Benefits and ethical concerns associated with methods and models of biomedical research and therapeutics

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Abstract
Although the focus of biomedical researchers is diverse, the overall aim is to address several questions that may translate into clinical practice for the benefit of both human and animal health. The history of biomedical research is longstanding and comprises numerous Landmarks. Biomedical research as we know it today, uses ultra integrated approaches and experimental models and methods with very different but complementary functions. These methods include in vitro/cell culture, in vivo/experimental animal models and the mathematical modeling/computer simulations. These models have also made a huge difference in biomedical research and therapeutic strategies. Despite the benefits of these models of biomedical research to human, many ethical matters arise in their use. The ethical concerns tend to come up only when researchers virtually steer issues with extensive hands on life. This review work explores the benefits of models of biomedical research and their ethical dilemma involved in their use in research and therapeutic strategies.

Key Words: ethical concern, bioethics, therapeutics, biomedical research, models.

Introduction
Although the focus of biomedical researchers is diverse, the overall aim is to address several questions that may translate into clinical practice for the benefit of both human and animal health. Existing research methods and models have been extensively explored, while emerging new techniques are developing. Thus, contributions made in the biomedical research process answers questions of biological uncertainty and is critical to the advancement of human and animal health. Specific methods or their alternatives in biomedical research and therapeutics remain a needle in a haystack. In the process of discovery and consolidation of vaccine manufacture, practically all levels and models of biomedical research are employed. In recent times, the concept of complementarities is of increasing

Fundamental importance in biomedical research and therapeutic activities. While few specific problems can be faced entirely using a particular research method, biomedical research remains an integral activity with specific goals and objectives. Our article verifies the effective growth in benefits and ethical concerns accruing from major complementary methods and models in biomedical research and therapeutics.

Historical Perspective
The history of biomedical research and therapeutics is longstanding. The practices come from a very remote period with even a biblical inference on King Nebuchadnezzar’s diet therapy in 500 BC. In fact, that
which could be referred as the first recorded biomedical trial took place just from the King’s order to keep a diet of only meat and wine which he believed would give his people better physical well being. Some objectors of royal blood who preferred to eat vegetables were however, allowed a diet of legumes and water. After 10 days of experiment, the legume diet appeared as better nourishment than the meat diet.[1] Supposedly, the experience of the diet therapy enriched the King’s treasure of knowledge and his subsequent decisions for the health of his people. Since the King’s experience up to our time, biomedical research and therapeutics has had constant progress, passing through what could be termed unplanned and un-detailed experiments to randomized and controlled trials. All in all, the guiding spirit of the progress of biomedical research and therapeutics has been evident in ever increasing benefits of its practices for the general well being.

Landmarks in the history of biomedical research and therapeutics may include: the Ambroise Paré experiments in 1537 which disproved the alleged healing qualities of unicorn horns. The discovery using boiling oil to treat gunshot wounds had a negative effect.[2] The James Lind experiments in 1774 used oranges and lemons for the prevention and cure of scurvy.[3] The Austin Flint experiment in 1863 engaged the placebo effect for the treatment of rheumatism.[4] The Medical Research Council (MRC) UK experiment in 1943 used extract of Penicillium patulinum for the treatment of common cold and the Medical Research Council (MRC) UK experiment in 1946 used Streptomycin in the cure for Tuberculosis. This 1946 UK randomized controlled trial (RCT) methods has affected virtually every area of clinical medicine. [5]

Today, biomedical research and therapeutics encompass an extensive cluster of endeavours channeled to better human and animal medication. Thus, biomedical research and therapeutics could be said to embrace the general health care system. It is a broad area of science that looks for ways to prevent and treat diseases that cause illness and death. However, the evident benefits of biomedical research and therapeutics manifest in the enormous improvements in healthcare. This is due to better science knowledge deriving from increased activities of scientists to keep researching for innovations for better health and longer life. On the other hand, concerns on possible trespassing of ethically acceptable confines on the manipulation of life itself remains real. This is largely because to take biomedical research and therapeutics as a field involving only clinical trials merely as in its early history, would mean remaining on a perspective to the detriment of the evolutionary process going on in medical research. Today, we have experimental medicine, biotechnology, bioengineering and a lot of other specialties globally making up or aiding the activities of biomedical research and therapeutics. The Human Genome Project, cloning, stem cell and fertility research activities are examples. There is no doubt, the new horizons of biomedical research is open to enormous therapeutic benefits, as well as to disruptions and or displacements in nature. Hence, as new horizons of biomedical research and therapeutics optimistically arise, there are ethical concerns for ethical guidance in research.

