CLINICAL INVESTIGATION

PEARL translational network: an infrastructure for person-centricity and improved clinical outcomes

Healthcare systems should be transparent and easy to use and considered a joint venture between the various stakeholders with the goal of improving the diagnosis, treatment and clinical outcomes to control nations' rising costs of healthcare. The stakeholders are many including an educational component, practitioners, payers, government and industry providing the treatment and medications. All of these variables and more contribute to cost escalation. Within this complex framework is the nations' abiliy to provide some level of basic care for public health assurance of its populace possibly through the concept of 'person-centricity'. The Practitioners Engaged in Applied Learning & Research (PEARL) Network was conceived through government funding and has evolved into a not-for-profit private enterprise. The PEARL Network is a hybrid network incorporating the benefits of an academic practice based research network into a practice based translational network with the principles of conducting pharmaceutical level clinical studies for regulatory submission. PEARL incorporates the philosophy of 'person-centricity' and operationalizes it conducting 'person-centric clinical trials.'

Keywords: comparative effectiveness • engagement • healthcare • person-centric clinical trials • person-centricity • pharmacovigilance • regulatory agencies

Frederick A Curro*[,1], Dennis A Robbins[2], Frederick Naftolin[3], Ashley Grill[4], Don Vena[5], Louis Terracio[6] & Van P Thompson[7]

[1]PEARL Translational Network, Emerson, NJ 07630, USA & New York University, PEARL Network, 421 First Ave., Rm.1036-W, New York, NY 10010, USA
[2]PEARL Network Director Translational Ethics & Policy, 130 Evergreen Ave., Imperial Beach, CA 91932, USA
[3]PEARL Network Medical Director, Department of Obstetrics & Gynecology, New York University School of Medicine, 180 Varick Street, New York, NY 10014, USA
[4]PEARL Network Clinical Coordinator, 421 First Ave., New York, NY 10014, USA
[5]Data Management, The EMMES Corp., 401N. Washington St., Rockville, MD 20850, USA
[6]PEARL Network Advisor, New York University, 421 First Ave., New York, NY 10010, USA
[7]Kings College London Dental Institute, Guys Hospital, Tower Wing 17th Floor, London SE1 9RT, UK
*Author for correspondence:
Tel.: +1 212 998 9219
fac3@nyu.edu

The USA has one of the most complex healthcare systems in the world delivering to a populace who for the most part do not expect to contribute much to the direct cost of their healthcare [1]. Healthcare is often viewed at times as an entitlement but like all entitlements requires financial or personal support from all those who benefit from it. While not everyone can contribute financially they can certainly contribute personally through the philosophy of 'person-centricity' [2]. A necessary consequence of freedom is responsibility. The current system is not flexible enough to be inclusive of the 'person' when one considers 'personalized medicine' and where the burden of health and healthcare is increasingly placed on the 'person.' Traditionally healthcare has focused on a disease oriented approach where a 'person' interacting with a clinician, at times, becomes a 'patient' and receives treatment. The cornerstone of clinical medicine remains the clinical encounter, a specific event in which an individual seeks counsel and care from a clinician and assumes the role of a patient rather than a person in expectation of living a longer or better life [3]. This top-down care from the clinician to the patient has been traditionally one way and is relatively static where the patient is the recipient of that care and contributes very little to the ultimate outcome.

The cost of drug development today is estimated at 2.6 billion and has now become a limiting factor in the advancement of health and suffers from the same syndrome as healthcare; the reluctance of the populace to contribute to the development and advancement of medical science for improved healthcare coupled with a sense that the pharmaceutical industry has placed profits over care [4]. The model of rising cost for drug development, treatment and care

FUTURE SCIENCE part of fsg

along with a top down disease oriented approach from clinician to patient, excluding the person in the process, only diminishes compliance and leads to less than optimum outcomes. Currently the driving incentive of the system is reimbursement and the cost of waste and redundancy has been estimated to be some 65 billion a year [5].

