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Outcomes Research in Childhood Autoimmune Diseases

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Synopsis

This article provides an introduction to key aspects of outcomes research in pediatric rheumatology with focus on arthritis. Patient centered outcomes research addresses questions of interest to multiple stakeholders in order to guide the best health care decisions suited to a particular patient's circumstances and preferences. Discussion includes the importance of maintaining high quality longitudinal patient registries and use of valid clinical and patient reported outcome measures. Rapid, reliable translation of research on best practices into clinical care, as facilitated by quality improvement learning networks, leads to timely and meaningful improvement in patient outcomes.

Keywords

Outcomes Research; Patient Outcome Assessment; Registries; Quality Improvement; Rheumatology; Pediatrics; Health Services Research

Introduction

Outcomes research, also known as patient centered outcomes research or comparative effectiveness research is oriented towards studies of health care practices such as specific medications, behavioral interventions, care delivery systems and their impact on best outcomes for individual patients [1,2]. For this research to make a difference, there must be investment in activities to disseminate this knowledge, to implement the findings into practice, and to measure and improve quality of care delivered [3].

Although this is not a new field of study, there has been increased emphasis and enthusiasm for this line of research as a result of changes in federal legislation and recent substantial funding for comparative effectiveness research (CER). The American Recovery and Reinvestment Act of 2009 allocated \$1.1 billion to fund CER between The Agency for

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Healthcare Research and Quality, the Department of Health and Human Services, and the National Institutes of Health. In 2010 the Patient Protection and Affordable Care Act served to establish the Patient-Centered Outcomes Research Institute (PCORI), a not-for-profit, independent organization funded through the Patient-Centered Outcomes Research Trust Fund (PCORTF) with income from the Treasury and from a fee to Medicare, private insurers or self-insurance plans. It is estimated that PCORI will receive \$3.5 billion through September 30, 2019 [4,5].

The spirit and distinguishing characteristics of this research are evident in the definition of CER used by the Federal Coordinating Council for Comparative Effectiveness Research (FCCER):

Comparative effectiveness research is the conduct and synthesis of systematic research comparing different interventions and strategies to prevent, diagnose, treat and monitor health conditions. The purpose of this research is to inform patients, providers, and decision-makers, responding to their expressed needs, about which interventions are most effective for which patients under specific circumstances. To provide this information, comparative effectiveness research must assess a comprehensive array of health-related outcomes for diverse patient populations. Defined interventions compared may include medications, procedures, medical and assistive devices and technologies, behavioral change strategies, and delivery system interventions. This research necessitates the development, expansion, and use of a variety of data sources and methods to assess comparative effectiveness [6].

The emphasis is for delivery of high quality topics of relevance and importance to patients and families that allows them to make informed decisions about their healthcare. A central aspect of that evidence is the analysis of the impact of a particular intervention, (i.e., as so defined above) on patient relevant outcomes. These may include patient reported outcomes of symptoms or function, side effects, economic impact, impact on social or societal participation. CER thus necessitates high quality registries for longitudinal patient follow-up and outcome measures that have proven to be valid and responsive to change. Another distinguishing feature is the recognition that there are multiple stakeholders who require this information to make informed health care decisions which include, not only clinicians, researchers and patients, but also policymakers and insurers [2]

Once information has been generated from outcomes research on what interventions or treatments are most effective, it needs to be efficiently distributed in such a way that it can identify in which setting the intervention will be most beneficial. It has been well described that there is significant time lag in translation of research evidence into clinical practice [1]. Furthermore, there are widespread disparities in care received where people who might benefit from a treatment do not get it [7]. The CER definition places emphasis on the mission “to inform”. The quality of actually delivered care may be monitored and evaluated in part whether patients who would benefit from a given treatment receive it [8].

Registries in Pediatric Rheumatology

Longitudinal registries with high quality data are essential to the validity of patient outcomes studies. Clinic based data sets, in contrast to administrative data sets such as medical insurance claims, allow for collection of information on disease severity such as clinician measures of disease activity and patient reported outcomes measures.