The first bold and broad ethical guidance to researchers was in 1947 as the Nuremberg Code. The code, is a set of research ethics principles for human experimentation during the Second World War, implemented to curb the atrocities of human experimentation which were committed.[6] In 1964, the World Medical Association (WMA) declaration of Helsinki, enabled ethical principles for medical research involving human subjects. From this period, the Helsinki declaration has passed several amendments among which: the amendments in October 1975 by the 29th WMA General Assembly in Tokyo, Japan; October 1983 by the 35th WMA General Assembly in Venice, Italy; September 1989 by the 41st WMA General Assembly in Hong Kong; October 1996 by the 48th WMA General Assembly in Somerset West, Republic of South Africa; October 2000 by the 52nd WMA General Assembly in Edinburgh, Scotland; October 2002 by the 53rd WMA General Assembly in Washington DC, USA; October 2004 by the 55th WMA General Assembly in Tokyo, Japan; October 2008 by the 59th WMA General Assembly in Seoul, Republic of Korea and finally the amendments in October 2013 by the 64th WMA General Assembly in Fortaleza, Brazil.[7] The frequent amendments suggest vivid consciousness of ethical problems amidst the progress and prospects of biomedical research. The growing ethical concerns can no longer be minimized, if considered from the causative fact of growing multidisciplinary nature of biomedical research and therapeutics. As biomedical research and therapeutic activities grow in scope, benefits and prospects, ethical concerns mount on the experimental models of application interaction and influence on our existence.

**Complementary Experimental Models in Biomedical Research/Therapeutics and their Benefits**

Biomedical research, uses ultra integrated approaches and experimental models with very different but complementary functions. In this essay, to limit the multidisciplinary scheme of biomedical research, we would uphold the fact that its activities can be investigated under three broad levels: molecular, cellular and organism. Each of these levels of investigation is characterized by the use of models which provide specific answers to integrated effective knowledge for disease cure and increased longevity. Basically two broad experimental methods, namely, *dry lab* and *wet lab* encapsulate the activities of biomedical research on all levels (molecular, cellular and organism). The *dry lab* is based on the use of computers and information technology on biological research activities. The *wet lab* is based on the use of purified molecules, cell cultures, per fused organs as well as animal organisms including humans. These methods are in turn divided into, *in vitro, in vivo* and *in silico.*
Use of in vitro cell cultures

In vitro refers to the technique of performing a given procedure in a controlled environment outside of a living organism”.[8] The in vitro method is that which makes use of isolated organs and per fused ex vivo organisms. Examples of the in vitro method are cell culture and tissue culture, providing model systems for studying the normal physiology and biochemistry of cells and tissues. Perhaps the simplest truth regarding the benefits and merits of the in vitro method is that great steps all through the history of modern biomedical research and therapeutics may not have been realizable without in vitro applications.

The use of in vitro cell culture is of paramount importance in biomedical research. Provided appropriate measures are taken in terms of media used, serum, antibiotics and right temperature, CO2 and humidity, cell culture is a versatile tool used in cellular and molecular biology, providing excellent model systems for studying the normal physiology and biochemistry of cells, including metabolisms and aging. In addition, the effects of drugs and toxic compounds on the cells, mutagenesis and carcinogenesis can be evaluated using cell cultures. It is also used in drug screening and development, as well as in large scale manufacturing of biological compounds including vaccines and therapeutic proteins. Hence, the importance of in vitro cell cultures in biomedical research cannot be over emphasized. For instance, consistency and efficient reproducibility of results that can be obtained from using a batch of clonal cells is of importance not easily forfeitable in the field of biomedical research.

Use of in vivo/experimental animal models

In vivo experiment otherwise known as “within the living” in Latin, is the use of the whole living organism rather than partial or dead organism. The two types of in vivo experiment are animal studies and clinical trials. It is believed that in vivo studies often has the potential to offer conclusive insights about the nature of medicine and disease.[9] Generally, the need for in vivo experimental models is crucial in the study of human pathology, both for what relates to the etio-pathogenesis and for what concerns the therapy. This method has proved fundamental for the progress of biomedical research, placing animal testing as a pivotal subway for critical clinical trials. Although animal activists oppose the use of animals for biomedical research, experimental animal model has made a huge difference in the development of therapeutic strategies. Evidently, experimental models of disease in animals are used to extrapolate to the human situation. The procedure allows to evaluate the effect of the experimental drug substance in a much more comprehensive and meaningful manner than would a hypothetical cellular model. Therefore, the biomedical trend is to use in vivo experiments for the pathogenesis of disease by comparing the effects of bacterial infection with the effects of purified bacterial toxins; the development of antibiotics, antiviral drugs as well as other new types of drugs. The in vivo method reaches forth to new surgical procedures. For instance, through the use of experimental animal models greater knowledge of surgical level of the heart and central nervous system are at the disposition of scientists.