One of the hallmarks of the Affordable Care Act is for the person to be more inclusive and take on a substantial role in prevention and risk assessment. The purpose of the manuscript in this issue is to describe the role of the PEARL Practice Based Translational Network in supporting the person/patient clinical encounter, clinical comparative effectiveness studies, its role in drug development, faculty recruitment, benefits to payer organizations and in promulgating the philosophy of person-centricity through person-centric clinical studies. This manuscript will describe the current state of the PEARL Network.

PEARL network

Practitioner Engaged in Applied Learning & Research (PEARL) was initiated through a United States National Institute of Health grant in 2005 as one of three funded initiatives to construct a practice based research network (PBRN) with the goal of conducting studies whose outcomes would be 'generalizable' to the profession [6]. The Network was originally designed for the profession of dentistry as medical PBRNs had been in existence since the mid-1970s in USA. The funding was large enough to sustain recruited practitioners and keep them engaged over the funding period through annual meetings, conference calls, continuing education programs and foremost their participation in a clinical study that they had input in its goals and outcomes for them to incorporate the results in their practices. PEARL was built as a hybrid PBRN based on incorporating the principles of Good Clinical Practice (GCP) so that the data are not only generalizable but can be submitted to regulatory agencies for possible label changes and or extension of label claims as well as pharmacovigilance. PEARL was the first PBRN built on the principles of GCP and conducting studies that can influence a positive change in the way private practitioners treat patients. The details of recording information and following a protocol under GCP readies the practitioners for what is to come in electronic health/medical records, improving their recorded medical information as reflected in the source documents of the study records, and in general looked upon very favorably by malpractice insurance companies for cost reduction of practitioner premiums. PEARL has conducted some twenty studies to date ranging from prospective, retrospective, to randomized controlled clinical studies all standard of care where we use the term 'patient' instead of 'subject' as PEARL is no longer a 'research' network but is now termed a Practice Based Translational Network (PBTN). PEARL conducts studies that essentially do not require a controlled environment, where safety of the drug is not in question, and is ideal for pharmacovigilance studies and Phase IV study commitments for regulatory agencies. The role of such a network in drug development lies in patient recruitment. For the most part the Network conducts 'studies' and the term 'trials' is reserved for clinicals directed toward drug development where safety may still be a question and a controlled environment may be required. Recruiting patients (persons) of record from a practitioner with a known medical history having a long standing relationship with that practitioner adds to the improved outcome due to increased patient compliance and robust data as the drug is used as it would be in practice. PEARL is now a not-for-profit private enterprise bridging academia and industry with practitioners and payers.

Role in healthcare

The concept of the PEARL Network is to conduct studies that are person-centric as well as including patient reported outcomes. PEARL merges the principles of clinical research based on Good Clinical Practice with clinical practice to optimize the clinician/person encounter. It creates an audit trail of the encounter which should diminish redundant costs. PEARL provides the infrastructure for not only conducting clinical studies but which can be extended to everyday practice. It requires that the practitioner educate the person to their condition and health. It requires that the person become active in their own health and care. Rather than adding additional layers of organizations to monitor the clinician/person encounter it is designed to optimize the encounter and make it more efficient for both the clinician and the person. PEARL is an example of an infrastructure capable of integrating research into a healthcare system recently described in a report by the Institute of Medicine [7]. PEARL supports the person's health care literacy in order for the process to become transparent and allows for self-determination by the person/patient. PEARL has formalized the observational study so that each patient encounter is a valid data point. This quality assurance component ensures data integrity and provides an audit trail to diminish fraud and provide savings for both government and private payer organizations. The concept of person-centricity and the conduct of person-centric clinical studies requires the cooperation and consent by the person/patient to be transparent in their medical outcome to be considered, for exam-

ple, in the 'big data' platform. The model of a PBTN study is somewhat opposite that of a randomized controlled clinical trial where a small number of highly trained specialists/investigators recruit a large number of subjects in a controlled environment. PBTN studies recruit a large number of practitioners/investigators each recruiting a small number of patients which is consistent with large scale responses for healthcare outcome improvements.

The infrastructure of PEARL can serve as a forum for continuous learning in the healthcare system for both person/patient and practitioner. At a time when people are most vulnerable from disease, age or depression and under the care of a relative or friend what is most needed then is a source to provide direction and reliable information. Having a network of practitioners who can practice at the research level can provide some assurance that the advice and guidance provided is up to date and peer reviewed. The infrastructures primary role is the dissemination of quality data to its practitioners and by participating in clinical studies and being part of the data generation the practitioners are more readily to incorporate change and the results into their practices.