There is a growing number of national and international registries in pediatric rheumatology of which only a few such examples are described here. The organizing principles, format,

frequency of visits, measures collected, disease populations, funding sources and other features vary across the registries. This renders aggregation of the data or replication of study findings challenging.

PharmaChild is a network of registries from multiple European Union (EU) countries for the purpose of pharmacovigilance regarding treatments of juvenile idiopathic arthritis (JIA). PharmaChild is funded by the EU, pharmaceutical companies, and organized by the Pediatric Rheumatology International Trials Organization (PRINTO) [9]. In North America the Pediatric Rheumatology Collaborative Study Group (PRCSG) has maintained post marketing surveillance registries after completion of randomized controlled trials for JIA treatments [10].

The example of national, population-based databases provides an illustration of comparative effectiveness studies under favorable circumstances. Such registries confer advantages such as reduction in bias, full ascertainment of the population avoids selection bias and ensuring representativeness of the sample. A national registry minimizes censoring and loss to follow-up. Equally important is the standardization of outcomes assessment for patients across different clinic sites.

Studies from Germany, such as the German Etanercept Registry have described long-term safety and efficacy of etanercept in JIA. Another recent German registry examined the clinical experience with oral versus subcutaneous administration of methotrexate on disease control, as well as adverse effects of treatment. Investigators found no advantage of using subcutaneously injected methotrexate over orally administered methotrexate [11], despite practitioner debates to the contrary. Is this a question of interest to the patient? A study by Mulligan et al. showed the importance of addressing this question as far as implications for health related quality of life (HRQOL) of patients and caregivers. In the study, methotrexate use in general was described as having a negative impact on HRQOL, but administration in the form of injections was identified as a significant independent predictor of distress [12].

The Dutch National Biologics Register provides another example of a registry providing longitudinal follow up of etanercept treated patients used to address a question likely of general interest to the public, payers and policymakers. Do the treatment benefits of etanercept justify the relatively high cost of the biologic medication? The study entailed an economic evaluation comparing estimates of costs and utility in the 12 months preceding the medication use and 27 months following initiation. The Health Utility Index Mark 3 was given to the majority of sites that participated (7 of 9), in order to calculate quality adjusted life years, in addition to routine collection of clinical variables and patient reported outcomes. It was concluded that the medication was cost-effective [13]. Note that in the United States it is stipulated that CER is to focus on effectiveness of treatments rather than results to be used in policy decisions to minimize costs.

In the US the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry has representation of 62 pediatric rheumatology centers and over 6,000 JIA patients enrolled. The CARRA registry also collects information on multiple childhood rheumatic diseases including systemic lupus erythematosus, juvenile dermatomyositis, linear scleroderma, vasculitis, fibromyalgia and others. One of the purposes of the registry is to identify patients eligible for clinical trials, in addition, to conduct CER, and long-term safety studies. Cross-sectional studies have characterized a descriptive epidemiology of the study population including disease and demographic characteristics and prescribing patterns in the US [14, 15]. Longitudinal follow up is planned and underway. The CARRA registry overlies an informatics framework based on the Informatics for Integrating Biology and the Bedside (i2b2), and NIH-funded National Center for Biomedical Computing [16]. It is a scalable,

federated system whereby individual centers have ownership of their own data, and can contribute data to network studies with permission [17].

The ARChiVe (A Registry for Childhood Vasculitis), based in Canada, is a registry targeting children with ANCA-associated vasculitis, established in cooperation with the CARRA network [18].

Comparative effectiveness in observational databases confers significant challenges to the validity of findings. Principal among these are bias, of which there are several types, and confounding [19]. For example, confounding by indication occurs when both the study outcome of interest and the treatment selected are related to the severity of disease. A choice of treatment that is thought to be the strongest may thus go to the sickest most refractory to treat patients, and the potential benefit of the treatment for the disease may be underestimated. There are statistical analytic techniques that minimize these, such as use of propensity scores or instrumental variables but these may not be able to sufficiently overcome the problem and risk of flawed conclusions.

