



## The Ethics of Step Therapy: Next Steps

November 17<sup>th</sup>, 2015

In 2015, the International Foundation for Autoimmune & Autoinflammatory Arthritis (AiArthritis) led a six month investigation into the ethics of step therapy, which is an insurance company policy whereby patients must try a less costly treatment first and fail it before the insurer will cover a more expensive treatment. In other words, the patient is stepped up to the costlier treatment after failing the cheaper one, thus the term step therapy.

While bioethicists provided the background information, the conclusions were formulated by IFAA Chief Executive Officer, Tiffany Westrich-Robertson, the author of this paper. Ironically, it was her personal experience as a patient who was denied access to a clinical trial due to ‘atypical’ presentation that became the “ah-ha” moment that unveiled the major ethical implication of – and potential solution to - step therapy.

We hope this paper can shed light on the importance of patient inclusion at the table, as sometimes it takes the patient perspective to see what others cannot.

The International Foundation for AiArthritis helps those, like us, affected by autoimmune and autoinflammatory diseases with arthritis as a major clinical component (AiArthritis) have a voice - alongside other stakeholders as equals - so, together, we can identify and solve problems that impact education, advocacy, and research.

## METHODS

AiArthritis researched, reviewed, analyzed, and participated in current efforts to minimize negative effects on patients resulting from questionable ethics in step therapy policies. The team interviewed and selected two bioethicists, M. Sara Rosenthal, Ph.D., Professor and Director, University of Kentucky Program for Bioethics, Department of Internal Medicine, and Michael A. Santoro, Professor, Department of Management and Global Business, Rutgers Business School-Newark and New Brunswick, Ph.D in Public Policy, Harvard University. They were contracted to review information about autoimmune/autoinflammatory diseases and step therapy, and then to use their professional knowledge of the principles of bioethics to determine, in their opinions, where ethical issues may occur<sup>1</sup>. Additionally Kathleen Arntsen, President and CEO of Lupus and Allied Diseases Association, Inc., was enlisted as the Public Policy Expert to advise on current and past legislative efforts surrounding step therapy. The AiArthritis team consisted of Tiffany Westrich-Robertson, CEO and Project Manager; Kerry Wong, Executive Assistant; Laura Schaaf, Administrative Assistant; and Monica Johnson, Public Policy Assistant.

Bioethics is the study of typically controversial ethical issues emerging from new situations and possibilities brought about by advances in biology and medicine. It is used to analyze moral discernment as it relates to medical policy, practice, and research.

- The Project Manager initially worked independently with all team members:
- Bioethicists: Scheduled phone meetings and online communications regularly to provide information and answer questions about AD patient issues regarding the step therapy process, current Clinical Practice Guidelines (CPGs), and locate any additional documentation about the diseases or current research that could assist in their opinion development. They additionally participated in all draft reviews and final edits. Their opinion papers will be published separately in journals to be determined by the bioethicists.
- Public Policy Expert: Weekly phone meetings and email communications were scheduled to exchange information on legislative efforts and to discuss current and proposed changes to policy in regards to step therapy. Additionally she submitted recommendations for paper inclusion and participated in final reviews.
- IFAA Internal Team: Public Policy Assistant reached out to IFAA contacts to locate the most current database of national efforts towards addressing public policy issues. Administrative Assistant collected documentation about current Clinical Practice Guidelines (CPGs) and research. Executive Assistant helped review, edit, and shape the final document. Project Manager orchestrated all communications and was the author of this position paper.

The project team began collaborations through a private, online document sharing group using Huddle software. They gathered for an in person meeting in New York City, NY to review the bioethicist reports and to further discuss the effect of step therapy on patients. The meeting was video recorded. This video was used by AiArthritis to review discussions and to form follow up questions for the bioethicists. In addition to social media outreach, AiArthritis communicated with the American College of Rheumatology and Patient Advocacy Foundation to

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<sup>1</sup> While autoimmune/autoinflammatory diseases are the focus in this paper, the findings can be translated to any disease where the patient population has non-traditional, or atypical, patients.

assist in identifying current legislative efforts nationally and patient stories that might coincide with identified ethical infringements.

