Review Article

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Global comparative healthcare effectiveness research: Evaluating sustainable programmes in low & middle resource settings

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The need to focus healthcare expenditures on innovative and sustainable health systems that efficiently use existing effective therapies are the major drivers stimulating Comparative Effectiveness Research (CER) across the globe. Lack of adequate access and high cost of essential medicines and technologies in many countries increases morbidity and mortality and cost of care that forces people and families into poverty due to disability and out-of-pocket expenses. This review illustrates the potential of value-added global health care comparative effectiveness research in shaping health systems and health care delivery paradigms in the "global south". Enabling the development of effective CER systems globally paves the way for tangible local and regional definitions of equity in health care because CER fosters the sharing of critical assets, resources, skills, and capabilities and the development of collaborative of multi-sectorial frameworks to improve health outcomes and metrics globally.

Key words Comparative effectiveness - low income countries - observational studies - research methods - technology assessment

Introduction

Historically, clinical research has provided objective scientific information to healthcare providers about a specific disease condition in terms of its diagnosis, symptoms, manifestations, progression, management, and treatment. This in turn provides the consumers and caregivers a variety of alternatives to evaluate and choose the most appropriate treatment for a specific condition. However, amidst a lack of clear evidence of comparative effectiveness between disease-specific or system specific strategies, the process of making choices that maximize value to the individual while balancing the needs of society for health care equity becomes challenging or impossible[1-6]. Comparative effectiveness research (CER) informs patients, providers and

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caregivers about the most effective treatment option available in a given circumstance by assessing wide-ranging health related outcomes by comparing different interventions such as medications, procedures, medical devices, technologies, behaviour change strategies, and health care delivery systems[7,8]. CER is defined as: "*the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels*"[6]. This definition indicates that CER must involve direct comparisons between established treatment(s) and valid comparator treatment(s) to show the real marginal benefits of proposed treatment(s). Also, to generalize CER results to an entire healthcare system, the research subjects included in CER studies should be adequately representative of the patient seen typically in different clinical care settings, as appropriate for the circumstance under study[9].

The variability of implementation of treatment options is partly responsible for differing costs and outcomes. The need to reduce the ever mounting healthcare expenditures along with an efficient usage of the existing therapies is one of the major drivers stimulating rigorous CER across the globe. CER establishes rigorous criteria for the mode of implementation of different options, thus creating a uniform and consistent basis for comparing outcomes. CER conducted in highly resourced nations provides a framework for low- and mid resource countries to establish and manage an efficient and sustainable comparative effectiveness (CE) programme[10].

CER & drug development

The process of drug development has been evolving rapidly in recent years. In addition to approval of a drug by regulatory authorities, pharmaceutical companies are witnessing a trend whereby private and public payers are subjecting drugs to health technology assessments (HTAs) to better define their utilization and usefulness in different populations. CER can serve as a tool to perform value based appraisal of HTA and for determining reimbursability.CER employs a "real world" comparison of an upcoming drug or technology with an existing one as a basis to evaluate multiple outcomes of interest for individuals and society. The application of CER thus could be thought to lend holistic appeal to the process of manufacturing pharmaceuticals.

One approach to accelerate knowledge acquisition about the exact cost effective applications of drugs would be to encourage pharmaceutical and medical device developers to modify the standard existing R&D (Research & Development) pathways by designing post-market observational research methods aimed at demonstrating real-world value, addressing multiple investor demands, and formulating a transparent and standardized CER evaluation protocol. The long-term goal of CER should be to steer R&D towards innovation and production of value based products that meet the needs of both the patients and investors[11].