Variation in how patients are treated in clinical practice also poses additional difficulty to analysis and interpretation of observational data. According to clinical practice, geography, and other considerations there is wide variability in the care patients receive [20]. There is inconsistency in the way providers may approach patients that makes it difficult to analyze clinical data. For instance, there may be differences across providers in treatment selection, medication dosing, follow-up intervals, whether clinical variables and outcomes measures are assessed and if so which measures are used, missing data – all which introduce significant “noise” into the database. In the face of such unwarranted variability even sophisticated statistical techniques are unlikely to be able to detect whether an intervention is effective.

A way to try and minimize variability as well as bias is the use of treatment guidelines that if followed drive standardization. For example, guidelines may provide specified treatment options and dosing, approach to intensification or taper of medication regimens, standard visit intervals, and assessment schedules which specify clinical lab and patient reported outcomes measures to obtain. There are examples of treatment guidelines by various professional organizations, including consensus treatment plans generated by CARRA for systemic arthritis, juvenile dermatomyositis, localized scleroderma, lupus nephritis [21, 22, 23, 24] and polyarticular JIA (not yet published).

Networks for improvement and research

The Pediatric Rheumatology Care and Outcomes Improvement Network (PR-COIN) is an international quality improvement network that aims to improve the outcomes for children with JIA [25]. Learning networks are practice based clinical networks that use data to conduct research, including CER, and employ proven quality improvement (QI) methods and tools to improve process of care delivery and child health outcomes. Such networks function as collaborations among clinicians with patients and families, along with researchers and communities [26]. PR-COIN is a growing network, which was launched in 2011, and now includes 10 active PR-COIN sites, over 1000 enrolled patients with close to 4000 encounters.

The network sites of PR-COIN and the Rheumatology Clinical Registry of the American College of Rheumatology use a shared registry platform for longitudinal data collection. [27]. Data is collected at point of care on process measures of care and outcome measures. Process measures of care and target goals are based on published proposed process measures of care for JIA [28]. For instance, data is recorded to determine whether children with JIA

receive uveitis screening according to published guidelines in order to reduce risk of unrecognized inflammatory eye disease and avert development of vision loss. Other process measures track medication safety monitoring, and whether assessment of clinical outcome and patient reported outcomes is performed with reliability. Outcome measures are based on clinical outcomes prioritized by stakeholders and reflect the proportion of patients with 1) inactive disease, 2) optimal physical function and 3) no or mild pain.

Data is used in a timely manner to inform on improvement activities. Registry data is used to generate statistical process control charts, funnel charts, and other graphical presentations of site performance on measures over time. An individual site's performance is compared against other sites' performance and network aggregate benchmarks on a monthly basis. This prompt feedback on performance is used to direct subsequent QI activities and learning. For example, if a site is not meeting targets for uveitis screening, 90 day goals are set and teams design and carry out small tests of change with plan-do-study-act cycles. Sites then adapt, adopt or abandon the test interventions depending on whether they result in an improvement [29].

Quality measures are based on experience with the health care system and include: 1) site performance at baseline leaves an uncomfortably high number of patients with active disease, physical disability and more than mild pain, and 2), there is variation in performance across centers. However, as a network, with sharing of learning and QI activities, there has been initial improvement in performance on process measures of care. Interventions and change in concepts for improving care are based on the improving chronic illness care model [30], using the model for improvement for reliability of implementation.

The ideal state for the PR-COIN registry would be to meet the goal of “data in once” with repurposing of data. Currently one site has piloted upload of data from the electronic health record into the registry database – effectively being able to reuse the data starting with entry once for clinical care. Subsequently the same data are being used for quality improvement, and research purposes. Re-use of data becomes an essential strategy for such networks as it reduces costs of participation in the registry, by eliminating double data entry. This gain in efficiency allows for enrollment of a larger proportion of a clinic population into the registry, enabling spread of interventions (such as the concept of pre-visit planning) to more patients, generating a more representative sample of patients thereby reducing bias and increasing validity of findings, and also giving a more accurate picture of the health status of the clinic population and quality of care delivered [26].