This position paper uses specific autoimmune and autoinflammatory diseases as a reference, however issues of step therapy - both in the United States and abroad - pose some ethical concerns for any patient with chronic illness who does not meet the “general patient population” or typical symptom presentation. We hope those outside of this specific community can use this publication as a springboard to determine ethically questionable practices that may be prevalent in their own community or country of origin. This project was made possible due to a \$50,000 grant awarded by Celgene Corporation.

The Ethics of Step Therapy Investigation is step one to what we hope will be used to education public officials and health care stakeholders to consider the atypical patient in both policy and in developing value measure frameworks. We will focus on the current state of health care, as well as its continued expansion into the future, with special attention on putting patient care back into the hands of the doctors who are educated and ethically obligated to treat them.

In a world where innovation is expanding and the community of patients who require access to advanced treatments to sustain an acceptable quality of life is growing, it is imperative that the relationship between individual patient and practitioner remain intact and only health care professionals familiar with a patient's personal medical history and uniqueness should be making treatment decisions. As we usher in an era of personalized and precision medicine, patient-focused research and patient-centric medicine, insurance protocols must be revolutionized to keep pace with biomedical innovation and to ensure ethical responsibilities are being met.

## The Ethics of Step Therapy Investigation

*Authored by Tiffany Westrich-Robertson, AiArthritis, with consulting contributor Kathleen Arnsten, Lupus and Allied Diseases Association, Inc. Position based on ethics opinions submitted by M. Sara Rosenthal, Ph.D., Professor and Director, University of Kentucky Program for Bioethics, Department of Internal Medicine, and Michael A. Santoro, Professor, Department of Management and Global Business, Rutgers Business School- Newark and New Brunswick, Ph.D in Public Policy, Harvard University.*

### Kathleen's Story

*(Kathleen Arnsten, Ethics Investigation Public Policy Contributor and CEO of Lupus and Allied Diseases Association, Inc.)*

In November 2013, Kathleen, a Systemic Lupus Erythematosus (SLE) and Sjögren's Syndrome (SS) patient, was experiencing pain, sensitivity, and a rash, complications not uncommon with autoimmune disease patients who have compromised immune systems. Initially diagnosed with conjunctivitis and acne, this was soon changed to shingles in the eye. She was prescribed antibiotics to avoid infection and a generic steroid drop to address the inflammation of the eye (called uveitis). She immediately had a negative reaction to the drops and it was determined she was allergic to their preservatives, so treatment was revised based on her individual needs and known contraindication.

Over the next few months the shingles further stimulated her autoimmune diseases and caused a considerable spike in the uveitis, which led to glaucoma. Additional complications arose, as the continued uveitis (inflammation) mixed with the shingles led to glaucoma [1]. Unable to control the situation, and knowing her allergy to eye drop preservatives, her doctor provided samples of a specialty drop, which proved beneficial. However, the insurance company refused her access to these expensive treatments until she first failed two other preferred drops- both which contained preservatives. After a lengthy and unsuccessful appeal process, the doctor was forced to prescribe the insurer-recommended treatments.

Kathleen, desperate for relief, tried both of the insurer-recommended drops. Immediately she had reactions to both, including severe inflammatory responses and elevated pressure in the eye. In an attempt to expedite access to the preservative-free drops originally prescribed, the doctor wrote a letter to the insurance company that explained the failures. After several weeks, and no response from the insurer, the doctor's office followed up and learned they did not receive an answer because the proper form was not filled out and they wanted another preauthorization. Another week later she received the medication originally prescribed by her doctor.

Finally the pressure and inflammation in the eye was under control. However, due to delay in proper treatment and the use of drops when the insurer was informed of contraindication, an ulcer formed in her cornea and the glaucoma worsened. Still today the cornea is fragile and shedding and she is currently blind in her right eye.

Supporters of step therapy may argue this is a unique case and that rarely would a patient experience permanent harm due to delays in treatment. They may say that most insurance companies would not knowingly force a patient to use medications that have been proven ineffective or harmful in the past. Thousands of patients

and practitioners are likely to say otherwise. Step therapy may be an efficient tool when the conditions are treatable with low cost treatment options and symptoms are universal.