Animal studies/models are also necessary for research that seeks to understand complex questions of disease progression, genetics, lifetime risk, or other biological mechanisms of a whole living system that would be unethical, or technically unfeasible to allow the use of human subjects.[10] Therapeutic strategies based on the use of stem cells of different origin in surgery, in animal models have enabled creation realistic enough to ischemia at the level of major organs such as the heart and brain. Models such as these are used for the development of pharmacological interventions in therapeutic value. With these types of experimental models, it has recently been possible to demonstrate the cardio-protective effect of administration of recombinant erythropoietin and its non-erythropoietic derivatives. Furthermore, it is virtually impossible to study the underlying mechanisms of sensations such as appetite and satiety, pain, sedation, or psychological situations such as depression, without utilizing in vivo models that mimic this physiological or pathological state of being. The research and the use of appropriate experimental animal models has been the basis for the development of entire classes of drugs. The clinical use of anti-hypertensive drugs would be non-existent if we did not have access to models that would allow us to examine the mechanisms underlying the phenomena of arterial and venous pressure. Also, think of the possibilities of studying the pathways of neuronal transmission of stimuli engines or noxious stimuli without the use of in vivo/experimental animal models.

Mathematical modelling and computer simulations (the in silico method)

The in silico method denotes computer simulation experiments. The term in silico has been in use since 1989 when Pedro Miramontes, a mathematician from National Autonomous University of Mexico (UNAM) used it as a methodical expression for utter computerized biological experiments. Though it is the most recent in biomedical research activities, it already has a very vast application. For instance, “in silico models for predicting toxicological, biological and physico-chemical properties are models able to find relations between particular characteristics of molecules and the property of interest”.[11] These belong to in silico methods, the bacterial sequencing techniques—alternative to in vitro methods for identifying bacteria, for example, the polymerase chain reaction (PCR); the molecular modeling technique—that demonstrate how drugs and other substances interact with the nuclear receptor of cells; the whole cell simulation techniques—using computer models of bacterial cells to test the response to sugar, simulating the behavior of living cells. Recent use of mathematical modeling, database analysis, and computer simulations in biomedical research is increasingly aiding in research and therapeutics. These
computational methods are utilized to analyze large volumes of historical experimental data in order to highlight biological trends and high priority research objectives. They also serve to compile large volumes of experimental data into virtual biological systems and networks. Within the bounds of current knowledge, they are capable of making predictive assessments of research questions.

The use of recombinant DNA technology by scientists worldwide to follow the inheritance pattern of specific DNA sequence differences in families with genetic diseases for which neither the gene nor the biochemical defect is known is not left out. Recombinant DNA technology opens new vistas. Scientists hope to use the technology to find the causes of many diseases that cannot be prevented or treated satisfactorily today. Furthermore, the use of Nuclear Magnetic Resonance (NMR) tools is not only restricted in research laboratories to study chemicals in test tubes but also in conjunction with computers to provide detailed pictures of the body’s interior. Its application in diagnosis as Magnetic Resonance Imaging (MRI) and radio frequency energy has aided in the provision of more information about the biochemical state of tissues and organs. It may also help diagnose some types of stroke earlier and better, reveal disease buried in dense bone, expose tumours and determine if these are malignant or benign. It also indicates whether a heart attack has occurred and how much damage it has caused.[12]

All in all, some of the benefits of biomedical research can be seen with traditional measures of health and well-being, such as morbidity and mortality rates. Generally, people around the globe are living longer and are less likely to succumb to the scourges of the past. Nowadays, there is fast identification of many illnesses due to better diagnostics. With this improved diagnosis comes a better prognosis for treatment and recovery. Though for many diseases the rates of incidence are not decreasing, the outlook for patients has dramatically improved. Patients of many diseases live fuller and better lives due to improved methods of treatment. Furthermore, though quality of life is harder to summarize in a single statistic, the benefits of advancements in biomedical research and therapeutics are extremely important to the process of disease and their environment.

