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Review article

From Nonclinical Research to Clinical Trials and Patient-registries: Challenges and Opportunities in Biomedical Research

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ABSTRACT

The most important challenge faced by human beings is health. The only way to provide better solutions for health care is innovation, true innovation. The only source of true innovation is research, good research indeed. The pathway from a basic science study to a randomized clinical trial is long and not free of bumps and even landmines. These are all the obstacles and barriers that limit the availability of resources, entangle administrative-regulatory processes, and restrain investigators' initiatives. There is increasing demand for evidence to guide clinical practice but, paradoxically, biomedical research has become increasingly complex, expensive, and difficult to integrate into clinical care with increased barriers to performing the practical aspects of investigation. We face the challenge of increasing the volume of biomedical research and simultaneously improving the efficiency and output of this research. In this article, we review the main stages and methods of biomedical research, from nonclinical studies with animal and computational models to randomized trials and clinical registries, focusing on their limitations and challenges, but also providing alternative solutions to overcome them. Fortunately, challenges are always opportunities in disguise.

De la investigación no clínica a los ensayos y registros clínicos: retos y oportunidades en la investigación biomédica

Palabras clave:
Investigación biomédica
Ensayo clínico aleatorizado
Registro clínico

RESUMEN

El mayor reto que afronta el ser humano es la preservación de la salud. La única vía para generar mejores soluciones a los problemas de salud es la innovación, la verdadera innovación. La única fuente de auténtica innovación es la investigación, la investigación de calidad. El trayecto desde un estudio de investigación básica a un ensayo clínico aleatorizado es largo y no está libre de «baches» e incluso «minas». Estos son los obstáculos y las barreras que limitan la disponibilidad de recursos, dificultan el proceso administrativo-regulatorio y constriñen las iniciativas de los investigadores. Asistimos a una creciente demanda de evidencia que guíe la práctica clínica, pero paradójicamente acometer investigación biomédica se hace cada vez más complejo, caro y difícil de integrar a la práctica clínica, por el aumento de las barreras a la realización de los aspectos prácticos de la investigación. Nos enfrentamos al reto de aumentar el volumen de la investigación biomédica y al mismo tiempo mejorar su eficiencia y sus resultados. Este artículo revisa las diferentes etapas y modalidades de la investigación biomédica, desde los estudios no clínicos en modelos animales o computacionales a los ensayos aleatorizados y registros clínicos, centrándose en las limitaciones y los retos a los que se enfrentan, pero también aportando soluciones y alternativas que pueden ayudar a superarlos. Afortunadamente, los retos son siempre oportunidades disfrazadas.

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Abbreviations

EHR: electronic health records
RCT: randomized clinical trial

NONCLINICAL INVESTIGATION IN MEDICAL THERAPEUTICS

Animal research has been the fulcrum of controversy from the outset. In 1543, Andreas Vesalius published *De humani corporis fabrica* (On the Fabric of the Human Body), and in doing so not only founded modern human anatomy as a scientific discipline but simultaneously placed in question the value of comparative anatomy. He insisted that study of human anatomy required dissection of humans and not close relatives such as apes. Major anatomical findings abounded thereafter but little in the way of animal investigation for medical science. Some 230 years later, the naturalist Stephen Hales described the first measurement of blood pressure. In volume II of Statical Essays,[1] he explained how he inserted brass tubes into the crural artery of a restrained, awake mare, and how he then fitted a glass tube into the brass tubes to accommodate the column of rising blood, observing and recording the oscillations in the rising column as a quantitative measure of blood pressure. He did not continue his research, however, focusing his naturalist tendencies on less animate objects, like plants, as his vivisection was greatly criticized. In 1718, his good friend the poet Alexander Pope, a renowned dog lover, reportedly said of Hales: "He commits most of these barbarities with the thought of their being of use to man. But how do we know that we have a right to kill creatures that we are so little above, such as dogs, for our curiosity, or even for some use to us?"[2]