## **My Story**

*(Tiffany Westrich-Robertson, Author of Ethics of Step Therapy Investigation, CEO of IFAA)*

In 2006 I was in my mid-30's, climbing up the corporate ladder to Vice President of Business Development and Project Management, taught college, and participated in several sports – including softball, volleyball and kickboxing to name a few. So in 2007, when I suddenly was struck with debilitating fatigue, fevers and connective tissue and joint pain, my life changed. For the first two years I was labeled “the mystery patient”, as I was not meeting text book criteria for any one disease. By this time the disease had progressed to 22 locations, I was sleeping over 16 hours a day, I had been running a low grade fever for four and a half weeks, and I had spent over \$10,000 in medical bills trying to find an answer. Finally in 2009, after several different specialists, my second rheumatologist diagnosed me with sero-negative Rheumatoid Arthritis (RA).

So why such a delay, when RA is the number one type of autoimmune arthritis and the second most common arthritis? I, like many patients, was atypical; my disease did not present, nor evolve, like the majority of those diagnosed with RA. I was told I likely had some “overlap”, and in time the non-traditional RA symptoms may evolve into additional full blown diseases.

At the time I was diagnosed the healthcare system did not allow patients with pre-existing conditions to obtain any better insurance than they had when their condition began. As someone who was young, and in great physical shape, I never thought to purchase more expansive care. Unable to afford the treatments I needed, I began to apply for clinical trials that tested medications for RA patients. I applied for twelve trials, but was only accepted into two, because I did not meet study the inclusion criteria – either my inflammation was not high enough or my joints were not swollen enough – so I was denied participation. Little did I know at the time that being denied access to clinical trials, due to being an ‘atypical’ patient, would later become the missing link necessary to identify major ethical issues surrounding step therapy.

Ten years have passed since I had my initial onset symptoms. The doctor who diagnosed me as overlap, and warned I'd likely develop co-morbidities, was right. As of today I have also been diagnosed with Axial Spondylitis, Sjögren's Syndrome and am currently being considered for Behcet's Disease (which may or may not replace one or two of the initial diagnoses). Most recently I had a Transient Ischemic Attack (TIA, or “mini stroke”) which may be due to vasculitis associated with my autoimmunity.

Those who manage our health care system, including the payers who choose best treatments for patients with RA, do not consider non-typical patients when creating their formularies. They only site scientific evidence that is inclusive of patients who are typical enough to meet inclusion criteria for the clinical trials that test safety and

efficacy of therapies. Equally, those establishing value frameworks do include diseases evolution in their methodology, so patients like me - who often develop co-morbidities and make up a large percentage of the overall autoimmune and autoinflammatory community – are not considered in the measurements.

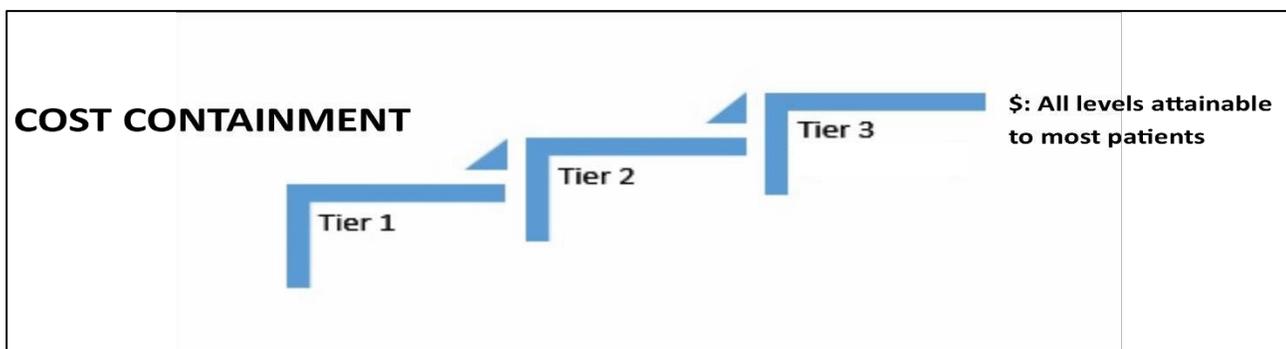
If the end goal is to ensure patients are prescribed with the safest and most effective treatments that truly benefit the overall healthcare costs, then more than one subset of patients must be considered in the equation. Otherwise the scientifically credible research cited as applicable to all patients may end up being exactly what is causing economic crisis and long term healthcare inflation. It's time to change the quarter-century old protocols and modernize step therapy and other measurement frameworks to adhere to the real world patient community.

