CLINICAL INVESTIGATION

Person-centric clinical trials: defining the N-of-1 clinical trial utilizing a practice-based translational network

A person-centric clinical trial is inclusive of both the investigator and the person and as such represents point-of-use data generated at the practice level and encompasses both health and disease. Raising the clinical encounter to a research encounter and providing an infrastructure to support a level of quality assurance creates a synergy for efficiency for healthcare delivery. The interface of translational studies and clinical research poses an opportunity, whereby person-centricity can support transparency, facilitate informed consent, improve safety, enhance recruitment and compliance, improve dissemination of results, implement change and help close the translational gap. The model represents robust clinical data from persons of record allowing for improved interpretation of drug/device side-effects and for regulatory reviewers to expedite the approval process.

Keywords: clinical trials • comparative effectiveness • healthcare infrastructure • patient-reported outcomes • person-centric • regulatory change

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The US healthcare system is primarily focused on managing disease and sickness, whereby a person comes to a provider or provider organization as a patient seeking care and treatment. This defines the clinical encounter an event that should be directed at the person/patient but has been compromised with administrative and financial demands. The incentive for improved health for some time has been misdirected, whereby the provider is paid on the basis of what services and procedures are performed, rather than on the quality or focus of the condition as well as behavioral changes to avoid recurrence. Moreover, in many cases, persons seek medications to essentially allow themselves to continue to pursue a lifestyle that created the condition and need for treatment in the first place. Additionally, the process is designed to virtually exclude the person (patient) from responsibility in determining their health and treatment. It is, for the most part a passive process with the majority responsibility falling on the provider limiting the clinical encounter with the person. The person need not and should not be passive in this process for as a person he/she can and should self-determine and shape their choices consistent with their self-interest. This shift in mindset moves the person from a perspective of sickness to a health-oriented paradigm. Self-determination logically entails personal responsibility and is a consequence of a free society. This is an essential component of person-centricity. Furthermore, an informed person is more likely to want to improve their own clinical outcomes and lives by participating in clinical studies. This shared interest is core to the interface of practice-based healthcare delivery and in conducting clinical studies. The person's participation allows for one on one interaction that keeps the person engaged as well as enhances their health literacy, transparency and self-determination. This opportunity has obvious benefits to the person, clinician and researcher. Integrating real-time clinical care with translational studies has profound implications for all stakeholders in closing the clinical and scientific gap impacting the nation's healthcare cost. Applying this dynamic person-centric conceptual

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framework to the drug development process provides an operational model that includes the 'person' thus broadening the data input, being inclusive of the person and the investigator, on the outcome of the clinical study. Issues of clinical research such as recruitment, compliance to ensure data integrity and drug safety and loss to follow-up can be improved by considering the role of the person. Healthcare delivery manifested at the practice level has many parallels to clinical research and the 'person' is pivotal in linking the two venues to optimize similar clinical outcomes. Person-centric clinical trials and its attendant infrastructure can provide a model that will provide real time point-of-use data (live analytics) that will be more robust than that generated in a controlled environment as well as initiate the signaling of drug side-effects, and in the long run, reduce black box warnings. This paper discusses the rationale supporting the concept of person-centricity and its application to clinical research, its transition to healthcare and education and a proposal to include person-centric clinical trials in the clinical drug development program for regulatory approval. Supporting the integration of the principles of clinical research to healthcare delivery can improve both quality and cost. Additionally, this paper discusses the employment of a hybrid practice-based translational network (PBTN) to support person-centricity and to conduct clinical studies that are generalizable and suitable for regulatory submission as well as serve as a model infrastructure with the potential to significantly influence healthcare delivery. The need to improve subject recruitment, accelerate the approval process and enhance safety is paramount to containing cost. The cost/benefit ratio in healthcare is rapidly becoming a worldwide issue as budgets are constrained. These concerns are exacerbated by rising costs of preventable lifestyle related illness and non-compliance. One attempt to address these multiple factors is illustrated in the Patient Protection and Affordable Care Act (ACA) in the USA [1]. This piece of national legislation affects every citizen personally and financially. We have used the USA as an example to propose a new model that integrates clinical research, healthcare delivery and the concept of person-centric clinical trials. We believe the model can be applicable for worldwide healthcare systems reform. The model utilizes an existing infrastructure supporting the 'person' and merges the principles of clinical research with that of clinical practice to create a continuous data base that facilitates best practice and the regulatory approval process.

Evolution of patient-centered to person-centricity

The concept of patient-centered is evolving to accommodate the distinctiveness and importance of the person and is describing significant differences between the patient and person. This shift is a significant departure from the passivity so often associated with the patient component of the doctor-patient (person) relationship or even that of the consumer. The term consumer was used for the person to be more discriminative about healthcare in a competitive market. Models of both patient and consumer engagement based thinking do not account for the complexity and comprehensiveness of what falls under the broader umbrella of the person. The person who comes to us to seek care, respite, treatment or advice unwillingly becomes transformed into someone other than the person they really are. This is seen in managing chronic conditions such as pain. Each person defines him/herself by their past, their values, preferences and aspirations. While some may find this approach 'too philosophical,' we contend that we have been too un-philosophical by reducing the person to how others perceive him/her in terms of a particular temporary status they are assigned such as patient reducing the person to a billing number or code further distancing the person toward anonymity.

The cynosure of our model is the person and we contend that decision-making must be person-based and driven. People are more likely to change than patients. It must be reflective of how we actually make decisions rather than some artificially imposed template or construct. All that happens must revolve around the person and in this sense rather than speaking of a person-centered approach we have replaced 'centered' with the more dynamic term 'centric' drawn from the Greek word *sentrikos* in which all either comes from or to the person as the regulating fulcrum as choice and circumstance dictate. Person-centricity is a dynamic and transformative concept supporting the person as the regulating fulcrum from multiple pathways to self-determine his/her future, choices and destiny consistent with his/her personal preferences, values, beliefs and aspirations. Engaging as a person rather than a patient profoundly transforms how we perceive and interact with our world around us. The role of the clinician or health coach or trusted guide would help us define options and make more informed decisions. The person's self-determination acutely represents the essence of personal involvement and choice much more profoundly than models of consumer or patient empowerment, centeredness, engagement and activation.