CER and continued medical education of physicians

CER provides a useful aid to physicians to frame and practice evidence-based recommendations specific to unique circumstances faced by patients[12]. Amidst numerous pharmaceuticals and medical technologies, CER assists physicians to recommend options after considering cost effectiveness and safety through the results of CER. Useful outcomes of CER studies can be user friendly, web based decision-making tools that enable the physician to share with the patient the process of entering personalized key parameters found to be useful determinants of efficacy and cost effectiveness. One study[13] showed that physicians arrived at the consensus that CER is an especially useful tool for subpopulations that show variations in treatment response. Once a CER study is conducted, the next equally important step towards widespread utilization of the findings is prompt and targeted physician and health care practitioner education about the study's findings. Part of promoting CER hinges on instilling a culture whereby there is open-mindedness about potential outcomes of CER. For instance, recently, the findings from studies such as the Cardiac Arrhythmia Suppression Trial (CAST)[14] and the Clinical Antipsychotic Trials Intervention Effectiveness (CATIE) trial[15], failed to show an effectiveness of certain anti-arrhythmic drugs and newer antipsychotic medications, respectively[16].

CER and medical devices

Comparative effectiveness research (CER) increases beneficial population health outcomes with simultaneous reduction of healthcare costs. With rare exceptions, such as cardiac stents[17-19], there is a paucity of CER data for judging the effectiveness of ubiquitous medical devices such as prosthetics, meshed hernias, and vaginal/uterine prolapse repair, as well as biomarkers to detect occult metastases, genetic variations in cancer, radiological screening for cancer

and computed tomography (CT) for medical imaging. In order to conduct studies comparing the effectiveness of different medical devices, it is necessary to classify and build upon appropriate measures that can be tracked and evaluated on the basis of the end results obtained from those studies.

Maintaining transparency about reporting adverse events (AE) and off label usage are the two serious concerns that pharmaceutical companies and medical device companies have to face as the focus of regulatory bodies continues to shift towards standards of quality and outcomes. Because medical devices often require complex interventions to be functional (such as orthopaedic procedures for joint prostheses or thoracic surgery for certain cardiac devices), the careful reporting of adverse events occurring at different stages of this complex process must be rigorously accounted for in effectiveness research studies. As an example for orthopaedic prostheses, AEs that occur in hip and knee replacement procedures amount to about 5.1 and 6.6 per cent of devices implanted, respectively[19]. AEs that occur with Class III medical devices are classified under three categories: AEs during implantation, AEs after implantation, and medical device failure after implantation. One survey studying the complications during medical device implantation by orthopaedic surgeons found evidence that the orthopaedic surgeons experienced 29 per cent equipment errors during implantation surgery[20]. The malfunction of implantable defibrillators resulting in failure and fracture during attempts at resucitation[21-23], exemplify other aspects of device failure that belong in a thorough analyses of their effectiveness in comparison to supportive management with physical therapy and medicines.

Even though device failures in CER are relatively uncommon, when these occur after approval has been issued, it causes enormous burden on the regulatory authorities to restrict approval of such devices or to end the further distribution of ineffective or faulty devices, if these are already in the market[24]. For example, the total reverse shoulder prostheses was initially developed and approved for glenohumeral arthritis with an irreparable rotator cuff or irreparable rotator tear and glenohumeral instability. However, physicians now use these prostheses for the treatment of osteoarthritis of the shoulder[25]. Unavailability of clinical and outcomes data about the potential risks and benefits of this quite widespread off label use of these prostheses limits the objective outcomes information available to patients and doctors to make decisions. Patient registries that record outcomes data about medical device usage in real-world clinical settings can be a useful source for obtaining valuable safety information for both the physicians and the patients.