Some of the most profound advances, e.g., the isolation of human stem cells and the mapping of the human genome, has demonstrated the vast therapeutic potential. Major benefits of biomedical research are among others, vaccines for measles and polio, insulin treatment for diabetes, classes of antibiotics for treating a host of maladies. The benefits also include medication for high blood pressure, improved treatments for AIDS, statins and other treatments for atherosclerosis, new surgical techniques such as microsurgery, and increasingly successful treatments for cancer. New beneficial tests and treatments are expected as a result of the Human Genome Project.[13] Hence, in front of facts and prospects, the increased longevity of humans over the past century can be significantly attributed to advances resulting from biomedical research and therapeutics.

**The Ethical Concerns**

Awareness relating to ethical issues in biomedical research and therapeutics has manifested even since the symbolic diet therapy of King Nebuchadnezzar.[14] The objectors of the King’s order to keep a diet of only meat and wine doubtlessly delineate some dose of ethical concern; their preferring to eat only vegetables, legumes and water show convinced vegetarian moral stance perhaps in spite of their knowledge of the obscure benevolent facts of the King’s therapy or potential health benefits of their own diet. However, ethical concerns on biomedical research and therapeutics were initially sporadic. There was less to debate alongside the potential health benefits from the field. Ethical concerns tend to come up only when researchers virtually steer issues with extensive hands on life. Hence, virtually the evolution of the field is the evolution of the manipulation of life whereby, every step is ethically considered according to its approach and its experimental models.

The in vivo approach and its experimental models has the most distinct and perhaps the most disputed ethical concerns. Its first ethical debates relate to issues in the use of animals in biomedical research. As early as 500 B.C., Greek writers have already expounded precious knowledge of the physiological processes and the inner working of animals gained through dissection of living animals by physician-scientists. Using vivisections to test specific hypotheses and explore biological phenomena, researchers of all ages have been able to make important discoveries in the study of anatomical structures, for biomedical research and therapeutics. Though the early stages of the practice did not meet relevant ethical opposition, it has not always been the case. Perhaps, this is because researchers were more inclined to embracing conceptions like the Cartesian notion that animals lacked souls. Animals could certainly be taken as non-sentient automatons incapable of experiencing pain or pleasure like humans. Biased by the sentiment of the epoch, the first sustainers of animal use such as Claude Bernard had no more than the mere argument that the sacrifice of animal lives was essential to the advancement of medicine.[15] On the other hand, since the mid 19th century, ethical concerns regarding uses of animals in biomedical research has increasingly exposed doubts on the metaphysical exclusion of non-human animals from the capabilities of sensation (of pains, sufferings and emotions). Since the mid 19th century, moral debates regarding the use of animals in biomedical research has had favourable philosophical grounds from the utilitarian viewpoint. Masterminded by philosophers like Jeremy Bentham and John Stuart Mill, the utilitarian masters evoked doubts on whether animals truly lacked sentient capacities of pain and pleasure. They evoked the idea of moral community where the sentient capacities establish the defining features of membership. They
advanced the notion that all pain and suffering (including pains and sufferings experienced by animals) are important in the assessment of moral rightousness of actions. Based on the utilitarian stance, actions morally upright maximize pleasure, (the utilitarian moral good). Actions morally wrong, maximize pain (the utilitarian moral bad). Effectively, it could be said that all trends against the use of animals for biomedical research owe something to the utilitarian philosophy. The unfortunate bias and prejudice befalling animal use for biomedical research remains indeed, a conceptual dispute.

Advancements in the field of biomedical research and therapeutics seldom come without bias and prejudice. The in vivo experiment maximizes the alarming rate of ethical concerns, especially when allegations are involved. History shows that without adequate constant monitoring, cruel use of humans for research purposes could be made. In fact, the Nazi use of humans for biomedical research in the 1940s induced the World Medical Association to come up with ethical codes that would guide for medical research with human subjects. The first of these codes, the Nuremberg Code—1947 came up in ten points among which voluntary consent, fruitful results by other methods or means of study, properly formulated scientific experimentation, absence of unnecessary physical and mental suffering, injury and death are made to stand out as important ethical points where human experimentation is involved.

As ethical concerns in all situations especially, concern for the risk of disease and other complex ethical concerns relative to genetic engineering and the inevitable ethical concerns relative to genetic engineering of human embryos. No doubt, issues like this open to preoccupations regarding wide ranging dimensions of biomedical research in the spheres of the in vitro and the in silico.