Previously in our efforts to clarify and define patient-centered care we realized we needed to take the next step and move from patient to person, consistent with the dynamic and continuous way that is relative to the person's life space [2]. This shifts the mindset away from unidimensional models of consumer or patient

empowerment, which are too restrictive to accommodate the breadth of the person. Person-centricity promotes enhanced decision-making resulting from both self- determination and good counsel from professional caregivers while ensuring that healthcare delivery is consistent with the wishes and best interests of the person as they so choose, ultimately defined by the person himself. This process also minimizes any ethical issues that are brought into question as we transition from healthcare to health by continuously having the person in the loop.

We need to move to a more intensive healthcare paradigm and an immense need to change the trajectory of the aftermath of poor health and healthy behaviors in America. We contend that the core of these debates must include a rethinking of moving from the patient to the person and changing the debate from discussions of sickness and healthcare to health and well-being. However, if our ultimate goal is to promote and sustain healthy living change and have an impact on the rising trajectory of health and healthcare related costs we need to promote a rethinking of personal responsibility and personal choice and of changing the culture of healthcare towards a healthier solution.

The prescription for health, centers on meaningful changes in behavior in concert with person-centric solutions rather than impersonal ones. This important person-centric nuance has significant implications for research as well. The difference between an anonymous research subject versus a person is pretty intuitively clear. Unlike the research subject, the person is no longer a passive, anonymous participant without a voice. Furthermore, if we perform research in a practice-based context dealing with familiar and known persons in a given medical practice we can derive results more reflective of what actually occurs in persons and populations rather than prefiltered subjects with restrictive exclusion and inclusion criteria that are unreflective of the real world. The interface of translational studies and clinical research poses an opportunity, whereby the concept of person-centricity can be supportive of transparency to facilitate the informed consent process for both clinical care and research. Patient-centricity depends upon the triad of self-determination, transparency and healthcare literacy together supported by an infrastructure that provides the person with the information to make an informed or shared decision on their health or healthcare outcome (Figure 1).

The clinical drug approval process in the USA consists of conducting a study against a placebo allowing for a large number of drugs available for prescribers to almost 'personalize' treatment. Although not cost-effective it is an advantage for the person and for pharmacological advancement [3]. For the treatment of hypertension there are currently eleven therapeutic classes totaling 65 antihypertensive medications (American Heart Association) [4]; for treatment of diabetes there are eight therapeutic classes with a total of 20 diabetes drugs (American Diabetes Association) [5]; and for pain management there are three therapeutic classes

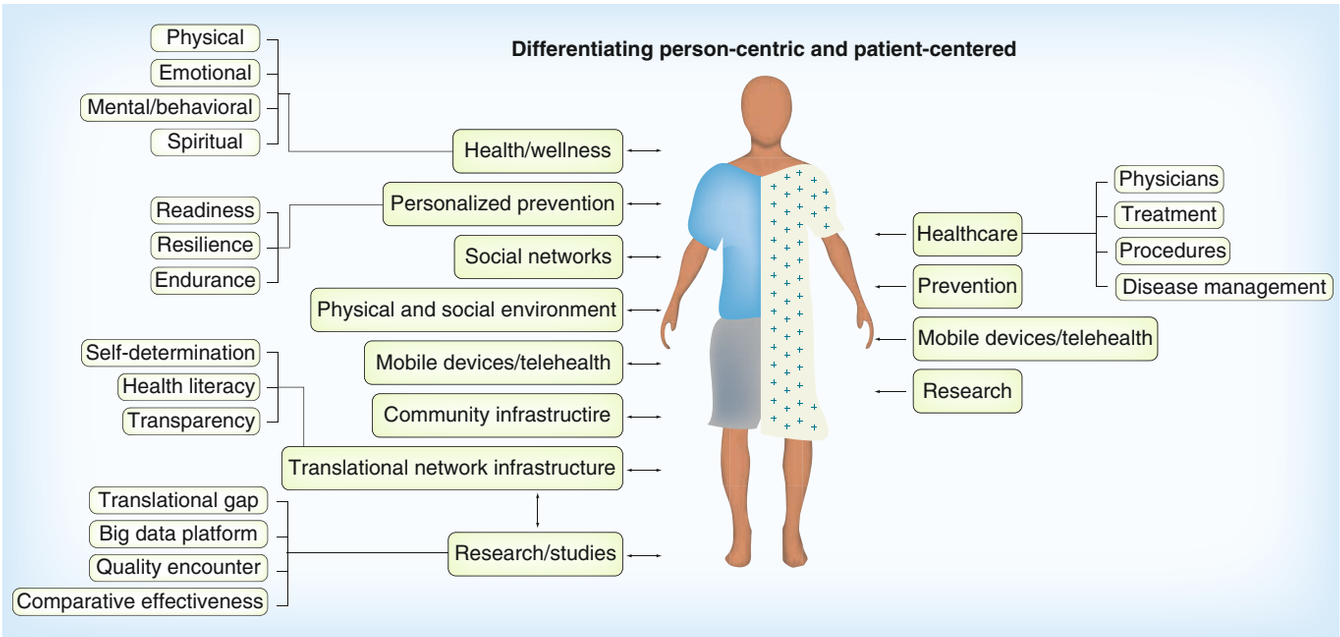

Figure 1. Person-centricity creates a more dynamic and involved approach to a person's health and disease. When a person is perceived as a patient, the focus is on the disease not the person who becomes passive with little or no participation in their health and wellness outcomes.

