ScienceDirect

Contents lists available at sciencedirect.com
Journal homepage: www.elsevier.com/locate/jval

VALUE HEALTH. 2019; 22(5):607–610

HEOR in the Broader Context of HTA/CER

Looking Backward 2143-1943: The Rise and Fall of the RCT

Marcellus Pastor,[1,*] Dominus Feneratorius[2,3]

[1]Consultant, New York, NY, USA; [2]9363980 Canada Inc, Ottawa, ON, Canada; [3]University for Health Sciences, Medical Informatics and Technology GmbH, Hall in Tirol, Austria

Editor's note (January 4, 2144): *The following commentary was accepted for publication in December 2143. Although it is not particularly well written, little has been published in scholarly journals discussing the demise of stand-alone human clinical experiments. The title alludes to the enormously popular 1888 science fiction novel Looking Backward: 2000-1887 by Edward Bellamy.*

In the fall of 1943, British scientist healer Philip D'Arcy Hart was asked to investigate whether the fungus *Penicillium patulum*, administered by nasal spray, could "cure" a low-morbidity respiratory disease known as "coryza," which was a viral syndrome largely caused by enterovirii and subsequently eradicated after the introduction of the late 21st-century nano-atomospheric cleansing procedures and modern-day global approaches to atmospheric regulation. This now eradicated and largely forgotten ailment, also called "the common cold," afflicted human populations living in densely populated conditions, such as urban dwellers and soldiers in close quarters, as recently as the mid-21st century. Although not fatal, coryza inflicted maddening discomforts to large numbers of individuals; anecdotal evidence before that experiment led some to believe that the patulin formula would end the host's symptoms and alleviate suffering.[1] To investigate whether this was true, Hart conducted the first blinded randomized controlled trial (RCT) of the 20th century—an approach through which subjects and matched controls could be studied and results analyzed without previous knowledge of treatment assignment by either the subjects or the researchers.

Hart's human experiment took place several centuries after the idea of experimentation had already been widely accepted as a means of understanding causal relationships and physical phenomena[2,3]; this approach to inquiry had been articulated in the 16th century by thephilosopher Francis Bacon and practiced in the 17th century by the pioneering scientist Robert Boyle. And soon after Hart's RCT, "experimental philosophy" became the basis of many similar, sometimes large-scale, clinical trials conducted over the ensuing 150 years. The concept of the controlled trial actually goes back many centuries, with human trials reported in the Jewish Ketuvim (Daniel, Chapter 1) and published principles for testing proposed by Abu Bakr Muhammad ibn Zakariya Al-Razi (ca 841-926).[4] The RCT design addressed difficulties inherent in determining the relationship of an exposure to its observed effects—blinding also addressed error introduced when the nature of the exposure is known either to the patient or to the scientific investigators. Such experimental designs also aimed to identify and compensate for various other known and unknown factors that might contribute to the experimental findings.

The RCT became the basis of government-led regulations introduced in the mid-20th century requiring experimental proof of the effectiveness of new medical treatments before their authorization as therapies for use in human beings. It also became the basis of proof of other healthcare innovation, including new procedures or approaches to service delivery or processes of care, and changes to healthcare structure or governance. RCTs were generally expensive, cumbersome, and inefficient endeavors that tested homogeneous groups of subjects to maximize the ability to detect a treatment effect. To detect a promising signal of proof through statistical testing, the conditions of the RCT could, at times, be quite artificial—that is, the number of patients who were analyzed in some cases was very small in relation to the number of patients who ultimately would be eligible for treatment. Moreover, among those patients recruited for studies, the number of patients whose data were eventually analyzable could also be a fraction of those recruited.