## STEP THERAPY

### History

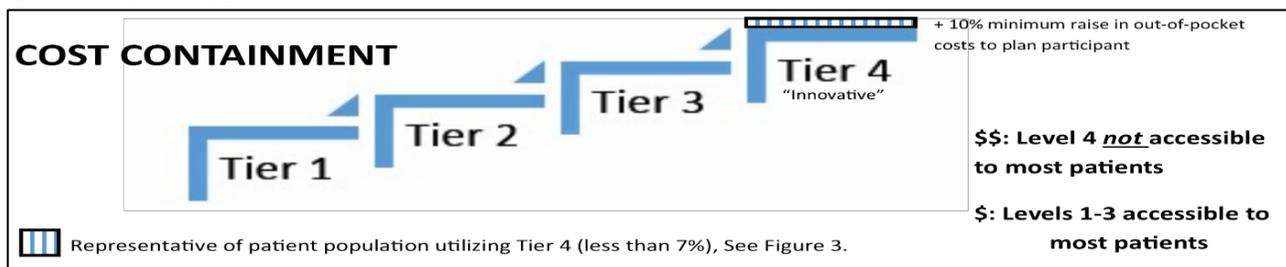
In the early 1980s cost for medication was rising, which presented challenges to the states, who mandate insurance companies, and to the insurers, who are expected to balance the budget so that the greatest number of people can gain access to quality care. In response to rising costs of healthcare, a new protocol - step therapy - was developed to manage medication so that the most cost-effective treatment would be prescribed before a more expensive option. Those drugs that cost the least, such as generics (or low cost medications whose active ingredients are interchangeable with brand medications) were labeled as “Tier 1”, higher priced treatments as “Tier 2”, and “Tier 3” was reserved for the most expensive therapies (See Figure 1)[2].

Figure 1: Step Therapy Model 1980s



In the late 1990s, innovative drugs such as biologics were introduced to treat Rheumatoid Arthritis, an autoimmune disease affected more than 1 million patients in the United States [3]. The healthcare system was not equipped to handle coverage for such novel treatments, so insurers responded by amending step therapy to include a new specialty “Tier 4” that put these drugs on a high-cost platform and additionally raised the coinsurance at least 10 percent (See Figure 2). This expansion began raising ethical questions, since the high cost for the patient made these treatments accessible only to those of high financial status [4]. However, steering patients away from these