with a total of 74 analgesic drugs with NSAIDs alone having three therapeutic classes totaling 61 medications as an example (Arthritis Foundation) [6]. The numerous drugs per category allows a prescriber the choice of a medication ultimately winding up with the most effective drug that the person is compliant with to take, given the pharmacokinetics and side effects over a period of time. This broad spectrum of choice is seen, for example, in nonsteroidal analgesics where in one chemical class there may reside a number of different compounds but each compound has its own effect on that one person [7]. The wide choice of medications by some can be construed as a form of personalized medicine where one can search for the drug with the best fit or effect for that person. In some cases the multiplicity of medications defined alternative pathways, for example, cox 2 inhibitors, to improve drug development as in the case of analgesics and cardio protective medications. However, it is the area of clinical outcomes that the focus of drug effectiveness is now manifested in the term 'comparative effectiveness research' (CER). Clinical effectiveness research can be described as primary referring to direct generation through experimental methodology or secondary by a systematic gathering and evaluation of primary research information [8]. Pragmatic trials also measure effectiveness and the benefit the treatment produces in routine clinical practice and the term is often used interchangeably. Drug efficacy in drug development is compared in the USA against a placebo in the early phases and its effectiveness is determined once approved for market distribution in studies termed 'comparative effectiveness studies.' CER studies have been the mainstay of economies that have fixed cost national formularies such as in socialized countries in Europe. Every new drug must show its effectiveness over existing drug(s) in the formulary and if approved less effective drugs are removed to maintain or limit cost increases. For the purpose of this manuscript a 'clinical trial' is for a study that is part of a drug development program for regulatory submission and the term 'clinical study' is for an approved drug in a Phase IV, pharmacovigilance or CER study. Comparative effectiveness studies to determine best practice for already approved drugs are designed to fit the criteria for practice-based research networks. PBRNs were a concept initiated in the UK circa 1900 and first presented in the USA by Dartmouth Medical School [9,10]. PBRNs gained interest in the late 70's and today there are over 150 PBRNs mainly with central funding through American Healthcare Research Quality (AHRQ) [11]. The PBRNs work with practitioners in the community and respond to issues and/or questions raised by the practitioners usually through a medical school, university or health science center. Many of the PBRNs are survey oriented responding to local practitioner interests and for trend analysis and limited in conducting clinical studies whose findings are generalizable as they do not follow the principles of Good Clinical Practice (GCP).

This paper addresses the formation of a hybrid network model that can conduct clinical studies that are generalizable and suitable for regulatory submission as well as serve as a model infrastructure that has the potential to change healthcare delivery in the USA and significantly influence the health of the nation.

Person-centric clinical trials: defining the N-of-1

The ACA centerpiece term of 'patient-centered care' first described in the 1980s is limiting [12]. The term 'patient' places the person in a subservient position and for the most part does not invite or allow them to participate in their own clinical outcome. Clinical research now recognizes the importance of the person significantly contributing to their clinical outcome. Having the principal investigator interpret the clinical data is one thing but to have them interpret for the person interjects a loss of objectivity from the person to contribute to the outcome as to the effect the medication is having on them. Patient reported outcomes is now recognized by the FDA and described in a guidance document for industry to make label changes of already marketed drugs [13]. Thus for the purposes of clinical research the person becomes part of the clinical team but in the healthcare context the team supports the person in challenging assumptions, weighing alternatives and identifying or suggesting best practices and best products. After evaluating options alternatives and counsel the person ultimately makes the decision. Without the person having ultimate authority, the team concept is insufficient as a model for person-centricity. The team can help but not absorb the person as an equal partner for the person always trumps the team. A distinguishing characteristic from the clinical research environment where the person does not trump the principal investigator but their input is considered.

The N-of-1 defines that 'one person' involved in a clinical trial or study and their clinical outcome described for that person (personalized) which can be summed for all persons in the study for a cumulative effect. Person-centric clinical trials provides meaning to the N-of-1 study and places limits on the involvement of the person in a study while recognizing the importance of getting directly from the person the effect of the drug and not an interpretation by the investigator of that effect. It is inclusive of the person and refers back to the statement of Hippocrates *"It is*

more important to know what sort of person has a disease than to know what sort of disease a person has."

The personalization of therapeutics although now being driven by cost and an enhanced understanding of how human genetic variation affects an individual's response to a drug or treatment may prove to be cost effective. Developing therapeutics aimed at discrete groups of patients appear to be particularly timely, given that an estimated 55% of drugs consumed in the USA, including as many as 80% of approved anticancer therapies are thought to be ineffective in the patients who receive them [14]. The estimated annual cost for such unwarranted or 'wasted' care ranges from $250 billion to $325 billion [15]. The primary goal of personalized therapeutics is to minimize side effects and optimize efficacy which will contribute to reducing healthcare costs. A personalized N-of-1 clinical study requires that providers know intimately the persons health history and record which is an advantage for practice-based conducted studies.

Traditional definition of the N-of-1 trials in clinical medicine are for multiple crossover trials, usually randomized and often blinded, conducted in a single patient. N-of-1 trials are a specific form of randomized or balanced designs characterized by periodic switching from active treatment to placebo or between active treatments ('withdrawal-reversal' designs) [16]. Our definition of 'person-centric' as applied to clinical trials is inclusive of the traditional N-of-1 definition. Person-centric clinical studies are a continuum of the study by the person beyond the time frame when they come in for data collection. It is the contribution by the person to optimize the clinical study outcomes by being an active participant and adhering to study compliance. Person-centric clinical trials are exemplified by studies for chronic conditions, studies assessing over-the-counter medications and any ambulatory study which requires the patient to continue the study in an unsupervised environment.

Person-centricity: fulcrum for clinical research & health

Patient recruitment is considered the most challenging aspect of conducting a clinical study (Lasagna's Law) [17]. Equally important is the dropout rates and lost-to-follow up for patients can be very costly. Attrition in drug development is still cripplingly high, with approximately 16% of the compounds making it through, with toxicity the leading cause at all stages in the drug development pipeline [18]. It has been estimated that a 10% improvement in predicting failure before the initiation of expensive and time-consuming clinical trials could save upwards of $100 million in the costs associated with drug development [19]. This cost only increases if toxicity is identified in the later stages of clinical development. Incorporating the concept of signaling early on in the clinical program can only be cost effective. Additionally, drug development should be including both predictive toxicology and pharmacology to maximize cost savings. Many of the side effects can only be seen at the clinical level, such as drug distribution and binding, metabolism, sensitivity reactions etc. Any model designed to improve the current system should at least improve recruitment, lessen dropout rate, identify side effects early on in the clinical process and allow for better interpretation of those side effects. People recruited from a practice have known medical histories reducing the subjective interpretation by the investigator for what are a true drug side effect and/or adverse event. Long-standing persons of a practice have a sense of loyalty to the practice, which should improve lost-to-follow up and dropout rates. Engaging the whole practice and their persons to assist in medical advancements only benefits the nation as a whole.