Issues related to implementation of CER in low to middle resource countries

A recent report by the Institute of Medicine, USA has suggested some recommendations for launching a sustainable CER programme at the national level[26]. These are: *(i)* Selection of CER topics should be made with regards to emerging disease conditions, practical interventions and public need**.** *(ii)* A successful CER programme requires significant participation from everyone including stakeholders, people, physicians, health care personnel and patients. The process of outlining and designing research questions should involve public participation. *(iii)* The potential CER topics should be selected on the basis of protocols with strong evidence of literature, robust methodology and practical interventions. The protocols should be designed by researchers who are experts in their fields and who have updated knowledge of treatment guidelines. *(iv)* An updated portfolio of the ongoing CER study should be maintained by researchers to provide evidence of continuous quality improvement to the prioritizing body. *(v)* An advisory panel overlooking the application and utility of the CER programme should be established. Studies should be designed to include and advantage racial and ethnic minorities and underrepresented patients like elders and children. *(vi)* Support and participation from patients, health care personnel and physicians is essential at every step of CER namely, developing, planning, prioritizing, peer reviewing and publishing. *(vii)* CER studies involving observational data and data from clinical trials should be guided by accurate and valid methodology, informed by prior research and be likely to be prospective or longitudinal in nature. The studies should also evaluate short term and long term advantages and disadvantages. The focus of the CER studies should be directed towards patient outcomes measures like morbidity, mortality and quality of life. *(viii)* There is a need for establishment of centralized data networks for consolidating data to assure its efficient usage. The studies performed using such data can thus drive real-world clinical decisions that can aid in better decision making for the public, patients, clinicians, or policy makers. *(ix)* Provision of financial and technical support can improve the capacity of the CER workforce to successfully conduct CER research. *(x)* The CER programme should be characterized by effective utilization of CER findings, speedy distribution of information based on new and

old CER findings among healthcare personnel, and adoption of CER recommendations to drive current practice guidelines[26] (Table).

Some issues surrounding the successful implementation of the CER programme are: defining CER, appropriate use of CER, scope of CER and financing CER. CER is assessment of clinical effectiveness and is different from cost effectiveness and cost-benefit analysis. This difference should be explained to the researchers and various other stakeholders funding and participating in the CER programme. It should also be clarified if CER will include assessment of only drugs, medical devices and procedures or if the scope of the same should be broadened to include health care delivery, integrative health practices and chronic disease management interventions. The use of CER evaluations by the public health system can vary. CER provides information to physicians and patients to help them make better decisions. Hence, it is possible that CER evaluations might be considered similar to patient reported outcomes research. It is important to clearly define the scope and depth of the CER programme. The nature of CER research in terms of setting priorities and the person appointed to do so can sometimes challenge the authority and power of the various key stakeholders involved. The role of identifying priority topics and research questions for CER evaluations should not be affected if the stakeholders are non-governmental or are manufacturer of pharmaceuticals, drugs and devices. Another challenging aspect is to make sure that the populations for whom a particular therapy is not generalizable are not being discriminated against. It is advisable to involve nonprofit corporations for the sake of protecting the interests of the people as well as to ensure fair CER evaluations. Even though the presence of diverse practice patterns especially private practitioners can hinder the uniform use of the CER based guidelines, these might be appropriate to local settings based on the physical and cultural characteristics of the population. Some questions might be better answered by healthcare personnel working in the healthcare facilities while some questions are better answered by stakeholders making the important healthcare policy decisions. In low resource countries with limited funds, it is challenging to provide funding in a sustainable manner. Also, once the CER guidelines are in place, the challenge lies in deciding whether CER should drive the physician decision making or should incentives be provided to physicians to follow CER based guidelines[28,29].

Preliminary CER efforts in low to middle income countries

This section presents an overview on ongoing efforts and challenges in low to middle income countries, particularly with the development of evidence-based clinical practice guidelines, an important first step in facilitating CER.

India

Indian officials in certain states like Andhra Pradesh and Kerala have been partnering with NICE (National Institute for Health and Clinical Excellence, UK) officials to improve the clinical guidelines and healthcare system at the local and state level. This partnership characterized by exchange of NICE guidelines development methods; case studies and discussions can foster establishment, adaption and standardization of both the existent and new clinical guidelines[30]. The State of Kerala introduced health insurance in form of fixed copayment about two years ago. Given the changing health care scenario in Kerala, the need for establishing quality standards has become more than necessary. NICE is currently working with the Ministry of Health of Kerala in collaboration with several academicians, physicians and other health care personnel working in urban and rural settings towards the development of clinical guidelines for the Rural Health Mission Reforms. The medical colleges, professional associations and the Clinical Epidemiology Resource & Training Centre (CERTC) of Kerala are striving to standardize clinical guidelines to target high priority chronic disease conditions prevalent in the State. Many physicians in Kerala have been trained in UK and have the necessary technical expertise. For disease conditions like leptospirosis which have a high prevalence and widely accepted cure, the frontline users *i.e.* the UK trained Indian physicians have to provide practical evidence to the key decision makers about the treatment process through field testing. However, there are concerns that if the guidelines are established, the health care system in Kerala might have to face some challenges for legalizing and standardizing the same due to practice variations among urban, rural, private, public, primary and secondary practitioners[30,31]. Kerala has the highest literacy rate in India and the Ministry of Health in Kerala has had some success with regards to establishing best practices for palliative care like morphine administration by caregivers and home tapping of malignant ascites[31]. Following the footsteps of Kerala, Indian Institute of Public Health (IIPH) and State decision makers in Andhra Pradesh and Tamil