Learning networks aspire to the model of a Learning Health Care System as described by the Institute of Medicine. Information technology may facilitate use of electronic medical record data as infrastructure for research, and support integration of health care, health care improvement, outcomes research and innovation. Communities of patients, clinicians and researchers engage in generating and addressing research questions of interest to guide decision-making and quality improvement activities [26].

Clinical Outcomes Assessment

In outcomes research consistent, reliable and routine assessment of health status using standard outcomes measures is important for objective measurement of disease progression over time. In quality improvement clinical outcomes assessment can feature either a process measure of care e.g. are complete joint counts being performed, is physician global recorded or measures to evaluate quality of care with respect to health outcomes.

For clinical trials, use of the American College of Rheumatology Juvenile Idiopathic Arthritis Core Set of Variables is a means of describing treatment responses in terms of

percentage of improvement. The core set variables include: 1) physician global assessment of disease activity; 2) parent/patient assessment of overall well-being; 3) functional ability; 4) number of joints with active arthritis; 5) number of joints with limited range of motion; and 6) erythrocyte sedimentation rate or C - reactive protein. For example 30% improvement as defined in terms of changes to core set variables - 30% or more improvement from baseline in 3 of any variables in the core set, with no more than 1 variable worsening by >30%. When a patient achieves 30% improvement, they are classified in the proportion of responders to an intervention meeting a "JIA ACR 30" response. 50% improvement corresponds to JIA ACR 50, and so forth for 70% response, 90% response and 100% response [31]. There are also criteria defining flare of disease in terms of the core set variables [32].

While the ACR JIA Core Set is an established measure of change over time used in randomized clinical trials, and in longitudinal outcomes studies, it is not typically used in routine clinical practice due to the fact that it is not a continuous measure of current health status, but rather a measure of change, and it is not straightforward to calculate. Furthermore, not all components needed to calculate the measure are collected at each routine clinic visit.

At this point an easy to use and continuous measure of disease activity for JIA has until this point not been established. However, a promising new disease activity score is the Juvenile Arthritis Disease Activity Score (JADAS) for which a validation study in a clinical practice setting has recently been published [33]. Fundamentally it is a composite disease activity score comprised of four variables: 1) Active joint count, 2) physician global assessment, 3) parent/patient global assessment of well-being and 4) erythrocyte sedimentation rate (ESR). There are various versions depending on the number of joints assessed, with the numeric modifier indicating the total joint count JADAS-71, JADAS-27, JADAS-10 [34].

In recognition that requiring an ESR to determine a JADAS scale score will be problematic in patient situations where blood draws are not being performed concurrent with a visit, or do not seem indicated based on a patient's having excellent clinical status, an alternative version, the JADAS3 has been studied. The JADAS3 omits the ESR from calculations and is well correlated with the full JADAS. The JADAS3 alternative will reduce a missing data problem in evaluating this measure routinely to track patient clinical status.

There is a dichotomous measure of JIA disease activity, the ACR provisional criteria for defining clinical inactive disease [35]. There are six components to this measure, all of which values must be as noted for a patient to be considered in clinical inactive disease: 1) No joints with active arthritis, 2) No fever, rash, serositis, splenomegaly, or generalized lymphadenopathy (i.e., features of systemic arthritis) attributable to JIA, 3) No active uveitis (per SUN working group), 4) ESR or CRP within normal limits established by performing lab, unless known elevated to other cause (e.g. concurrent illness), 5) physician global assessment at best possible value on scale, 6) duration morning stiffness less than or up to 15 minutes. As noted in the example with the JADAS, the requirement of inclusion of the ESR lab value may result in a missing data point in a clinical setting. This measure is clinician based, and aside from the morning stiffness value does not consider patient report.