The Patient Centered Outcomes Research Institute (PCORI) supports the 'person' with assuming a level of involvement, participation and responsibility for their treatment outcome in clinical research [20]. Person-centricity as applied to clinical studies should improve study compliance, a variable for a study considered for regulatory submission which should be at least 80%. However, the question remains how much compliance should there be in healthcare and what should be done for a person who is recalcitrant to comply? However, the more meaningful the study is to the person, the more likely they are to care about the outcome and comply accordingly.

The standards for conducting clinical research are considered higher than for a practitioner practicing in their offices and the question remains should that be the case. The difference between the two is that one has accountability for treatment in an audit trail for clinical research and responds to any questions arising during the study and in its final assessment, as queries. However, practicing medicine has responsibilities beyond the practitioner as it involves the government and private payers for reimbursement. The variables may differ between clinical research and private practice but the outcomes should have the same result. The patient/provider encounter should be defined by quality standards enough for that encounter to be uploaded in the 'big data concept.' Why should the patient provider encounter be any less than any other encounter including a clinical research encounter using that as the gold standard? Accountable care organizations (ACOs) involved in overseeing quality of the patient/provider encounter provide administrative oversight designed to

fill a void in the quality of that encounter and adds additional cost to the healthcare system. To date there are almost 500 public and private models of ACOs, and increasing in number, whose focus is quality but more often they operate on the less is more paradigm trying to limit costs. The goals of ACOs are to improve quality outcomes, improve the experience of care and lower costs. ACO agreements are currently blended into existing contractual relationships between payers and providers and differentiate various health plans. ACOs are provider based where the financial and quality responsibility lies in the hands of the people who are delivering the care as opposed to those who are paying for it [21]. To complicate the matter as of 2012 a US News & World Report analysis identified nearly 6000 health insurance plans marketed to individuals and their families differing in the types of coverage such as prescription drugs, maternity, etc. [22]. It is clear that the 'person' needs to step up and take control of their own health [23]. The variables in private practice are accountability and controlling costs due in large part to defensive medicine, waste, redundancy and especially fraud estimated to be some 65 billion per year [24]. Additionally, with the concept of 'big data' where clinical outcomes are based on a large number of clinical inputs every person becomes accountable for their clinical outcome and treatment result [25]. If the concept of shared decision making and/or responsibility is the focus then every person's encounter, whether it is for research or an annual visit should be a data point with ensured integrity. Such data manifested as clinical outcomes for the patient would be worthy of real time input into a 'big data' assessment and for its response as best practice at that moment for the patient. Studies conducted for clinical research purposes follow the principles of GCP as described in the Code of Federal Regulations (CFR) [26]. Incorporating these principles into private practice would greatly improve the quality of medical records, accountability for treatment by both provider and person which could lessen malpractice complaints and limit fraud, and overall set a national standard of care that would be transparent for every practitioner. The goal would be that every medical or healthcare encounter/event would be accountable and usable as data for best practice outcome by a big data platform. The person becomes the fulcrum for research and in health as well as in sickness and they become integral parts for the success of the treatment outcome. Certainly, if the person is to be included in research protocols from start to finish then they can be naturally and seamlessly included as part of their own treatment. For our discussion the term subject is used for a clinical trial describing the various phases of drug development. The term patient is used for practice-based studies as they are already marketed products used for standard of care studies such as CER and translational studies moving drugs/devices used by specialists to primary care providers to increase use and reduce cost. This terminology is more descriptive for the review process by Institutional Review Boards in facilitating the approval process for PBTN studies.

PBTN: infrastructure for change

The ACA has created to date, as part of the process of change, many disparate sources and pieces of what is to become a new healthcare paradigm. In this selection of the fittest, notwithstanding political lobbyists, it is hoped that a new healthcare to health system will emerge. Part of this change is the commoditization of healthcare where cost will eventually influence the treatment outcome and where patients will be seen by clinics and/or pharmacies designed for screening and categorizing certain conditions from identifying HIV infection to checking fertility levels to giving memory tests for early signs of Alzheimer's by ancillary healthcare personnel much like the CVS Minute Clinics that presently exist [27]. The Nation can no longer view healthcare as an infinite resource for the treatment of its populace. Moreover there are increasing discussions of changing our focus from sickness care to ways in which we can promote and sustain healthy behaviors and lifestyle changes. Whatever shape, form or design the new healthcare model takes there will be a need for an infrastructure to optimize and support a person's healthcare delivery, provide oversight for the treatment outcomes, provide a means whereby a person's data can be utilized for the greater good, provide continued surveillance of drugs for improved drug safety programs, minimize fraud in the system and not be at odds with the healthcare providers. What is this infrastructure and what role will it have in this new system is still to be determined. We are proposing an infrastructure in this manuscript for consideration and discussion but whatever shape it takes some infrastructure needs to be in place such that persons, providers and payers can go to for the resolution of treatment outcomes.

Originally a PBRN was defined as a group of ambulatory practices devoted principally to the primary care of the person, affiliated with each other (and often with an academic or professional organization) in order to investigate questions related to community-based practice. PBRNs typically draw on the experience and insight of practicing clinicians to identify and frame research questions whose answers can improve the practice of primary care. By linking these questions with rigorous research methods, the PBRN can produce research findings that are immediately relevant to the clinician and, in theory, more easily assimilated

into everyday practice [28]. One aspect of PBRNs that has become a foundation for decision-making in clinical practice and health policy are comparative effectiveness reviews. Comparative effectiveness reviews are summaries of available scientific evidence in which investigators collect, evaluate and synthesize studies in accordance with an organized, structured, explicit and transparent methodology. They provide clinicians with scientifically rigorous information for comparing the effectiveness and safety of alternative clinical options. Further, they approach the evidence from a patient-centered perspective; explore the clinical logic underlying the rationale for a service; cast a broad net with respect to evidence; assure internal validity; and, present benefits and harms for treatment and tests in a consistent way [29]. The two operational phrases are 'scientifically rigorous' and 'internal validity' which becomes somewhat difficult to assure in a review. A network capable of conducting the study itself can assure the science and validity of the data and when the practitioners generate the data than they have the confidence to incorporate change in their practices. For a network to conduct a study to satisfy the above criteria as well as generalizability it must have an infrastructure to ensure data integrity.