Table. Comparative effective evaluations based on study typology[27]

Comparative Effectiveness Evaluation

Clinical trials

(a) Head to head trial:
Trials comparing 2 groups of people suffering from the same disease but receiving 2 different treatments or therapeutic agents.

(b) Cluster randomized trials:
Trials where the groups are randomized instead of the individuals in the groups. Hence, here the group is the unit of analysis as well as the unit randomization.

(c) Adaptive designs:
The decisions to conduct these trials are adapted on the basis of observations obtained. These are also called response adaptive designs.

(d)Practical/Pragmatic trials:
Prospective trials that provides scientific evidence for catering to the needs of health care personnel and patients

Observational studies

(a) Natural experiments:
These are observational studies whereby the treatment assigned to the study group is nature induced instead of being experimenter induced.

(b) Registries:
These comprise organized systems allowing users to collect, store, retrieve, analyze and distribute patient related, disease related and risk factor related data.

(c) Database studies:
These studies make use of databases which are computerized systems used for archive data of population cohorts. The data stored in the databases can be used to compare differences in health outcomes between the exposed and unexposed groups. Two further sub-methods are commonly used.

(i) Instrumental variables:
This method is used when there is a correlation of the independent variables with the error terms. This might occur if there are omitted independent variables, when independent covariates have measurement errors or when at least 1 of the independent variables is subject to causation by the dependent variable (reverse causation).

(ii) Propensity score matching:
This method is used for observational studies to obtain unbiased treatment effects since the assignment to the treatment group is non random or unbalanced with the control group.

Syntheses

(a) Synthesis & meta-analysis
While writing a literature review, the researcher might encounter inconclusive results at times. Also, it has the author's interpretation of the literature, giving rise to a personal bias. This limitation is overcome by meta-analysis technique which helps to quantify and objectively complete research.

(b) Simulation & Modelling
This method is used in health economics for generating estimates for demand and supply, risk management and incentivisation.

Policy topics and translation

Knowledge translation refers to the gap between what is known and what is practiced. It determines the exchange of research based knowledge between researchers and users for the benefit of the latter.

Nadu, National Health Systems Resource Centre (NHSRC) in New Delhi and Orrisa Health Sector Plan (OHSP) in Orissa have also jumped in to improve the clinical practice guidelines and quality of care for their people. These States are seeking the technical, strategic and operational expertise of NICE to improve decision making, quality of care, standardization of clinical guidelines, health care policy, practice and equity to health care access. Hopefully, in the years to come, with the aid of NICE, the Indian states can set an example for the neighbouring nations by working synergistically towards a well regulated healthcare system in the nation[31].

China

NICE has set up an international advisory board to partner with developed and developing nations to improve practice guidelines driving quality, efficacy and efficiency. NICE has partnered with the China Centre for Health Economics and the Chinese Ministry of Health to support the currently ongoing Rural Health Reform which largely aims to improve access and quality for the population living in rural parts of China. Together, these entities are striving to build infrastructural capacity in the rural parts of China to standardize practice based guidelines characterized by efficiency and equity[32]. A conference held at Renmin University, Beijing, led to the exchange of dialogues between the NICE staff, the Chinese researchers and various government officials promoting the development of health technology assessment to drive evidence based policy decisions in China[32].

Turkey

The health care system in Turkey is undergoing a number of reforms. It will soon see the establishment of a national entity that will review the CER based evidence. This evidence will act as an important driver to set quality standards, regulate professional leadership and provide coverage decisions characterized by guaranteed drug supply and other services. The guaranteed provision of services by the government of Turkey is a strong motivator for including CER based evidence in order to make day-to-day coverage decisions[33,34].