The in vitro and the in silico research attract echoes of ethical concern more on questions of the possibilities and prospects of the manipulation of embryos, especially the human embryos. Focusing on the term of genetic engineering of human embryos, seldom ethical concerns regarding genetic engineering do not exclude the practices of in vitro fertilization of human embryos and embryo screening. The fascinating possibilities offered in this field are also enticing to the point of creating situations of real ethical dilemma. Think that non-infertile people in today’s society including both male and female homosexual couples, single men and women, and post-menopausal women are seeking for assisted reproduction. The practice enables children to be conceived, who have no genetic relationship to one or both of their parents. Children can also be conceived who will never have a social relationship with one or both of their genetic parents, e.g. a child conceived using donor sperm. These create unceasing ethical concerns in all situations especially, concern for the child and his or her welfare, including the right to have one biological mother and father. “The fragmented family created by certain assisted reproduction can disconnect genetic, gestational and social child-parent relationships which has typically been one and the same in the traditional nuclear family”. [17]

Equal reverberation of ethical issues come from the Human Genome Project (HGP). Today, HGP and the research community at large are faced with numerous ethical questions in genome research. Questions such as: “what are the ethical and legal implications of using our advancing knowledge of genetics to, enhance human by replacing or repairing the genes associated with increased risk of disease? Is enhancement ethical for certain sub-populations, such as the aging, but not for others? Can eugenics, the science of selectively breeding superior human with better genes ever be used ethically, or is the concept inherently discriminatory? Will cloning be used to improve the genetic makeup of individuals, or are the ethical considerations too divisive? What does stem cell research portend for the future of regenerative medicine? [18]

The National Human Genome Research Institute (NHGRI) is presently assisting in addressing the above mentioned questions by funding examination of issues that are related to manipulation of human genetic materials. Information and other controversial topics as genetic engineering and enhancement is available. Nonetheless, issues related to stem cell research and cloning are yet to be addressed. It is remarkable that knowing the possibility of misuse of information by research personnel, NHGRI established the Ethical, Legal and Social Implications (ELSI). The organisation inform the development of federal guidelines, regulations and legislation to safeguard against misuse of.

http://www.jabsdirect.com
genetic information. [18]
There are other numerous institutions established for ethical matters in research. For instance, Guidance for Ethical Conduct in Aboriginal and Torres Strait Islander Health Research in Australia, is an institution designed to provide guidance to researchers. Human Research Ethics Committees (HRECs) and Aboriginal and Torres Strait Islander, specific HREC’s or subcommittees on the conception, design and conduct of research; the National Health and Medical Research Council (NHMRC), designed to assist Assisted Reproductive Technology—ART, (a laboratory or clinical technology to gametes and/or embryos for the purposes of reproduction). All reproductive medicine units offering ART services comply with the NHMRC Ethical Guidelines in use of assisted reproductive technology in clinical practice and research. NHMRC also guide certain institutions on issues of ethical matters for research involving human fetus or human fetal tissues. Although NHMRC has a primary focus with privacy in relation to research, it tends to balance the need to facilitate access to data for research purposes. [19]

Summarily, in past and present times, the major area in which value conflicts are never lacking is the spectrum of ethics. Today more than ever, there exists stimulus for value conflicts in our societies concerning social and ethical evaluation of novel practices in biomedical research. Obviously, as science and technology improve, cultures and traditions seem hardly prepared to cope with the rapid value alteration. Value divergence is taking place within the ethic of societies. [14] The solutions to the debates in ethical matters are rarely straightforward and involve complex trade-offs for scientists, clinicians and health care organizations. How such questions are answered strikes at the heart of what it means to conduct biomedical science and deliver health care with human decency and fairness.

Conclusion
Biomedical research and therapeutics poses evident and continuing ethical issues that need to be addressed constantly. We believe, regulating and raising the profile of ethical practice is the most effective way of protecting both researchers, consumers and maintaining professional standards. Evidently both researchers and participants await the conclusion of the unfinished ethical debate. The methods and models used in the progress of basic biomedical research and therapeutics is constantly progressing. As biomedical research and therapeutic activities grow constantly in scope, benefits and prospects, ethical concerns will continue on the experimental models and applications of biomedical research. The extent to which ethical issues can interact and interfere influences our existence.

Finally, it is noteworthy that the worthwhile recognition of funding agencies and national healthcare institutions need be relentless in the vital field of biomedical research and therapeutics. The increase in funding and provision of modern research facilities is encouraging for future medical and scientific research. Scientific developments in the next decade will be the true testament of the success of current translational biomedical research programs.

Conflict of Interest: None Declared

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