The Practitioners Engaged in Applied Research & Learning (PEARL) Network was designed to incorporate 'rigorous research methods' into the private practice setting by following the principals of GCP and screening and educating practitioners to conduct clinical studies capable for regulatory submission which is the benchmark for internal validity and rigorous research methods. Since the studies conducted are primarily standard of care the word 'research' was changed to 'translational' as it is more relevant and descriptive since the goal is to have the findings assimilated into everyday practice as well as technology translated from specialists to primary care physicians. Other changes include use of the term 'person' instead of subject and defining the use of clinical trial versus clinical study. Standard of care in this context is defined as the use of a drug, device or treatment that has regulatory approval and a risk profile for use in ambulatory persons.

The PEARL Network was initiated as a grant proposal funded by the NIDCR/NIH in 2005 and was supported for a total of 7 years [30]. The objective of the grant was to build a Practice Based Research Network (PBRN) for the dental profession similar to medical PBRNs that were supported by AHRQ. The one exception and point of differentiation was that the data generated by PEARL was to be 'generalizable' and that the practitioners be continuously engaged.

The infrastructure of PEARL is designed by merging the merits of a pharmaceutical industry clinical group with the advantages of what a PBRN can deliver such as patients of record, interested practitioners in advancing the knowledge base for treatment and data eligible for the 'big data concept.' This hybrid network has also modified some terms to clarify its operations and expedite approval by local IRBs. The PEARL Network is the first PBTN built on the principles of GCP such that the studies it conducts are in compliance with regulatory agencies and can be submitted to satisfy drug development requirements primarily in the spaces of Phase III and Phase IV. Design of studies allows for the persons to have input in accordance with the FDA guidance document for patient reported outcomes including quality of life for person-centric assessment. N-of-1 person-centric clinical trials can be grouped by treatments since they are standard of care for equipoise and adopted to implement creative changes in clinical design. Equipoise is reached when a rational, informed person has no preference between two (or more) available treatments [31].

PEARL has conducted some 20 studies over the funding period ranging from observational, retrospective, prospective and randomized controlled clinical studies and has partnered/affiliated with other medical/dental based PBRNs. It is presently conducting a practitioner/patient survey study with the FDA to assess the use of an Opioid Patient Provider Agreement. A designed infrastructure for healthcare can provide regulatory agencies with assistance in their initiatives to protect the populace. The FDAs Safe Use Initiative is an example of how large-scale practitioner input can make a difference in the amount of data collected to make meaningful decisions [32]. The largest study to date that PEARL has conducted consisted of almost 1900 patients and for the randomized controlled clinical studies it conducted had a patient compliance rate as high as 98%. The advantage of PEARL lies in its ability to recruit highly motivated practitioners who are screened to ensure no licensure limitations, recruit long-standing patients of record that have a known medical history to identify early side effects (signaling) and provide real-use data, which is more robust than that generated from a controlled environment.

PEARL's scope broadened when it moved beyond its origin and roots in dentistry to an interdisciplinary practice-based network which has expanded its infrastructure into healthcare with a published philosophy based on the concept of Person-Centricity conducting Person-Centric Clinical Trials [33]. The PEARL infrastructure allows for every clinical encounter to be considered a data point [8]. PEARL is an added value entity that brings together persons and practitioners with entities interested in advancing healthcare such as academic centers, payers and the pharmaceutical

industry. The pivotal component of the model is that practitioners are themselves generating the data allowing for them to be their own best advocate for change within their office environment. The collaboration may reduce the translational gap, allow academic centers to market a real-time curriculum reflective of treatments based on clinical evidence, develop a pool of practitioners interested in becoming faculty members, benchmarking of the practitioners who participate in a clinical study to improve their skills, conduct CER studies, provide information dissemination to both practitioners and patients and function as the infrastructure for healthcare delivery based on the principles of Person-Centricity: self-determination, transparency and healthcare literacy.

PBTN creates an opportunity for continuous learning for both clinicians and students. If students are trained with the concept of quality integrated into each encounter, it is a natural next step to base decisions on patient specific measures. Providers trained with the understanding that every person has a basic right to n = 1 treatment, beyond the public health prevention model which would support the foundation of a healthy community. The individual's health responsibility needs to be acknowledged, translated and communicated for improved outcomes. To accomplish this, there is a need for collaboration throughout the health industry beginning with the schools. Clinicians practicing under the concept proposed should strengthen the educational aspect of training for both shared decision making and a quality person provider encounter. Generating continuous data for improvement in both treatment and healthcare delivery would produce a more concerned provider and in the process create a reservoir of potential clinical faculty for the medical center [34].

Person-centric clinical trials: drug development, regulatory change & early signaling for drug safety

Accelerating the time frame and improving the quality of clinical trials has been an elusive but sought after goal and the profession/industry has not challenged the present model proposed by regulatory agencies. Change can be limiting as the temporal and side effects of the drug can vary. The pharmaceutical companies are not in a position to challenge government agencies as they oversee every aspect of the drug being approved as well as marketed. Change in the clinical drug development process can be in quality of the data collected, improvement in patient recruitment and in the kind of patients being recruited to the study, the ability to collect robust data in real-time, the ability to improve 'signaling' of side effects during the clinical testing process and accelerating the continuous process of drug safety especially by having a study become a part of the sentinel program benefiting both the regulatory agency by early detection of side effects and the pharmaceutical company by lessening liability after the drug is marketed. In 2007, Congress passed the FDA Amendments Act (FDAAA), mandating the FDA to establish an active surveillance system for monitoring drugs, using electronic data from healthcare information holders. The FDA launched the Sentinel Initiative with the goal to build and implement an active surveillance system that will eventually be used to monitor all FDA-regulated products. The program, it is hoped, may reduce the size and scope of late stage clinical trials and of post-approval studies consistent with the goals of person-centric clinical studies [35].