Role in education

The interface of clinical practice and academia has long been a point of discussion. One vision is that PEARL functions as a bridge between academia and practitioners whereby PEARL can be the clinical network to interact with many universities standardizing the conduct of academic clinical trials, many of which have been shown not to be reproducible. However, there is currently no model designed to integrate the two and still maintain the independence of either system. If clinical practitioners practiced at the research level using the principles of GCP then the clinical encounter can also be a teaching situation should students be involved either by rotation or in residence. Additionally, as PEARL recruited practitioners a number of them became clinical faculty members of New York University and lessened the burden of faculty recruitment. The faculties recruited not only have the interest but are taught the principles of GCP for them to be aware of the details that are contained in the conduct of clinical research. Students who work with such practitioners and demonstrate an interest in becoming future faculty members and/or going into clinical research can benefit by participating in practiced based studies and possibly receive tuition cost reduction or remuneration from the sponsor. PEARL would then function as a firewall to students and faculty to maintain objectivity and bias. The process standardizes the patient/person encounter or at least documents appropriately a long standing variable of concern with academicians. Practitioners trained in this manner would also contribute quality data to the big data medical platform. For the national big data medical grid to function optimally the data submitted have to have some oversight to ensure data integrity. That oversight is the quality clinician/person encounter.

Working with industry

The evolution of PEARL from a government supported network to a not-for-profit private enterprise has allowed PEARL to broaden its mission and objectives. One of the objectives is in line with the NIH industry partnership initiative [8]. The PEARL Network after completing its NIH portfolio obligation of proposed studies realized that its potential exceeded that of the NIH. Becoming a private enterprise allowed PEARL a degree of freedom to pursue a broader objective in collaborating with the pharmaceutical and oral health industries, including manufacturers of over-the-counter medications. PEARL has positioned itself to be the venue for industry to comply with their Phase IV pharmacovigilance commitments and special populations, comparative effectiveness studies, pharmacoepidemiology studies, studies for additional label indications and/or changes, equivalence studies due to formula changes, generic equivalence studies, food effect studies, over-the-counter monographed products, retrospective and prospective studies related to treatment and/or treatments that have been performed using drugs and/or devices. The model can generate large scale data bases in a shorter amount of time. This allows for signaling or detection of adverse reactions and we are proposing that regulatory agencies consider for the Phase III commitment in drug development, one randomized controlled clinical trial and one practice based translational clinical study. This should expedite the shortening of the translational gap which currently is some twenty years.

Payers benefit by having their practitioners engaged in practicing at the research level with all the benefits to detail to support an audit trail to reduce cost, fraud and malpractice. Improving the patient's medical record to that of a research or source document level is a major philosophical change by the practitioner that benefits all stakeholders to reduce cost.

Conclusion

The complexity of a nation's healthcare system is unique and dependent upon the political system but has a common theme as the legislation affects all of the populace, both personally and financially as well as its future. The legislation should instill a basic public health net for the safety of all as well as being transparent for ease of use to maintain a certain level of confidence for one's health to be a productive member of society. There are so many