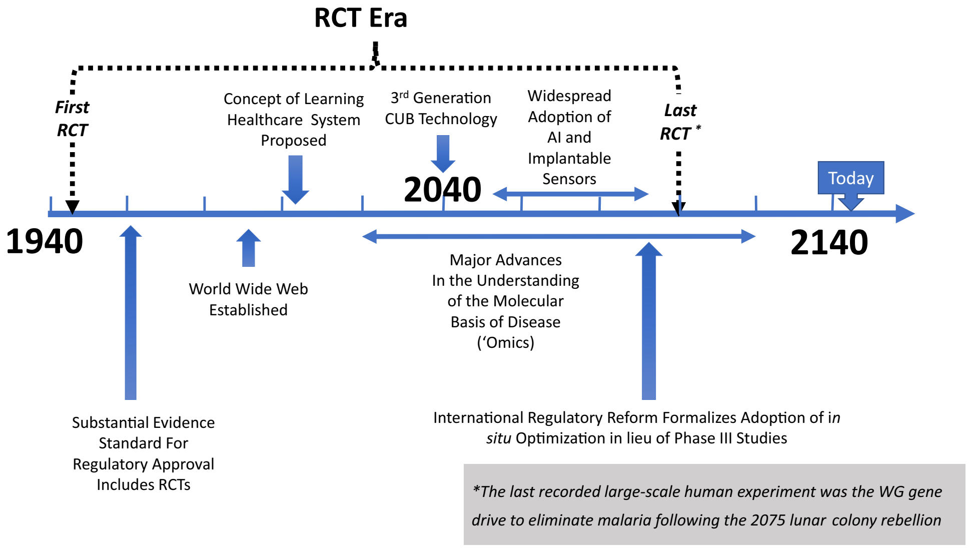
The period of time between 1943 and 2100 can be characterized as the RCT era within medical science (see Figure 1), during which somewhere between 500 000 and 1 000 000 such trials were undertaken. It has been estimated that, despite this seemingly large number of trials, fewer than 10% have actually led to substantial improvements in care. Today, of course, the public is generally unaware of the significance or even the existence of RCTs. The purpose of this brief article was to explore the historical demise of the RCT and to identify some of the factors that may have led to its gradual replacement by other approaches to knowledge acquisition.

---

* Address correspondence to: Marc L. Berger, MD, 301 West 118th St Apt PH2C, New York, NY 10026, USA. Email: mlberger301@gmail.com

https://doi.org/10.1016/j.jval.2018.10.009

Figure 1. RCT era within medical science.



**The last recorded large-scale human experiment was the WG gene drive to eliminate malaria following the 2075 lunar colony rebellion*

AI indicates artificial intelligence; CUB, concentric universal blockchain; RCT, randomized controlled trial.

The Evolution of Healthcare and Data Governance

In the early 21st century, development of information technology (IT) relevant to healthcare delivery greatly accelerated. This shift came relatively late to healthcare and reflected a larger change in public attitudes toward the application of IT as it affected many human endeavors. The disruptive influence of advances in IT was more readily adopted elsewhere at first, resulting in major transformations in standard practices for commerce and education; application of artificial intelligence (AI) and advanced analytics resulted in rapid advances in complex systems such as energy, aviation, and ground transportation.[5]

Enthusiasm in this new IT era led to many early attempts at evaluating medical innovation using “real-world” data. It also led to considerable debate regarding the reliability of these studies. Confidence in these study findings increased slowly and was supported by developments in data quality and analytic standards promoted through multiple initiatives led by private and publicly owned bodies. Although the concepts of a “learning healthcare system,”[6] and ultimately an “experimental society,”[7] were eventually embraced, the establishment of data quality standards required the assumption of control of information systems out of the hands of private ownership and into the public government-sponsored domain. This process took decades and was hindered, in part, by significant private sector investment in and control over a health information infrastructure that embraced high-throughput IT solutions using third-generation concentric universal blockchain technology to protect data integrity and patient privacy. Although these measures provided some level of reassurance to patients that their data were used only for proper purposes, concern remained that commercial third-party use of data might not always align with the public’s best interest.