Figure 2: Step Therapy Model 2000

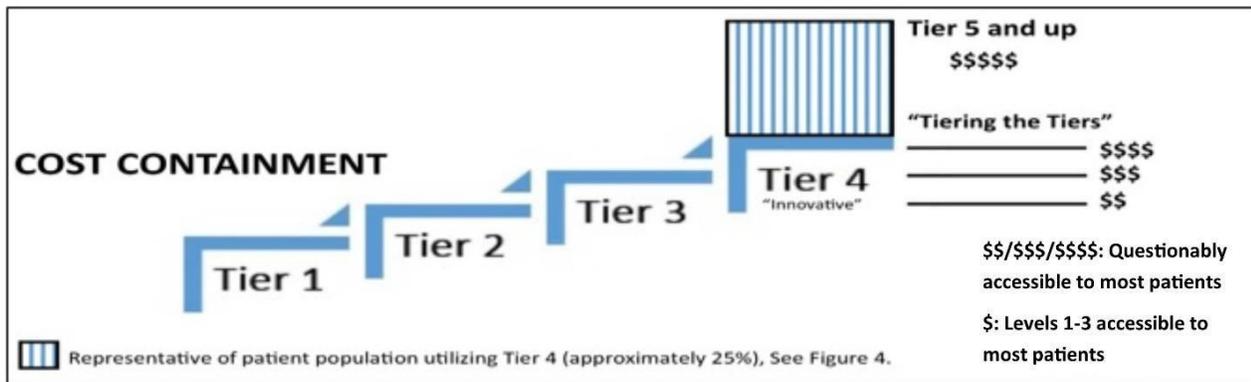


specialty pharmaceuticals was justified because it focused on protecting them from spending unnecessary dollars for “experimental” treatments that had little scientific proof of efficacy and were potentially unsafe. As a result of

minimal usage, there was little data collected to confirm drug effectiveness, and research continued to show that long term need for additional medical services did not outweigh the overall savings made by enforcing step therapy [3]. Yet as the decade progressed, biologics proved their efficacy and gained FDA approval to treat additional autoimmune diseases. Research began confirming that without proper treatment, patients risk poorer outcomes, which could lead to additional long term costs [3]; therefore, steering patients away from these innovative therapies was no longer feasible. As more Clinical Practice Guidelines (CPGs) and/or recommended treatment protocols emerged that listed biologics as a necessary step to treat autoimmune disease, the out-of-pocket costs for the average patient became inaccessible. Unable to address this problem within the step therapy model, drug manufacturers established Patient Assistance Programs (PAPs) to ensure access to those in need.

By 2010, with over a dozen biologics on the market to treat a variety of diseases, insurance companies could no longer use the argument that these drugs might lack efficacy. So they added tiers inside of the existing specialty tiers (also known as “tiering the tiers”) and some added a Tier 5 or higher, categorizing drugs with similar proven efficacy and safety profiles based solely on cost (See Figure 3).

**Figure 3: Step Therapy 2015**



Today, insurance companies have retreated back to the position they took in the 1990s, claiming that *new drugs lack sufficient proof of efficacy in the general patient population* and therefore, it is in the best interest of the patient to use proven treatments that cost the system less money. However, unlike in the 1990s, these drugs are no longer “experimental” and they are relatively equal in manufacturer costs to those currently on market. Some treatments may even initially show to have better safety profiles than those treatments currently preferred by insurers, but until more research is collected to substantiate these claims, cost will continue to dominate insurer positioning.

## Insurer’s Strategies

### Cost Control

Step therapy is strongly based on cost, but is *justified* by proof of efficacy through research as it relates to the general population. To help maintain the budget, insurers use Pharmacy Benefit Managers (PBMs), administrators

who interact with pharmacists and other clinical experts to find low cost treatment options [6]. PBMs often utilize rebate programs, or pricing negotiations with the drug manufacturers that offer cash incentives in exchange for preferred product placement. According to the Pharmaceutical Care Management Association (PCMA), PBMs will save companies, Medicare, and consumers nearly \$2 trillion on prescription drugs between 2012 and 2021, although much of this can be seen in the lower tiers and generic substitutions [7].

If these PBMs can secure low pricing for drugs that research shows are *just as safe and effective* as others in the same class *for patients who meet the general patient population criteria*, then enforcing the use of those preferred treatments is ethically sound, as it maintains a balance in the overall budget. This equates to significant savings (and profits) for the insurance companies and big profits for the PBM companies, which may then pass the savings on to the patient.

### **Efficacy and Safety Standards**

Insurance companies use Physician Review Committees (PRCs), or an established group of medical experts, to help develop their formulary benefit programs. These experts *rely on research based on a general patient population in addition to their own expertise* to approve a drug for preferred use. These committees may or may not include specialists who fully understand every disease in which they provide recommended treatments, but given that judgment is based on current published research, the rationale for their recommendations is substantiated.

### **Pros and Cons**

One could certainly argue that the more step therapy dissuades patients from utilizing innovative therapies, the more short term cost savings will occur. Many in favor of the protocol believe that if we continue minimizing use of specialty pharmaceuticals, we will be on the right path to achieving cost control. This is a novel approach when patients, unlike those with autoimmune diseases, do not actually require innovative therapies to best manage their condition(s).