It was the nineteenth century that propelled animal work, first through the pioneering efforts of the physiologist Claude Bernard, and then intriguingly through Charles Darwin's theories of evolution. Contrary to prevailing thought, Bernard insisted that all living creatures were bound by the same laws, and in a manner like inanimate matter, and Darwin hypothesized the descent of man from previous forms. Both thought processes suggest that there is much that can be learned from animal physiology of human processes, as the driving forces and laws of nature are preserved even when the anatomy differs. Both Bernard's and Darwin's ideas make the case that fundamental truths of the human condition could well and perhaps even more cleanly be examined in living animal systems. Bernard actively pursued animal work even in an era preceding anesthesia and discovered from this research the digestive properties of the pancreas, the glycogenic function of the liver, and the vasomotor system, creating the concept of *milieu intérieur*, which Walter Cannon was to term *homeostasis*. For his science and methods, Bernard is revered to this day, but for his embracing vivisection even his wife and daughter were to vilify him. Darwin was well aware and conflicted in understanding that his theories enabled and in part stimulated the use of animal work.

The advent of anesthesia removed the obvious and readily apparent aspect of the cruelty of absent pain management and enabled greater control over state and reproducibility of effect. Today, the harnessing of the controlled environment of animal work is essential to advance medical therapies including the optimization of life-saving medications such as insulin and virtually every impactful medical device. This is not, however, because animals can model human disease, as there are no models of human disease except in the human. There are no animal models of human disease. Rather, animals are beneficial because they enable what can rarely be performed in human clinical trials–testing in a precise framework of hypotheses regarding mechanism of action. Just as efficacy and safety can be hinted at in animals but only proved definitively in humans, the reverse is true of mechanisms. Hypotheses about mode of action can rarely be proved in the extraordinarily variable human conditions; they require controlled environments where many conditions can be held constant and ideas can be tested, ie, animals. Animal experimentation is critical because it is in these living beings that physiologic concepts can be validated in a manner that could not otherwise be tested. However, the value of such study necessitates that it be performed only with absolute commitment to respect for living beings and precision of trial execution. Inappropriate models, eg, ones where comparisons cannot be made, where the physiology is fundamentally different, inappropriate control of animal experiments, where poor or improper attention to animal needs is not only cruel and unethical but inevitably taints the results because distress states are uncontrolled, and where there is no human follow-up, all invalidate their value. In fact, once an animal trial is performed and confirmed, human trials must be performed to define safety and effect compared with predicate forms. This is an important, not a passing, caveat. Just as one should seriously worry when clinical trials are performed without the mechanistic support from animal work, so too should one consider that successful animal work that is not followed by clinical trials is wasteful and disrespectful. Thus, animal work should not be performed when there is no hope of a translational impact of its own or anticipation of ultimate clinical validation.

Here then are the modern dilemmas–what is to be done when animal work is so far from the human experience as to require creating devices unique to the animal, and then how should we consider the current rush to clinical trials before complete comprehension of effect? To a large extent, these are different sides of the same coin. The testing, for example, of percutaneous heart valves is significantly limited by the stark difference in the anatomy of the aortic arch between quadrupedal sheep or swine and upright, bipedal man. Valves that are to be considered for use in people are exceedingly difficult to insert through the steeple-like aorta of the former, limiting the usefulness of the animal model. Insistence on performing animal work with these devices might require the creation of devices that could only be used in animals. Such a solution is unnecessary and distracting. Distraction resides in the pursuit of an irrelevant model but the unnecessary aspect is because the animal is not the only nonclinical model and its inaccessibility does not mean that one cannot validate basic operational and mechanistic issues before human use. There are a multitude of even more appropriate models available on the bench and *in silico* that can provide conceptual insight before human trials. Eschewing these preclinical alternatives in favor of premature clinical testing is a violation of scientific method.

At the same time, the rush to perform trials has created a countervailing set of issues that are potentially equally damaging. The endovascular implant experience has fueled cardiovascular intervention in the most extraordinary way, propelling vascular biology and medical science in parallel with innovative technology. The hallmark of this experience, though, is deep attention to precise multimodal and multidimensional preclinical evaluation before pivotal human trials. The critical preclinical evaluation of bare-metal stents preceded clinical trials and Food and Drug Administration (FDA) consideration and approval by 5 years, and the first definitive publication of the promise and mode of action of drug-eluting stents came 5 years before FDA approval of these devices.[3,4] When issues arose with these devices, there was an abundance of animal, benchtop, and computational work to direct further clinical evaluation. In contrast, the same cannot be said for renal denervation and, to a lesser extent, for bioerodible scaffolds. The Simplicity III HTN trial was performed with rigor and care, and

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