As part of the PR-COIN learning network, sites are encouraged to collect all variables that are included in the ACR Criteria for inactive disease at each clinic visit (labs every 3 months), although quality measures are less stringent in terms of frequency of assessment. Given the speed with which new treatments for JIA take effect, interim changes may not be observed to characterize the trajectory of the disease course and timing of medication effect if assessments are only collected at 6 months intervals. Now that a validated continuous

measure of disease activity in the form of JADAS(3) is available, it offers a value by which to track patient status at a single point in time, in addition to the ability to monitor progress over time. This may prove useful in a clinical setting, and also as part of CER analyses.

Patient Reported Outcomes Assessment

Patient reported outcomes (PROs) add information that is complementary to other clinical parameters such as physical exam findings and lab tests to assess response to therapy, monitor disease control and track long-term outcomes. PROs are self-reports from patients that can capture a broad array of the patient experience including health symptoms (pain, fatigue), functioning, mental health, health related quality of life, participation in activities, self-efficacy and more [36]. Other topics such as, satisfaction with care, treatment goals and preferences can also be elicited by patient self-report. Assessing PROs gets to the intent of patient centered outcomes and provision of care that is responsive to patient needs that may not otherwise be identified in a clinical setting.

In selecting a PRO for a clinical study, or for clinical care, there are a number of factors to consider. These include the psychometric theory underlying development, whether it based on classical test theory or modern item response theory. The content covered by the measure, whether validity studies were performed, and measurement properties such as, sensitivity at high and low ends of the scale, and whether it is responsive to change need to be reviewed. There are some practical considerations such as whether a scale is publicly available or has licensing fees, ease of administration including the mode (paper and pencil, computer, hand-held electronic device, automated telephone surveys, or interview), respondent burden, ease of scoring, and interpretability of results. In pediatrics, another consideration is whether the scale is developmentally appropriate, and whether there is a companion proxy-administered version of the measure for young children unable to self-report (younger than eight years).

There are a multitude of PRO instruments to choose from in pediatric rheumatology. There are “generic” and cross-cutting measures intended to be used across diseases, and then there are disease specific scales. An important concept is that of a health ‘domain.’ A domain represents a one-dimensional health attribute, such as fatigue, or anxiety. Domain specific instruments can be “generic” and suitable for use across diseases because such health attributes are not specific to a given disease, although a given disease may have a characteristic profile of the attribute [36]. Disease specific PRO instruments lose the flexibility of being used across studies and conditions. A consequence of numerous PRO measurement options is that if the same instruments are not used uniformly across studies or clinical populations it results in the inability to compare results of interventions or treatments across different studies, or to perform meta-analyses of treatment effectiveness.

Development of PRO instruments has shifted from classical test theory to an item response theory approach. PRO instruments, or “tests”, are designed to measure an underlying health construct or attribute. Tests developed with classical test theory include a range of items to enable use for patients at high and low ends of the construct being measured. The entirety of items must be administered for the test to be scored. In order to administer items that cover the entire range of a trait without high respondent burden there is a tradeoff between efficiency and precision. Such tests may be subject to floor and ceiling effects, and not very sensitive to change.

For tests developed using item response theory (IRT), each item is calibrated on the trait along a measurement continuum. IRT models characterize the probability of the respondent's level on the construct based upon the response option chosen for a calibrated item. Some advantages are that “item banks” can be created for each health attribute that can

be quite large to allow for precision coverage at different levels of the attribute, yet any one respondent need to be given only a subset of items relevant to their level on the trait. For instance, a person who endorses ability to run a mile would not need to answer a question about whether they could walk on flat ground. Advantages are shorter instruments with fewer items (efficiency, less respondent burden), more precision of measurement and increased ability to detect change. Tests can be administered as static short forms, off-the-shelf or customized for a target level of a trait, or as computerized adaptive tests. The NIH Patient Reported Outcomes Measurement Information System (PROMIS®) cooperative network was created in 2004 to support a publicly available assessment system of PROs created with state of the art measurement science including IRT (www.nihpromis.org) [37].