***For Step Therapy:*** “Increased utilization, price inflation, and higher-cost drugs continue to drive up prescription drug costs. Planned efforts to keep costs under control, including step therapy, help to be able to offer consumers and employers affordable prescription drug coverage.” -*Leslie Moran, senior Vice President of the Health Plan Association*

Those who do not believe step therapy is entirely successful in managing costs could argue that delaying necessary treatment leads to long term healthcare costs, ranging from additional doctor visits to potential for advanced disease states.

***Against Step Therapy:*** “When the insurance company’s first choice medications do not successfully treat a patient’s condition, the insurance company pays more in the long run.”-*National Physicians Working Group*

An emphasis on the safety of step therapy appears to be a guiding proponent in why the protocol is beneficial, as it exposes patients only to treatments that have been *proven safe and effective over time in the general patient population*. However, no regulations have been established to determine how to measure when a drug reaches acceptable safety standards, so it may benefit the insurer to select those treatments that have been on market the longest, especially if the insurer has secured reasonable price negotiations. However, step therapy does not consider patients who do not meet the *general patient population* description. While it allows for appeals if the practitioner feels the treatment is not reasonable based on the uniqueness of the condition, there is no protocol in place to bypass the insurer's decision to override the doctor's recommendation.

## **SPECIALTY PHARMACEUTICALS**

Autoimmune and autoinflammatory diseases are *unique to each individual*, as genetic and environmental factors can both play a role in onset. Delays in treatment can lead to greater physical limitations, disability, poorer long-term outcomes, and higher costs for care than when the diseases are diagnosed and treated within recommended timeframes. While the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) suggest treatments for many of these diseases to begin within six months of symptom onset to ensure the best chance of limited progression, irreversible damage, and remission, currently the average time to detect, refer, and diagnose often exceeds this recommendation. There is evidence that delays of as little as three months can be associated with poorer outcomes in terms of disease progression and radiologically discernible damage, so prompt treatment can substantially decrease disability and improve long-term health status. This is a critical issue as treatment delays lead to greater physical disability and poorer long-term outcomes that potentially affect the ability of patients to lead fully functional lives [8-10]. Additionally, treatment varies depending on several factors including aggressiveness at onset, co-morbidities, tolerance to therapies, contraindications, and other considerations. For reasons such as these, it is imperative that these patients are treated with proper medications in a timely manner, and have access to a fair, transparent, and independent process for requesting an exception to a step therapy protocol when appropriate.

Biologic response modifiers, or “biologics”, are medications created from live organisms that target the proteins, cells, and pathways responsible for the symptoms associated with these diseases. Unlike chemically based drugs like aspirin, biologics target specific immune cells in the body that cause inflammation to the joints, tissues, and organs. [11]. While these treatments have proven to be beneficial for most patients, due to the individuality of these diseases it is not always possible to predict which will work best for each patient. In situations where the patient is *'atypical'*, such as with comorbidities and disease overlap, they may be *adversely affected* by specific components of a specific treatment.

The first biologics manufactured were called tumor necrosis factor (TNF) inhibitors or Anti-TNF agents. As research expanded, additional types of biologics were developed to target different cells and proteins (See Table 1). Some of these biologics recommend the additional use of methotrexate, a disease-modifying anti-rheumatic drug (DMARD) yielding 12 FDA box warnings, to be most effective. Treatments also evolved to include advanced non-biologics that moved from injections or infusions to pill form.

In some diseases, like Rheumatoid Arthritis (RA), Clinical Practice Guidelines first recommend treatment with disease-modifying anti-rheumatic drugs (DMARDs) prior to advancing to a biologic [12]. However, studies have shown that in some diseases, like Ankylosing Spondylitis (AS), DMARDs are typically ineffective so they are not recommended [13]. In special cases, such as if an RA patient has aggressive disease activity or advanced disease progression at the time of diagnosis, the doctor may choose to prescribe a biologic first *if s/he believes that use of a DMARD first could delay necessary intervention and cause harm* [14].