moving variables that one can get paralyzed by such a system. To move the system forward by improving care, maintaining costs and having all stakeholders working cooperatively is but a small start. Person-centric health and healthcare places the person as an integral part of the system. It requires a certain level of openness so that all clinical encounters can be assessed for future clinical improvement. Given what has transpired recently with cyber security I think that most people now realize that no data are 'secured.' Improving the medical encounter by applying research parameters is but a start to close the scientific translational gap to ultimately contain and/or reduce healthcare costs. The concept of the PEARL Network has been demonstrated to engage practitioners in clinical studies at the GCP level, demonstrate their willingness to learn for the advancement of the profession, to improve their patient encounter to that of a contributing data point, to sustain their interest over a period of time, to have them contribute directly to studies related to their needs for them to implement change, to generate thought leaders that other practitioners can relate to and to have practitioners directly involved in the drug development process to gain wider acceptance and quicker use of improved and novel treatments. Additionally, there are benefits on the patient side in that such a network can be used as a vehicle to help navigate the healthcare system, provide consistency in educational material, create transparency to understand the system and support the concept of self-determination. Further benefits reside with regulatory agencies and industry in expediting the drug development process by providing robust real-use data at the practice level, using patients of record for pharmacological interpretation of adverse drug reactions and side effects, generation of a large data base to assess signaling for potential issues in pharmacovigilance and all of this to possibly reduce the number of drugs that receive, at least in USA, black box warnings and/or get removed from the market. The big data concept is based on improving the quantity of quality data for meaningful interpretation to improve individual and/or share decision making related to health and healthcare. PEARL has been recently funded to conduct a Phase IV pharmacovigilance study the outcome of which may demonstrate further the important role of the practitioner in the pharmaco-healthcare system. We have presented a model based on a philosophy that we believe can have long term effects on the future of healthcare. The model is based first on quality of care having a secondary effect on cost savings on many of the components of the system, notwithstanding the many lobbyists that can redirect that purpose.

Future perspective

The future of PEARL resides in its dissemination and recruitment of practitioners and sponsorship by a number of supporters including foundations, government agencies, industry and third party payers. It is a cooperative effort to improve health and healthcare. A network such as PEARL also needs to gain acceptance by government agencies to be part of the drug development process by targeting to conduct focused clinical studies that can be used for meaningful change. Those areas of interest include pharmacovigilance, comparative effectiveness, label changes, product formula changes and other studies that lend themselves to practice based translational network. Other challenges include broadening the investigator base to include multiple healthcare disciplines and to show a definite cost reduction in healthcare over a fixed time period. The variables are many and include the person, clinician, payers, industry and all the components of business that have been created to oversee quality based upon the clinical encounter. The components of business manifested through lobbyists need to be tempered and remain probably the most difficult variable to reign in and control if healthcare reform is to be optimized for the best interest of the populace.

Executive summary

- Healthcare requires a philosophical shift in order for the person to play a more dynamic role in the healthcare system.
- Person-centricity describes an active role that a person can have to improve their life and healthcare outcomes.
- The philosophy of person-centricity is reflected in person-centric clinical trials to improve engagement and outcomes.
- Persons/patients can be of added value to clinical studies related to both healthcare and drug development.
- Person-centric clinical trials have advantages over traditional controlled studies.
- Person-centric clinical trials may be considered by regulatory agencies as part of the drug development process for regulatory submission.
- Person-centric healthcare bridges academia, industry, practitioners and payers to the person.
- An infrastructure such as the PEARL Translational Network can incorporate research principles into clinical practice to optimize the clinician/person encounter.
- PEARL Network infrastructure can function to oversee the quality of data to a national medical grid.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1 Wright R. Are you prepared for the pending personalized medicine revolution? *Life Science Leader* 2012, 31–35 (2012).

2 Robbins DA, Curro FA, Mattison J. Person-centric clinical trials:ethical challenges in recruitment and data transparency for improved outcomes. *J. Clin. Pharmacol.* 54(9), 1072–1077 (2014).

3 Kraus CN, Baldwin AT, Curro FA, McAllister RG. Clinical implications of patient provider agreements in opioid prescribing. *Curr. Drug Saf.* 10(2) (2015) (In Press).

4 Tufts Center for Drug Development. Cost to Develop and Win Marketing Approval for a New drug is $2.6 Billion (2014). http://csdd.tufts.edu

5 Medicare Fraud: Progress Made, but More Action Needed to Address Medicare Fraud, Waste and Abuse. GAO-14–560T. United States Government Accountability Office. www.gao.gov/assets/670/662845.pdf

6 Curro FA, Vena D, Naftolin F, Terracio L, Thompson VP. The PBRN initiative: transforming new technologies to improve patient care. *J. Dent. Res.* 91(Suppl. 1), 12–20 (2012).

7 Johnson K, Grossmann C, Anau J *et al. Integrating Research into health Care Systems: Executives' Views.* Institute of Medicine January 2015.

8 NIH Office of the Director. NIH, industry and non-profits join forces to speed validation of disease targets. www.nih.gov/news/health/feb2014/od-04.htm