy networks, HCP networks, and government.
- **Crowdsourcing**: has been used since long as a powerful tool to engage the masses in other industries. Wikipedia is one classic example.
- **Focus on patient education, engagement using technology:** US government is encouraging the use of Electronic Health Records (EHRs) via HealthIT.gov and encouraging doctors to use EHRs meaningfully to reduce errors and improve the quality of care. Companies are creating educative websites that can be accessed via mobiles or the internet for educating patients on diseases.

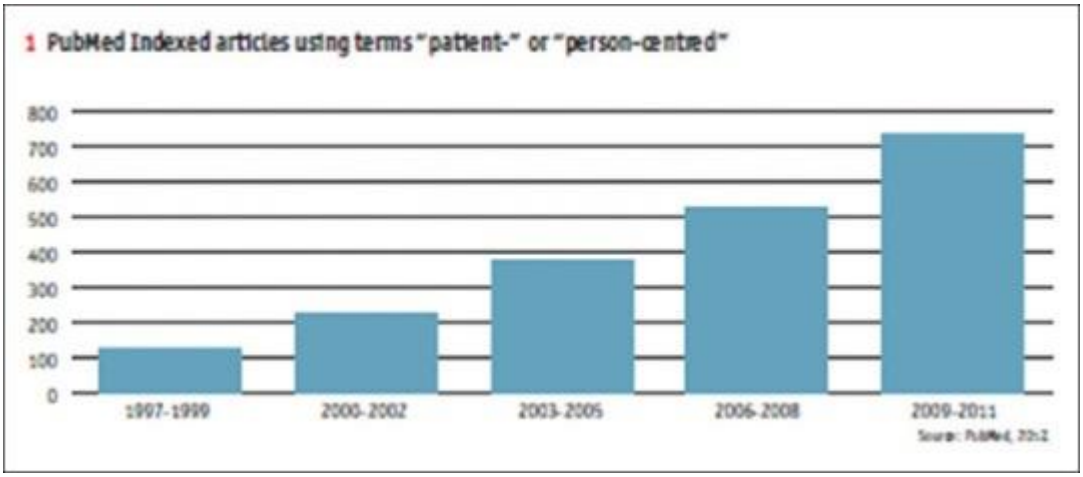
The way clinical research is developing is attributed to a very large extent to technology and its widespread access to the public. Health Patch MD, a wearable biosensor helps in efficient remote patient monitoring. Its sensors and advanced algorithm provide continuous measurement of respiratory rate, electrocardiogram grading, skin temperature, physical activity, heart rate, etc. [1].

Iodine, a health information website established a new web-based application for cold and flu season. The app helps their consumers to review >300 options related to medication for cold and flu and compare all medications that can help cure their own symptoms[2].

Registries for All developed by Genetic Alliance with support from Sanofi works on the principle of matchmaking between patients and clinical trials. The tool provides privacy and flexibility to patients to decide, which groups can have a view/access to their data thus empowering the patients

Treato, a data mining company, checks conversations of patients on Twitter, Facebook, and patient forums and helps pharma companies make sense of data that is being published by millions of patients across the world. The company collects near real-time comments from social media using a combination of patient language dictionaries, natural language processing algorithms, and big data analytics. These conversations help pharma increase insights into patients' lives and focus their efforts in the correct areas of drug development[3]

Patients may have strong inbuilt mechanism where data are pulled from government site such as clinicaltrials.gov each night and it is matched with the list of all registered patients across world helping the patients get better and updated their results pertaining to the trials that might be conducted in their vicinity. The site also offers a forum when open communication and information exchange occurs between patients and feedback can also be shared to improve the trial design [4]



The graph depicts a six-fold increase in the last 12 years related to several searches related to the term “patient-centered” in PubMed.[5]

The pharmaceutical companies that truly strive to become more patient-centric every day will find new ways to delight their customers and improve trust with industry partners. Patient centrism is not a promotional activity. It also cannot be viewed through a solely financial lens. It requires a transformation of the frame of reference through which a company operates.

WEARABLE TECHNOLOGY AND AN ASSESSMENT ON THEIR EFFICACY

There will be 29 billion connected and wearable devices across the world by the end of next year. For the pharma industry, the question of how wearables can be used in Research and Development is high on the agenda. Much of this current interest is related to clinical trials.

Companies are progressively looking to digital solutions to minimize costs, and improve efficiency and trial design, as the size and expense of physician-overseen clinical trials continues to spiral. Wearables, with their comparative low cost, are good example of such digital solution. Many trials incorporate wearables, with promising results for increasing participation and compliance – but questions remain how to use the data collected most effectively.

