comparative effectiveness research collaboration and precision medicine

Key message

Knowing and managing the cross cultural and multi-disciplinary benefits and limitations of comparative effectiveness research (CER) will be the key component in building a strong foundation for the proof of concept in precision medicine.Unprecedented funding for CER is now available but this often favors national applicants even though the research is completed in other nations. There is a spill-over effect into low and middle income countries (LMIC), where device manufacturers, pharmaceutical companies, and regenerative technology corporations are investing in for the benefits of reduced site costs, supplies, and faster turn around times.Corporations ostensibly enjoy the opportunity to work in relative obscurity, thus protecting the proprietary aspects of development in a more lenient regulatory milieu with reduced ethical scrutiny. These organizations are clearly enjoying a benefit, but the question remains: how can research quality and medical benefit for the LMIC nations be enriched by these collaborations to improve the host nation's medical education, research program and national health care?

Background for comparative effectiveness research (CER) and precision medicine

The Institute of Medicine defines Comparative Effectiveness Research (CER) 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."[1]

CER is thought to provide improved evidence for medical decision-making and is considered the gold standard for weeding out ineffective clinical interventions, thus lowering individual health care spending, and increasing the pool of resources available for unmet healthcare needs. A recent review indicates that how research findings are adopted and applied will determine the impact on the nation's return on the investment of CER.[2] Evidence that comes to the forefront in the midst of controversy and strong debate is more likely to sway public policy as witnessed by the traction received by hotly debated issues such as the statin guidelines, screening mammograms, influenza medications, prostate cancer screening, suicides associated with mefloquine (an anti-malarial) and hypnotic sleep-aids.

One criticism of CER is that it is perceived as only another form of clinical trial research that is population based and does not always represent the populations for whom the intervention is intended. Many excluded participants are those with co-morbidities, who are on multiple medications, or those, for whom the intervention may be effective, but who represent a very small number and thus fail to show up as a statistically significant beneficiary in the analysis.[3] A solution to these limitations is proposed through what is termed "precision medicine".[4]

Precision medicine is defined by the National Institutes of Health(NIH)[4] as "*the use of genomic, epigenomic, exposure, and other data to define individual patterns of disease, potentially leading to better individual treatment.*" The NIH goes on to report the term personalized medicine was overused, however "precision medicine" conveys a more accurate image of diagnosis that is person-centered and multifaceted. Nowhere does the description mention cultural or demographic differences, irregularities between the laboratory administration, and application in clinical practice.

Missing in this description are the social determinants of health plus the long-term experiences of patients and clinicians who can report the safety and efficacy of the intervention in clinical practice.[3] For example, precision is not possible without error-correction and fair reporting; however, some nations do not have a reporting mechanism in place, and employees and medical professionals fear retaliation by superiors or bad ratings by regulators,which could cause their institution to close or suffer financially and be left without sufficient resources to meet payroll needs.[5] In yet another illustration, the research may have good outcomes but when priorities are decided by researchers without patient feedback there are consequences inclusive of unmet patient needs.[6,7] In psychiatry the patients may be alarmed by loss of libido, exhaustion, confusion or fear, when using medications, so that even though the problem of psychosis is managed by the medication, the patients may not remain compliant.[8]

In another instance, two CER trials were completed for the treatment of hypertension in diabetics. The trials compared Telmisartan and Hydrochlorothiazide. The research concluded no differences in efficacy based on the endpoints chosen by the researchers.[9,10] A critical appraisal of the available research acknowledges macrovascular complications as the major burden of diabetes and confirms present guidelines suggest optimal glycemic control, along with aggressive management of hypertension and dyslipidemia. The author points out that the mechanisms used in angiotensin-converting enzyme inhibitors and angiotensin- receptor blockers may have different cardiovascular effects but because this question was not asked of the data the issue remains unresolved.[11] The author concludes methodologically sound randomized controlled trials are needed for evidence to support using any particular angiotensin-receptor blocker as a means of cardio-protection for diabetes patients.[11] Other research questions concerning patient experience, preference, ease of use and patient reported quality of life were also left unanswered.