The current system of the clinical trial approval process resides in negotiating with the regulatory agency on the design of the Phase III studies. Currently two randomized controlled clinical trials are required to establish safety and efficacy. The safety component is continuous and on-going but may be missed in a controlled study that is limited and does not reflect real use data. The efficacy component as well may not be reflective of real use as every aspect of the study is optimized and controlled from the investigator, patient and healthcare environment, again not reflective of how the drug may be ultimately used in a practice setting. The randomized controlled trial (RCT) designs and hegemony around systematic reviews have worked well to create an initial body of research but have not worked for producing replicable results that matter or translate [36]. The system that has been built stifles creativity and thinking by holding that efficacy RCTs are always the highest or only type of evidence considered [37].

The infrastructure of a PBTN can function as the operational structure to suggest some changes and improvements in the Phase III and IV requirements of the clinical development process. For the Phase IV postmarketing commitment that a company has with a regulatory agency to conduct drug safety surveillance reported by the annual reports having a network that providers can continuously monitor their patients and be discriminative about the quality of the drug side effects becomes essential to data integrity supporting the package insert and in monitoring of the drug. The percentage of marketed drugs approved and out of Phase IV compliance is estimated to be more than 70% [38]. Pharmaceutical companies will be able to complete their Phase IV commitments and be in compliance with government agencies. Phase IV studies on already approved drugs become standard of care are in the domain of a PBTN.

The process of a Phase III commitment becomes contingent upon the risk potential of the drug, predictive pharmacology of the molecule and overall safety of the drug to be allowed use in a practice setting. We are suggesting that a more robust presentation of the safety and efficacy of the drug being reviewed by regulatory agencies would be better served by conducting one traditional randomized clinical trial and the second study to be conducted by a GCP practice-based network. Variations of this combination of studies can be further constructed with the PBTN study eventually confirming the robustness of the RCT data generated. A practice-based network study can be viewed as the antithesis of the RCT in that it uses a large number of investigators each recruiting a relatively small number of patients, whereas the RCT uses a small number of investigators each recruiting a large number of subjects. During the early phases of drug development the RCT takes precedence but for later phases of clinical development where a large amount of safety and robust point of use data can be generated the pendulum shifts to conducting a PBTN study (Table 1). The same principles (GCP) apply to limit bias and ensure data integrity as in an RCT study.

PBTN clinical studies can be viewed as complementary to the traditional RCT and of adding value in generating a large robust dataset that is quality controlled by the principles of GCP, and most likely will identify drug side effects earlier compliant with the FDA sentinel program and lessen postmarketing issues for the pharmaceutical industry. Safety is the essential directive for a study to be considered for a practice-based network. The combination for one randomized controlled clinical study plus a practice-based clinical study offers advantages over the existing protocol for drug development for regulatory agencies such as the FDA. The model should shorten the clinical time in development, identify side effects more efficiently, make practitioners aware of the drug prior to market and be cost effective by reducing the size of the RCT Phase III studies due to their broad based clinical design to capture adverse side effects.

Operationally a practice-based translational study requires a central infrastructure to ensure that regulatory requirements are being adhered to, protocol compliance is maintained such as randomization and patient blinding. Randomization is best performed by the data coordinating center but can be done with an experienced site. Some studies randomize the sites if the outcome is based on a procedure, device or a specific drug that a physician may prescribe. The boundary parameter for a PBTN study is standard of care. Patients are asked if they want to participate in a study and each patient is formally enrolled as per the proto-

Table 1. Relative differences between the operations of a randomized controlled clinical trial versus practice-based translational network conducted clinical trial.

	RCT	PBTN
Number Investigators	Limited	Less limited
Sample size	Smaller	Larger
Population	Restricted	Broader base
Medical history	Not always known	Typically known
Clinical outcome	Efficacy	Efficacy/effectiveness
Generalizability	Lesser	Greater
Data source	Controlled	Point-of-care
Data integrity	GCP procedures	GCP procedures
Bias prevention	Blinding	Blinding (patient and practice level)
Outcomes	Limited	Broader
Type of study	Investigator centered	Person-centered
Scope of study	Low margin of drug safety	High margin of drug safety
Safety data	Limited	Broad
Adverse drug reactions/events	Many unexplained	Explained/known history
Screen failures	Greater	Lesser
Recruitment	Public	Practice
Study commitment/compliance	Lesser	Greater

GCP: Good Clinical Practice; PBTN: Practice-based translational network; RCT: Randomized controlled trial.

col. Blinding of the study is best ensured by the data coordinating center but can be performed by the site as well as a caregiver, for example, a caregiver can place pills in numbered envelopes to be opened on consecutive days maintaining the blind. The infrastructure is always present to support operational steps that are protocol specific. Persons can be monitored through mobile health technology and even by remote entry of their improvement and/or worsening of their condition. The infrastrucuture with clinical research associates can ensure the proper oversight of the patient. Data integrity and all the controls associated with an RCT are in place for a PBTN study such as queries and close-out procedures. Bias is minimized by the same blinding procedures that would be applicable to an RCT at either the patient or practice level with the infrastructure overseeing compliance.

Person-centric clinical trials: optimizing chronic disease outcomes

The concept of person-centricity is best exemplified by an individual diagnosed with a chronic condition where they themselves become pivotal in shaping the outcome of their condition and future [39]. The role of the person mandates moving beyond the passivity of the patient to the self determination of the person reflected in their own treatment choices and desired outcome, essential to optimizing person-centricity. It places the person in the forefront of accountability and responsibility for compliance of their treatment, behavioral modifications to make substantive changes in their lifestyle, which led up to their condition in the first place and initiates the process of the person thinking about their health rather than their condition. Healthcare today is directed toward chronic treatment and essentially maintaining the *status quo* of the person allowing them to continue to pursue a life style without changing the underlying causative factors to alter the course of the disease process and/or maximize the treatment prescribed. Obesity and its sequelae such as hypertension and diabetes are obvious examples where the philosophy of person-centricity can alter significantly the outcome of the treatment. This also produces a halo effect for the people around this person and directly and mutually benefits, for example, not only the person but the family and community. Family support as reported by the Institute of Medicine can be very influential and cost effective for the Nation in managing a chronic condition [40]. Other conditions such as chronic pain, drug addiction and depression may have an improved outcome under person-centricity in conjunction with family support and behavioral intervention. The N-of-1 trials as defined by person-centric are particularly suited for chronic conditions, with considerable savings to the healthcare system [3].