Increasing trial compliance and patient participation

One of the major barriers to trial participation is the hard requirements around data collection, where patients must travel to a physical location, such as a hospital or GP surgery. Wearable devices linked to mobile apps remove this barrier instantaneously. Wearables have the potential to rise compliance with therapeutic regimes, as participants can obtain ‘reminders’ on their device. The great advantage is that clinical trials can become decentralized, and even ‘site-less’, through this kind of patient-friendly mobile technology.

The benefits are strong; as wearables increase participation and compliance, overall trial efficiency is enhanced. This reduce costs for companies, but also more thorough collection of real-time data, directly from patients. The issue then becomes not one of participation, but of guaranteeing that any data garnered from a wearable during a clinical trial delivers true value.

Unprecedented access to real-world data

Ability to have immediate access to patient data allows trial designers to quickly identify anomalies and trends, or to spot, and act on, a drop-off in a patient’s use of a drug. These trends would have been a lagging indicator through typical clinical means. Additionally, what can be understood about an individual based on this kind of input – whether self-input through an app or monitoring input from a wearable – will transform the way we can therapeutically treat our patients.

The pace at which technology is developing is rapid, and the ability to collect and understand the context of data from wearables, must develop at the same rate as devices themselves. This is critical if the data is to truly be of therapeutic benefit to patients.

Blending science and technology expertise

Development of wearable devices from corporations such as Apple and Google have added to prospects of advancement. However, Google and Apple take a very wide approach to analysis, and simply lack the scientific intellect to reveal true insights from the data.

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. To derive additional information, pharmaceutical companies need a clear data management strategy for data harmonization.

STATISTICS

- 310 million wearable devices were sold in 2017 globally an increase of 17% from 2016, according to the forecast by Gartner.
- Bluetooth headset sales generate the largest number of units sold, growing from 150 million in 2017 to a forecast of 206 million by 2021.
- Sales of wearable devices generated a revenue of $31 billion in 2017, with smart watches accounting for $9 billion

Here is 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 monitor
- 22 million – Sports watch
- 6 million – Body-worn camera

The market for wearables will only continue to improve technologically and become more accessible over the next several years.

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 increase in regulation and scrutiny.

The constant push for national interoperability has assisted fuel the growth of secure healthcare data sharing. 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. Sharing patient data will help decrease readmissions, avoid errors, and decrease duplicate testing attempts. However, pharmaceutical companies need to consider state privacy rules and regulations when it comes to patient data. Violation worries are frequently cited as a main reason for not sharing patient data, different federal agencies are trying to ensure this is not the case.

Companies should understand the potential benefits of secure healthcare data sharing and how they could participate in such a program. Clinical studies using epidemiology disease tracking, cancer disease registries, health management, substance abuse, and even routine care in the emergency could be potential uses for such data sharing. In addition to its clinical use cases, data exchange is vital for ensuring that best practices can be shared between healthcare companies or government agencies. For example, data on different threat incidents including cyber threat incidents can be shared between healthcare companies.

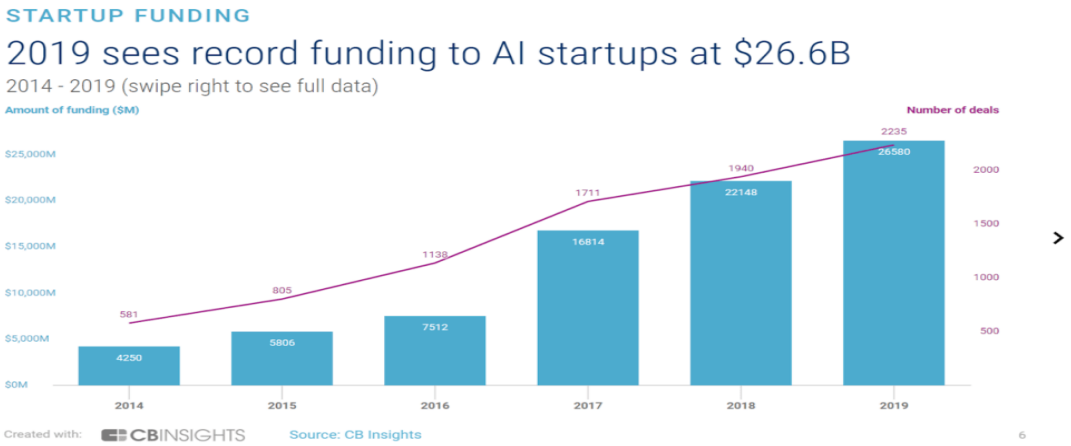
Development healthcare information sharing can aid incident communication and potentially prevent future cybersecurity incidents from happening. Data security are frequently one reason that providers are hesitant to share data. Federal regulations do allow for information to be exchanged in certain circumstances, including ability to access patients own data. Federal regulations must pay a continuous attention how they are expected to securely share data when it comes to providing proper care.