Support for publicly governed health IT infrastructure was also closely related to debates during the mid-21st century regarding the ability of free markets to provide for various services related to public welfare. This echoes the drama that may be found in debates revolving around the adoption of infrastructure for other domains relevant to the public good. See, for example, a scholarly article by Plaiss[8] dating from the same time period. Western governments initially dealt with these issues through patchwork regulation of privately owned ventures; ultimately, for practical reasons, the entire healthcare enterprise for most countries came under direct public sector control during the latter half of the 21st century. As described by Zelig and Wells,[9] those national populations already accepting of centralized government control (such as China and, subsequently, the United Asian States) were much faster to adopt these systems than were others with powerful privatized centers of control, and help explain “the global leadership of such nations within the healthcare field today.”[9]

Developments in AI, the Use of Implantable Sensors, and the Molecular Basis of Disease

In addition to increased governmental management of both healthcare systems and healthcare data, the silent demise of human experimentation through RCTs also appears to have been bolstered by several important developments: the routine use of AI (including anthropomorphic and other types of interfaces that simulated interactions with human healthcare providers) to enable self-service healthcare for routine problems; the increased demand for integration across other government-run data-driven services, such as education and justice; and, finally, the large-scale use of implantable sensors and robust anthropometry leading to a greatly improved understanding of the environmental, social, and molecular basis of human disease.

To understand the role of these factors, we must first remember that the RCT era, informed by experimental philosophy, was dominated by a scientific view that wholly separated the process of *acquiring knowledge* from the process of *care delivery*. The departure of the RCT represents an epistemic shift toward the proven experiences paradigm and away from the 20th-century ethos of evidence-based judgment informed by stand-alone experiments. Although perhaps difficult for us to imagine today, that is, before the 22nd century, a patient received treatment either informed by accumulated medical knowledge or by participating in RCTs. For many patients, the opportunities for participating in RCTs were few and far between. As a result, technology that promised to improve human health and well-being required sick and *future-sick* patients to wait—while sometimes suffering and dying—until separate studies were carried out. Thus, many individuals with terminal illnesses were in the unfortunate position of not receiving optimal care, including the promise of a potential cure.

During this time, patients also were fully reliant on the judgment of individual human agents (scientist healers or “doctors”), who fiercely debated the impact of new therapeutic interventions through their own personal interpretations of scientific studies. This meant that medical decisions could be far from optimal, relying on fallible human judgment, and without easily monitoring decisions and underlying rationales provided by the AI systems of today. Even more concerning is that medical beliefs were heavily confounded by reputational claims (ie, appeals to authority), intellectual property concerns, deliberate withholding and management of information,[10] and marketing schemes masquerading as science.[11] Although relying on human agents for decisions related to life and death may seem barbaric today, we should remember that many human welfare–related activities at that time also relied on human judgment including piloting vehicles and airplanes, managing wealth and finance systems, and creating and maintaining food supply. One must also be reminded that the ability to separate spurious from useful claims concerning the impact of technology on human health has been quite limited throughout most of the history of modern medicine.

Not only did AI provide consistently higher levels of consumer satisfaction, it also led to marked declines in health-related costs. In healthcare, AI-based care navigation provided a solution to expenditure growth that had outpaced economic growth because of an overreliance on human capital.[12] AI-based care also disrupted the eminence-led paradigm of medical knowledge generation dominated by “doctors,” which had been marked by the proliferation of authors appearing in scientific publications and the delay in adopting practice patterns on the basis of new findings until after these findings were published in prestigious medical journals.[11] One only needs to consult scientific reports of RCTs from the early 21st century to observe that author names occupied a large proportion of their front pages. Author names often commanded more space than was provided for discussion of potential harms (see study by Papanikolaou et al[13]).