The magnitude of all these moving parts requires a robust infrastructure to support them and maximize the patient/provider encounter. Healthcare plans differ in the number of minutes allowed for patient face time with the provider and even that is questionable as they are mostly looking at a computer screen. Provider time can be available directly, via phone and/or telemedicine and by mobile health (m-Health) devices for 24/7 monitoring whereby the information can be summarized on a daily, weekly or monthly basis for transmission to the practitioner. Infrastructures such as Kaiser Permanente which is a closed healthcare system approaches such an infrastructure but do not optimize the person/provider encounter to the level of a data point.

Person-centric clinical trials: managing big data

The 'Big Data' concept or a National Medical Grid as the repository for healthcare data and treatment outcomes is a concept used to align the many moving parts of the system. However, this requires an infrastructure to ensure that the data going into the system has been vetted and meets the conditions of data integrity and verification. This is the basis for optimizing the patient–provider encounter satisfying the parameters of a data point making this point worthy of being part of the big data platform. Encounters based on quantity over quality can be misleading for a person wanting to participate in the program and expecting a quality decision from their provider on the best practice treatment for their condition which may or may not be evidence based at that moment. The data would become 'evidence based' as the data trends and would be most evident when presented as a comparative effectiveness study otherwise the data are presented to the patient as 'best practice' at that moment in time. A subtle but distinguishing feature between the terms best practice and evidence based. The ethics of practitioners recruiting persons (patients) to such studies has been recently reported on in the literature [24].

The concept of a 'Big Data' platform or medical cloud or 'National Medical Grid' is consistent with closing the translational gap. The idea of designing a practical framework that allows for real time comparison of clinical outcomes creates a portal for the latest information to be incorporated into healthcare and would facilitate change. The infrastructure is essential for responsible sharing of clinical trial data [41].

The use surveys and administrative datasets for policy analysis and policy development is an important first step in decision making about how to best spend

healthcare dollars. However, the process requires a level of consistency in terminology across all healthcare disciplines [41]. Whatever the format, it is the quality of the input that we are discussing when applying the philosophy of person-centricity.

Point-of-use data generated by a GCP practice-based network as well as administrative and claims datasets have a role to play in the conduct of CER provided the data has been subjected to some standard of quality assurance. The use of CER is an important strategy to improve health outcomes decisions and balance healthcare spending. The potential pitfall of CER is that if policy makers and benefit providers (in an attempt to contain costs) use CER-generated results to choose services based on price alone, they may restrict patient access to necessary care [42]. Providing an infrastructure to function as a scaffold for healthcare can improve data quality and utility and be the interface to research [43].

Large healthcare datasets primarily consist of claims and/or hospital datasets that are based on diagnosis codes. They lack objective point-of-use data such as person (patient) reported outcomes, disease activity and other measures of health, that could be provided by a GCP PBTN/PBRN.

Currently ACOs are limited to claims and diagnosis data, and use administrative datasets to measure outcomes. These administrative datasets are a proxy for point of use data. The hundreds of ACOs around the country attempt to measure quality of care, accepting the limits of existing infrastructures and by relying on administrative data.

Person-centric clinical trials: transition to healthcare for collaboration between person, provider, payer & industry

The current healthcare system is not sustainable and does not adequately consider all of the variables from the person, provider, payer and the pharmaceutical industry and their common interests. To unravel this complex system would be a burdensome task for any individual. The attempt to re-direct healthcare to the 'person' through the ACA may be the path of least resistance. The many disparate parts of the healthcare system do not even communicate with each other making improvements and optimization very difficult if not impossible. The concept of expanding the principles of person-centric clinical trials to person-centric healthcare and providing an infrastructure of inclusion for all stakeholders is an approach which can only benefit each person and the community at large. Person-centric healthcare shifts the healthcare cost curve so that the person assumes some accountability and responsibility for their treatment outcomes. The basis for person-centric healthcare relies on the same foundation as person-centric clinical trials: transparency, healthcare literacy and self-determination as well as having an infrastructure to support the 'person' on its foundation. This shifting of healthcare on individual self-reliance rather than on medical paternalism is consistent with the essence of person-centricity and consistent with the American principles. The concept is transformative in that the person is no longer passive in the process but becomes their advocate for themselves to improve their own clinical outcome. This is truly the N = 1 or what personalized medicine or care should be, going beyond the traditional definition reserved for medicine, related to personalized drug development. Person-centric healthcare as it relates to personalized medicine embodies not only the drug development component but the 'persons' active role in the treatment to make it 'personalized' and to improve their health.

Making each person – encounter a quality encounter as governed by the principles of GCP can be cost effective and streamline a number of organizations that have been built on top of this encounter. The principles of GCP can be the common thread of quality that creates an audit trail to minimize redundancy of treatment, overtreatment, treatment of a questionable nature and healthcare fraud. Practicing at a level below GCP where the encounter now becomes less than acceptable as a data point compromises the data inclusion into the Big Data platform, requiring various levels of oversight to ensure 'some level of quality.' A GCP infrastructure would provide practitioners the ability to integrate research principles for quality improvement [44].