Brazil

The Brazilian government uses NICE guidelines to determine the eligibility of services to be included in the benefit package provided to its residents. The Ministry of Science in Brazil utilizes the NICE guidelines to determine the medical care needs of the Brazilians whereas the health economists in Brazil evaluate the cost aspect of the NICE recommendations that will be imposed on the Brazilians. Along with this needs assessment provided by the Ministry of Science and health economists, the needs of the physicians, hospital managers, and patient advocates are also being put forth to the Ministry of Health. The combination of all these needs put forth by different personnel determines the eligibility of services that qualify to be included in the final benefit package of the Brazilians[33,34].

Russia

The different regions of the Russian Federation (oblasts) have used CER to frame and allocate resources in a technically efficient manner. Currently, in Russia, where the resources are allocated in a highly centralized manner with a heavy hospital orientation, CER can help efficiently allocate resources by regulating evidence based practices, reducing hospitalization and improving drug supply in outpatient settings[35,36].

Discussion

Globally, every country's health care system is in need or in the process of some type of reform. Escalating costs of health care have put immense pressure on payers, especially government healthcare systems to make investments in the most cost effective technologies. However, we will not know what medical technologies work effectively in a particular country unless we have longitudinal real world outcome databases that allow us to examine these issues. The diversified healthcare systems across the globe require investment in CER to fill the void of providing to the public; credible, up-to-date and scientifically based comparative effectiveness information about drugs and other health interventions. In turn, usage of CER creates opportunities for provision of more efficient, high-quality health care and encourages development of innovative products that offer measurable value to patients.

There is preliminary evidence to suggest that CER will be a stimulus for the academic, medical and public health communities in low to middle income countries to develop a research agenda that is responsive to the needs of the clinical community, providing health care professionals with information for clinical decision making[33-37]. Harmonization of administrative medical claims data and patient registries is an important first step in this direction, and so is the development of longitudinal registries and nationally representative population based surveys covering health, nutrition, and medical care delivery. These efforts require

significant manpower and technology investments, and therefore, of particular importance is getting stakeholders involved right from the government to health care providers uniformly across the countries.

One of the key factors which will drive the success of global comparative effectiveness evaluations is the investment in health informatics and preventive medicine across the board in every country, and especially in low to middle income countries, partnerships with international centers devoted to global health research will foster the development of longitudinal database capabilities to track the quality and effectiveness of extant medical care. The National Health Informatics Project in Taiwan is a good example of an effort to harmonize health care data collected under a unified payer system. This project includes a registry comprised of 14 essential databases and registries related to population based health care in Taiwan and is being used to make effective evidence based medical care policy in this country[37].

Changing the global climate so that health care decision makers favour data from CER will create disincentives for the development of "me-too" medical technologies and render CER a catalyst for effective innovation. The first step in developing such capabilities globally is recognizing that health informatics is a cost effective investment to improve quality of health care, and maximizing the use of health informatics capabilities to track longitudinal medical-technology driven outcomes in populations. The development of effective global comparative effectiveness systems requires a commitment from all the players in the country's health care system to the concept of objective data driven health care effectiveness evaluation and policy making globally. The investment in technology resources needs to be complemented with a parallel investment in human resources devoted to this task. The time is right to form groups of "worker bees" globally who will devote the time, energy, and attract investments of governments (for developed countries) and philanthropists (for underdeveloped countries) in health care data harmonization efforts across the globe.

To enable the development of effective CER systems globally, an understanding for the concept of equity in health care and global effectiveness of health care is essential. In addition, there needs to be willingness to share critical assets, resources, skills and capabilities to facilitate the evaluation of the burden of a particular disease/condition in a region and development of collaborative frameworks to improve health outcomes and metrics globally. Finally, it is important to develop sustainable implementation science which will enable appropriate monitoring and evaluation of effective health care technologies and strategies to serve generations of future populations whose health care outcomes will continuously benefit from these investments in health care systems.

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