Solution-based problem-solving is not condemnation

Those in LMIC regions are dealing with higher patient per medical provider ratios, more extreme disease, patient poverty levels, outdated or inaccessible diagnostic equipment, and issues in accessing and implementation of appropriate healthcare information geared to present locally-relevant and technically feasible solutions rather than generic prescriptions.[12] In many instances students and instructors will not have access to plagiarism checking

materials or high bandwidth connections to learn from online resources. Power outages are frequent making dependable study hours less frequent. In low literacy areas patients may be unable to read their prescriptions or discern avoidable human error. Extra time may be needed to repeat to illiterate patients complicated instructions that they may forget to their own detriment. There is poor access to medical facilities and even such necessities as donor blood and available surgical equipment. In many regions, medical trainees will make life and death decisions for patients because no one else is available.

The recent trend where doctors, and trainees in LMIC nations are labeled as corrupt in high impact journals is unacceptable and demoralizing.[13] Corruption is apparent in every nation and industry. Crime and bad behavior does need to be dealt with in that individual or group practicing bad science or medicine, as society needs to see consequences for those inflicting societal harm; however, a murder or theft in a neighborhood does not make that entire neighborhood murderers and thieves. It is human nature to recoil from those who condemn with harsh words,*ad hominem* attacks even when help from that source is desperately needed. It would be most helpful if these journals and authors could instead refuse to publish the specific research and practice that contravene the moral practice of medicine and science.

It may be most useful to relay the solutions that work in other countries, which have struggled with and overcome the ravages of industry influence, corruption and exhaustion.

Prevention strategies for medical corruption

Educating against and limiting the direct to consumer marketing of medical interventions, curtailing commercial influences in physicians prescribing and medical student learning,[14] as well as being selective in how we support CER would be useful. A more robust evidence base that matches study outcomes with patient characteristics and preferences in the clinic could produce usable research and perhaps reduce indication creep.[15]

Medical students engaged in interactive learning in an evidence based milieu,[16] journal clubs,[17] or social action outreaches, such as the User Driven Health Care (UDHC) initiative are better prepared to think critically,[18] from both the scientific as well as social aspects.[19] Cochrane training[20] and workshops in how to search and access the literature are offered by medical librarians. Critical Appraisal Skills Programme (CASP)[21] meetings and free checklists as well as exposure to resources like the online Equator network[22] and no cost open access materials as well as online videos and teaching aids at the Center for Evidence Based Medicine (CEBM)[23] are freely available. These resources better prepare future scientists and clinicians to understand and keep up with the trends in science and medicine.

Aligning Policy and Practice

Centrally and internationally agreed, and legally binding ethical training for those within the country and those who enter to conduct scientific or medical research could be useful. One caveat is that teaching ethics provides knowledge of the standard required, however, implementation can only be ensured if the moral tenacity is ingrained in the practitioners or researchers: that cannot be rule or law assured. It is something more fundamental and personal. Medical students have reported early interaction with patients by taking responsibility for their treatment has helped them to understand treatment from the patient perspective and has helped them to grow in empathy and understanding.[24] Simplified and confidential adverse events reporting and automatic compensation for injury in clinical trials would promote public goodwill, safety and international confidence in multi-national research projects. Reciprocal agreements to enforce safety and efficacy agreements are suggested. This resolve could be strengthened if journals refuse publication to any research unwilling to meet these thresholds.

Registering all trials and reporting all results[25] can reduce harm as clinicians would not be deceived about the side effects or harms of the interventions they prescribe. It would also prevent duplication of efforts, especially with those interventions that demonstrate a detrimental outcome. It would highlight departures from protocol, which might influence outcomes. And above all, by having all the data in the open, public domain, it would promote an environment of honest reporting of research, free from financial or other pressures. Patients who trust their medical providers and have not had multiple negative experiences with interventions the doctor assured them were safe are more likely to be compliant in their intervention usage and to be more confident to approach their medical providers for help when it is needed.[26]

Conclusion

CER and Precision Medicine can make impressive strides when we are willing to learn together. In this age of global and local innovation through interdisciplinary participation in science and medicine, solution-based problem-solving can open doors for dynamic knowledge construction.[27] Collaborators may be multinational and bridge the gulf between patients, regulatory agencies, clinicians and consultants. Complex problems do not have to be complicated or solved in one session of dialogue.[28] Working to respect cultural differences, strengths and limitations while sharing resources, standards and experiences in research and medicine can empower us to benefit the practice of science and medicine in the corners of the world at which we find ourselves.

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