A coordinated effort by all stakeholders could lead to a meaningful, cost-effective and within-reason, a profitable healthcare system for all stakeholders. Healthcare has not made use of the efficiency and economy of scale that it requires if the system is to be meaningful, lean and efficient. Healthcare plans differ on face time that the person has with the provider with some so limited that you are encouraged to see someone other than the primary care physician. In a minimal time period one is to familiarize themselves with the person by reviewing the past medical history, listen to the person for their chief complaint, examine the person, assess the person and findings and make a decision on treatment. Would it not be better to build the quality up front within the encounter and limit all of these points of potential problems on the quality of the encounter? Differences in quality can be seen in the current system as variability in comparative datasets ([Electronic Health Record] vs claims data) have different end points but should be complementary to each

other [45]. No other legislation passed by Congress has the impact on the person as healthcare affecting the person directly in cost and the very nature of their well being. Person-centric healthcare functions best when the person is in control but is supported by the federal government in its ability to educate the populace.

The healthcare discussion would be incomplete if we did not include the state of science and how the populace values it. We have previously published the rationale why every person should be part of and contribute to the national data base through a person-centric healthcare model [24]. By increasing the cognitive level of medical advancements to the population people will gain further insight into what these advancements cost as they continuously add additional dollars to the healthcare system. The question of whether medical advancements are an entitlement and what is minimal care for public health concerns remains to be answered and must be addressed in an intelligent and fair manner. Medical advancements have been a key component of the increased costs of the nation's total healthcare spending. Real healthcare spending rose from $108 billion in 1960 to $1.6 trillion in 2002, a 15-fold increase [46]. For 2011 national health spending was estimated to have reached $2.7 trillion [47].

Conclusion

We have defined the N-of-1 clinical trial to be based on the person increasing the breadth of information to include treatment and health making the model more cost effective. The person and their response to participating in a clinical trial would complement that of the principal investigator with objective interpretation rather than having the principal investigator subjectively interpret for the person [48]. It presents an improved view of the clinical trial. Person-centric trials can be personalized and/or summed for their responses to satisfy statistical objectives. Person-centric clinical trials are clinical studies designed to generate increased safety and robust clinical data with the intent to assist both industry and regulatory agencies in facilitating the drug approval process without compromising the quality and quantity of data considered. Its intent is to generate data that are more robust than that collected in a controlled environment and to identify drug side effects while still in the clinical development stage. The advantages are numerous and include engagement of practitioners to have a quality encounter with the person, and as a consequence the standard of care will be set as a measure for consistency of the data being included in the big data platform. Using an infrastructure allows the person/provider encounter to be formalized to a level that observational data can be validated [49]. There should be no range of quality just one established standard and that would limit the cost of having a large number of organizations being involved adding to the healthcare costs. For clinical research the person-centric clinical trials, by recruiting patients with known medical histories, would produce more robust data and identify drug side effects while lessening idiosyncratic responses earlier in the development process rather than after the drug is marketed. A person/provider encounter recorded as a validated data point provides a continuum of data for drug safety, pharmacovigilance and pharmacoepidemiology analysis. Some pharmaceutical companies have already embraced data transparency for validation by multiple analyses and for clinical researchers to assess the clinical design with complex data consisting of the person, laboratory, investigator and other inputs such as genomics for what could be a once in a lifetime study for the drug due to cost and size [50].

We propose that the clinical regulatory commitment to satisfy the Phase III requirement be changed to include one randomized controlled clinical study and one GCP PBTN study. The combination of the two forms of clinical studies would provide data, which would assist a regulatory reviewer in the approval process. It is the goal of any submission to create a level of confidence for the regulatory reviewer that the drug is safe and efficacious and to anticipate the questions that may be asked of the reviewer by agency officials and/or by the public. Broadening the data presented to the reviewer and agency does just that.

The complexity of the healthcare system currently lacks objective data and an infrastructure to support that data. We are proposing an infrastructure based on the principals of GCP such as the existing PEARL Network. Person-centricity is based on self-determination, transparency and healthcare literacy and should be the cornerstone of every person's concern for the complete life cycle of the person. Person-centricity should remain a constant from the earliest time at which we can express ourselves as to what we want and do not want and what we are willing or nor willing to do each minute of our lives up to and including the time of our last breath. We believe the concept to be transformative in the approach to both drug development and healthcare and have the potential to be cost effective on both counts. Our proposal optimizes CER to individual care and treatment innovation to advance our knowledge about the effectiveness of various clinical strategies [51]. Additionally, adherence to person medication compliance should improve further reducing cost and improving clinical outcomes [52].

The person–provider encounter should inherently be one of quality to instill confidence in the person to be compliant to what has been prescribed for their treatment. We are proposing that the quality encoun-

ter be standardized to the level of GCP. Quality should not be negotiated and tied into healthcare and its outcomes through cost. The data generated through this process would allow the information coming into the big data platform to be worthy of provider feedback for improved treatments and outcomes.

Future perspective

Identifying common elements of the healthcare system with the principles of clinical research creates a synergy for efficiency that benefits both systems that have similar outcomes. The infrastructure proposed controls the burden of disparate add-ons to the healthcare system which can be costly and inefficient. The model provides for the flow of continuous quality information and person recruitment to facilitate clinical development and the big data platform for improved decision-making. Increasingly, cost has become a dependent variable worldwide in healthcare and its delivery affects all aspects of clinical research and healthcare and is the basis for improved quality and in closing the translational gap. Cost is also recognized in the WHO Alma Ata Declaration of 1978 for the definition of primary healthcare [53]. The more data fed into a system the better the decision-making process whether it be shared or individual. We are proposing a transformative model whereby the person supersedes the patient and the person/provider encounter is defined on the basis of quality improvement such that there is a continuous input of data to optimize healthcare decisions and expedite regulatory approval. The manuscript proposes using an infrastructure that has been developed under these principles that has conducted a number of clinical trials for proof of principle. The infrastructure will benefit all stakeholders and is applicable worldwide. Person-centric clinical trials define the N-of-1 using a GCP practice-based translational network that offers both a philosophy and model to accommodate issues of clinical drug development and healthcare.

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Executive summary

- Redefining key terms of clinical research for application to healthcare allows for quality improvement and an audit trail to maximize healthcare expenses.
- Considering the person and not the patient in this new paradigm is transformative.
- The model proposes an infrastructure that allows for continuous recruitment and data for drug development and optimization of healthcare delivery.
- The model improves the drug approval process by generating robust quality data for regulatory reviewers.

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