There are a number of instruments available for PRO assessment in pediatric rheumatology. The reader is encouraged to review measure validation studies prior to selection of a PRO measure as such detail is beyond the scope of this review. Generic measures of health related quality of life tested in pediatric rheumatic disease samples, and as reviewed by Hullman et al., include the DISABKIDS, Pediatric Quality of Life Inventory (PedsQL™) 4.0 Generic Core Scales and Quality of My Life Questionnaire (QOML) all described to be useful in clinical and research settings. The Child Health Questionnaire (CHQ) is lengthy for clinical use but perhaps more useful in a research setting. [38] Examples of JIA disease specific measures of quality of life reviewed by Carle et al., include the Pediatric Quality of Life Inventory (PedsQL™) Rheumatology Module 3.0 which was evaluated as useful in clinical and research settings. The Juvenile Arthritis Quality of Life Questionnaire (JAQQ) and Paediatric Rheumatology Quality of Life Scale may be most useful in clinical settings [39].

Physical function PRO measures studied in juvenile idiopathic arthritis include the Child Health Assessment Questionnaire (CHAQ) [40], Juvenile Arthritis Functionality Scale (JAFS) [41], and Activities Scale for Kids (ASK). The CHAQ is well known to have a strong ceiling effect that may limit its usefulness to detect differences at low levels of disability (or high function), nonetheless it is used widely in clinical and research settings. The ASK has been used in research settings more so for primary orthopedic disorders [42].

PROMIS offers IRT based measures that are available for use to assess a variety of health domains that have been tested in children with JIA (www.nihpromis.org). These include measures of mobility, upper extremity function, fatigue, pain interference, anxiety and depressive symptoms. Qualitative analysis show good content validity [43], construct validity and responsiveness studies are underway [44].

As PROs are developed that offer efficient, precise estimates of patient self-reported health endpoints with less respondent burden and time demand, it increases the feasibility of incorporating PROs into routine clinical care. PROs can be administered electronically and incorporated directly into the electronic health record. There are examples of health systems that are already using such systems to guide medical decision making [45, 46]. Electronic health record vendors, including Epic, are integrating such PRO packages into their software. The routine assessment of PROs in clinical care has potential to influence the focus of care at patient visits and improve disease management, particularly if a system is used whereby PRO scales are automatically scored and results presented to the clinician in an interpretable and actionable way. Routine collection of PROs in clinical care will increase the ability to use data from clinical encounters to monitor patient status longitudinally and conduct CER of treatments and interventions in a clinical setting.

Future Considerations/Summary

Patient centered outcomes research is motivated to inform about the best health care decisions according to a particular patient's circumstances and preferences. By understanding the impact of treatments, healthcare or quality improvement interventions on patient relevant endpoints such as disease control, function or quality of life, the appropriate treatment can be selected for a patient that will optimize his or her outcome. Longitudinal registries with high quality data are essential to patient outcomes studies and advances in information technology are anticipated to allow use of data from clinical encounters to be repurposed for outcomes research. Reliable and routine assessment of health status using standardized outcomes measures allows for objective, comparable measurement of impact of different interventions on outcomes. PROs assessment in a clinical setting, when entered into the electronic record will enable PROs to be part of the calculus on impact on patients of interventions being evaluated in CER. Rapid translation of research on best practices into clinical care, as facilitated by quality improvement learning networks, leads to timely and meaningful improvement in patient outcomes.

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Key points

- Outcomes research is the study of the impact of treatments, healthcare or quality improvement interventions on patient relevant endpoints such as disease control, function or quality of life.
- Longitudinal registries require high quality data for patient outcomes studies to be valid. Information technology may facilitate use of electronic medical record data.
- Reliable and routine assessment of health status using standardized outcome measures allows for objective, comparable measurement of the impact of different interventions on outcomes.
- Patient reported measures add unique information to other clinical endpoints to assess response to therapy, describe preferences, quality of life impact, and track long-term outcomes.
- Outcomes research has its most impact to optimize patient outcomes when research findings on best practices are rapidly translated into delivery of health care.