Eventually, the concept of a “separate healthcare system” became outmoded altogether as the public gained confidence across many venues in the reliability of AI-based service provision and as recognition that integrating disparate systems advanced public welfare. This was also driven by increased automation within the insurance industry, justice and education systems, and other government-run, data-driven systems intended to maintain or improve social welfare. Rather than a deliberate attempt to extinguish human experimentation and the RCT, the need for separate human-led experiments was simply reduced (and finally eliminated) by the ongoing use of data-driven decisions and the ultimate integration of healthcare and healthcare data with other social programs. By the 22nd century, data integrity was highly standardized across government-led programs, and healthcare data could be readily integrated with other data (eg, temporal-spatial data, financial data, and other domestic data) to allow robust analysis of any and all variables related to individual health and health decisions. Although there was a long-standing recognition that health was socially determined, an accurate understanding of these factors came only with the advent of large-scale data integration.

The demise of the RCT did not occur overnight, insofar as a significant change within the culture of science required a slow process through which those investigators who grew up with a 20th-century notion of clinical research were supplanted by those who came of age of richer medical data characterized by wearable devices, implantable monitors, real-time monitoring and other inputs, as well as the availability of robust advanced analytics and AI. Better data, in turn, led to significant advances during the 21st century in understanding the molecular basis of disease and the interplay of other social and environmental factors. This understanding led to rapid advances in the concept of treatments targeted for small groups of individuals rather than for heterogeneous populations.

As confidence increased in the use of data to automate decisions, demand increased for more and higher quality health-related data as a basis for better decision making. Widespread adoption of implanted sensors made the collection of data a continuous process. Advances in data-driven analysis (originally referred to as “machine learning”) facilitated the processing of this voluminous data into actionable insights. It became more and more possible to predict which patient would experience benefits or harms from particular treatments.

These developments also led to another disincentive for the use of RCTs—RCT design needed to account for all these informational advances, which made it increasingly difficult for clinical studies to be executed. In the early 21st century, many clinical researchers advocated for the widespread application of larger and more inclusive clinical trials[14] (called, by some, “pragmatic clinical trials”) to address the increasingly costly and cumbersome process of gaining timely information from the then standard RCTs. Although it may be difficult to understand why limited resources were not committed instead to the development of an information infrastructure with an eye toward our modern-age system, history is replete with examples of attempts to increase the scale of obsolete technologies—as in the examples offered by fossil fuel–based personal transport vehicles, battleships,[15] and manned aircraft.[16]

Toward a 22nd-Century Health System

The ultimate impact of these developments was a slow and collective realization that the randomization in human experimentation—to account for sources of variation among subjects—was less valuable than in the 20th century when sources of variability were not understood. Rather than being replaced entirely by data-driven systems, the RCT simply became embedded within in situ optimization algorithms within the context of regular healthcare service delivery using real-time monitoring and analysis of benefits and harms. That is, modern AI systems were able to more reliably predict the potential for unexplained variation and, when appropriate, conduct human experiments without the knowledge of patients when and where appropriate. Automation of pharmacy services means that blinding could still occur, if necessary, and predictive and actuarial models that are continually updated mean that individuals do not need to be followed for a lifetime. AI also informed improvements in the evaluation algorithms and analytic judgments used by themselves.

Indeed, it might be appropriate to say that the RCT lives on in the same way the theropod dinosaurs continue to exist as birds to this day. Experiments have simply become embedded into our fully integrated health IT infrastructure on an as-needed basis. This is illustrated by the common use of the term “Zelenation” by systems engineers today when discussing optimization algorithms for healthcare systems. The term is derived from the name of a late 20th-century scientist who proposed a novel RCT design[17] that was seen as difficult or impossible to operationalize during a time when experiments required special supervision and for patients to provide additional consent outside of regular care delivery.

As such, innovators now have a fair and level playing field. Common data systems have created clear signals regarding how a new drug or service will be delivered and what they might be worth. This has, in turn, been cited as a key factor in improving health innovation more broadly (ie, innovation from products, processes, or structural innovations), by allowing better predictions of care value and discouraging both private and public investments in innovation that may lead to suboptimal care. One must remember that the decision to experiment and the feasibility of experimentation, in and of itself, were also largely prone to errors in human judgment with widespread variation in ethical judgments that would even allow experimentation.[18] Harmonizing these judgments is reflected in large-scale international regulatory reforms that took place in the closing years of the 21st century in the United States, Western European Union, and the United Asian States.