Finally, this is a summary of benefits and disadvantage of electronic data sharing below

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 TECHNOLOGY

Artificial intelligence is advertised as the magic bullet for everything, and the technology may have enormous potential for streamlining the clunky clinical trial process, from remote monitoring, to machine learning. Artificial intelligence has the good potential to modify every stage of the clinical trials, from finding a trial to enrollment to medication adherence. An ideal solution would be special artificial intelligence software that retrieves information from medical records, compares it with current trials, and suggests matching studies. 2019 was a record year for AI investments having over $26B in funding [6].



Artificial intelligence is what we see all around us in computers nowadays: intelligent systems that have been trained or learned how to carry out specific tasks without being clearly planned on how to do so. Many studies still use outdated methods for data collection and verification AI software that extracts relevant information from a patient's medical records, compares it with ongoing trials, and suggests matching studies. The main challenge for environment: trial inclusion criteria is often riddled with medical jargon. A more promising solution is the use of patient-generated data.

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

Pharmaceutical industry leads in adoption of AI, experimenting with applications ranging from machine-assisted diagnostics to getting data from electronic health records. But artificial intelligence adoption is still in its early stages. Many trials still rely on paper diaries for patient information. The goal of artificial intelligence will be to close the gap between what patients have access now and what they need in the long-term to live healthier live.

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. The imperative to ensure that patient privacy is protected by a solid cybersecurity apparatus will become even stronger. **Intellectual property:** The data gathered in clinical trials ultimately decides the competitive potential of the drug, device, diagnostic tool, or vaccine on trial, and as such is considered sensitive intellectual property. If that data is stolen before a treatment is approved and arrives to market, sponsors stand to lose big in market exclusivity. **Company reputation:** After cyber-attack and data was compromised and it difficult for companies to win favor among sponsors.

Healthcare faces larger cyber risks than other industries because of inherent weaknesses in its security posture. It is one of the most targeted sectors globally: more than 110 million patients in the US had their data compromised in 2015 [7]. Only half of these companies believe they can defend themselves from cyberattack, and there has been a 300% increase in attacks during past three years Cyberattacks the healthcare sector is an attractive target for two simple reasons: a soft target and a rich source of valuable data. An aim of cybersecurity should be to strengthen resilience. Companies are less likely to have their security breached and suffer less harm when breaches occur. A simple method to improving resilience is by keeping secure and up-to-date backups, so an attack will not result in the permanent loss of data. A good cybersecurity must be incorporated into the creation of new IT projects from the beginning and must be inherent in all healthcare systems. Cybersecurity can be further boosted by national support. New security standards need to be created for the healthcare sector.

CONCLUSION

Statistics as a discipline for clinical investigation has a long history of over 50 years and has seen impressive development over last twenty years. The development has been with respect to new approaches and improvisation of current methods towards solving new study problems, as well as the scope and span of the application of statistics. The future promises to be exciting, with statistics getting progressively used for real world evidence, expansion of biosimilars, mining of adverse event data, and becoming an essential function in development of new drugs.

Clinical trials have been important in promotion the development of new treatments in pharma and for understanding disease analysis. One significant issue in this area is how they continue to change in a future. Clinical trial reporting has also been regularly developing to increase transparency during clinical trials conduct. Globalization is also having significant effects on the development of clinical research. With this fast-changing environment and progressively complex system, the training of clinical investigators becomes ever more crucial. 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.

In conclusion, the lessons from the past have made clinical studies safer and pay a big role in development of new drugs and treatments. However, in the era of globalization, new ethical challenges rise and require more training programs to continue the development in pharma industry.

REFERENCES

1. Vital Connect, Medidata partner on continuous vital sign monitoring. [Last accessed on 2014 Dec 26].
2. Iodine launches cold and flu app to help consumers find best OTC options for their symptoms. [Last accessed on 2014 Dec 26].
3. Wiggington C. Technology Trends that will Transform Clinical Trials. [Last accessed on 2014 Dec 29].
4. Baum S. Patient -centric clinical trial recruitment tools want to eliminate [medical] language barrier – Simple Language usage advocated. [Last accessed on 2014 Nov 17].
5. “Reinventing Biopharma: Strategies for an evolving marketplace. The patient Led R and D strategy. An Economist Intelligence Unit Report. Sponsored by Quintiles
6. AI in Numbers Q1’20: Global Funding, Corporate Activity, Partnerships, And R&D Trends. CBINSIGHT Research report Q1 2020
7. Institute for Critical Infrastructure Technology. Hacking healthcare in 2016: lessons the healthcare industry can learn from the OPM breach. 2016

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