In a larger sense, the so-called demise of the RCT was a lagging indicator of a more fundamental shift in the philosophy of medical science. The dominance of "experimental philosophy" in medicine as articulated by Francis Bacon was now complemented by the realization that spurious claims of medical science could be rapidly dismissed through the use of modern analytics of experiential information that is being continuously generated. Experimental philosophy still dominates scientific discovery in other disciplines such as physics, chemistry, and biology, but its dominance in clinical research has waned. In this regard, the RCT should be viewed historically as a stepping-stone to where we have now come and a best effort under historical circumstances. We should not mourn its loss. Rather, it could be viewed as a testimony to 20th-century human ingenuity.

Source of Financial Support

There were no sponsors for this research.

REFERENCES

1. Clarke M. The 1944 patulin trial of the British Medical Research Council. *J R Soc Med*. 2006;99(9):478–480.
2. Galison P, Hevly BW, eds. *Big Science: The Growth of Large-Scale Research.* Stanford, CA: Stanford University Press; 1992.
3. Wittenstein VO. *For the Good of Mankind? The Shameful History of Human Medical Experimentation.* Minneapolis, MN: Twenty-First Century Books; 2014.
4. Tschanz DW. The Arab roots of European medicine. *Aramco World.* 1997;48(3):20–31.
5. Shaddock S. Sensors and sensibility: GE apps are transforming industries. GE Reports. 2018. https://www.ge.com/reports/sensors-sensibility-ge-apps-transforming-industries/. Accessed August 4, 2018.
6. Institute of Medicine (US). Roundtable on Evidence-Based Medicine. *The Learning Healthcare System: Workshop Summary.* Washington, DC: National Academies Press; 2007.
7. Campbell D. Reforms as experiments. *Am Psychol.* 1969;24:409–429.
8. Plaiss A. Who gets to draw the map? The contentious creation of the American road/map system, 1917-1926. *Hist Technol.* 2012;28(1):3–24.
9. Zelig L, Wells H, eds. *Public Sovereignty and the Information Infrastructure: Ascension to Heaven*. New York, NY: Under A House Publications; 2011.
10. Ingelfinger FJ. The general medical journal: For readers or repositories? New England Journal of Medicine Group. http://www.nejm.org/doi/10.1056/NEJM197706022962204. Accessed August 4, 2018.
11. Biagioli M, Galison P, eds. *Scientific Authorship: Credit and Intellectual Property in Science*. New York, NY: Routledge; 2003.
12. Baumol WJ, Malach M, Pablos-Mendez A, et al. *The Cost Disease: Why Computers Get Cheaper and Health Care Doesn't.* New Haven, CT: Yale University Press; 2012.
13. Papanikolaou PN, Churchill R, Wahlbeck K, Ioannidis JP. Safety reporting in randomized trials of mental health interventions. *Am J Psychiatry.* 2004;161(9):1692–1697.
14. Concannon TW, Guise J-M, Dolor RJ, et al. A national strategy to develop pragmatic clinical trials infrastructure. *Clin Transl Sci.* 2014;7(2):164–171.
15. The rise and fall of the battleship (and why they won't be coming back). Popular Science. https://www.popsci.com/blog-network/shipshape/rise-and-fall-battleship-and-why-they-wont-be-coming-back. Accessed August 4, 2018.
16. Will the F-35 be the last manned fighter jet? Physics, physiology, and fiscal facts suggest yes. https://www.forbes.com/sites/toddharrison/2015/04/29/will-the-f-35-be-the-last-manned-fighter-jet-physics-physiology-and-fiscal-facts-suggest-yes/#2038d89b95fa. Accessed August 4, 2018.
17. Zelen M. A new design for randomized clinical trials. *N Engl J Med.* 1979;300(22):1242–1245.
18. Baron J. Against bioethics. https://mitpress.mit.edu/books/against-bioethics. Accessed September 28, 2018.