**Table 1: Examples of some biologics and similar treatments used to manage autoimmune diseases as of January 2016**

Biologic	Indicated to Treat	Year FDA First Regulated	Administration	Targets	Take with MTX
<a href="#">Enbrel®</a> (etanercept)	RA, PsA, AS, JIA, CD, PPs	1998	Injection	Anti-TNF	Not Required, <a href="#">may be recommended</a> for full efficacy
<a href="#">Humira®</a> (adalimumab)	RA, JIA, PsA, AS, PPs, CD, UC, HS	2002	Injection	Anti-TNF	Not Required, <a href="#">may be recommended</a> for full efficacy
<a href="#">Simponi®</a> (golimumab)	RA, PsA, UC, AS	2009	Injection/ Simponi Aria for infusion	Anti-TNF	<b><a href="#">Yes with RA</a></b> , Not Required with PsA, UC, AS but <a href="#">may be recommended</a> for full efficacy
<a href="#">Stelara®</a> (ustekinumab)	PPs, PsA	2009	Injection	IL-12 and IL-23 protein blocker	Not Required, <a href="#">may be recommended for full efficacy</a>
<a href="#">Actemra®</a> (tocilizumab)	RA, SJIA, PJIA	2010	Injection/ Infusion	Interleukin-6 (IL-6) receptor antagonist	Not Required, may be recommended for full efficacy
<a href="#">Cimzia®</a> (certolizumab)	RA, CD, PsA, AS	2008	Self-injection (prefilled syringe)/ Provider-administered injection (lyophilized powder)	Anti-TNF	Not Required, <a href="#">may be recommended</a> for full efficacy
<a href="#">Kineret®</a> (anakinra)	RA, CAPS/NO MID	2001	Injection	Interleukin-1 receptor antagonist	Not Required, <a href="#">may be recommended</a> for full efficacy
<a href="#">Orencia®</a> (abatacept)	RA, JIA	2005	Injection/IV Infusion	Selective T cell costimulation modulator	Not Required, <a href="#">may be recommended</a> for full efficacy
<a href="#">Remicade®</a> (infliximab)	CD, PCD, RA, PsA, AS,	1998	Injection/IV Infusion	Anti-TNF	<b><a href="#">Yes with RA</a></b> , not required by <a href="#">may be recommended for full efficacy in PsA</a>

	UC, PUC, PPs,				
<a href="#">Rituxan®</a> (rituximab)	RA, GPA, MPA (other non-Ads)	1997	IV Infusion	CD20-directed cytolytic antibody	<a href="#">Yes with RA</a>
<a href="#">Benlysta®</a> (belimumab)	SLE	2011	IV Infusion	B-lymphocyte stimulator (BLyS)	<a href="#">Not Required</a>
<b>Non-Biologic*</b>	<b>Indicated to Treat</b>	<b>Year FDA First Regulated</b>	<b>Administration</b>	<b>Targets</b>	<b>Take with MTX</b>
<a href="#">Xeljanz®</a> (tofacitinib)	RA	2012	Pill	Janus kinase (JAK) inhibitor	Not Required, <a href="#">may be recommended</a> for full efficacy
<a href="#">Otezla®</a> (apremilast)	PsA, PPs	2014	Pill	PDE4 inhibitor	<a href="#">Not Required</a>

RA: Rheumatoid Arthritis, PsA: Psoriatic Arthritis, AS: Ankylosing Spondylitis, JIA: Juvenile Idiopathic Arthritis, CD: Crohn's Disease, PPs: Plaque Psoriasis, UC: Ulcerative Colitis; SJLA: Systemic Juvenile Idiopathic Arthritis, PJLA: Polyarticular Juvenile Idiopathic Arthritis, CAPS/NOMID: Cryopyrin-Associated Periodic Syndromes/ Neonatal-Onset Multisystem Inflammatory Disease, PUC: Pediatric Ulcerative Colitis, PP: Plaque Psoriasis, PCD: Pediatric Crohn's Disease, SLE: Systemic Lupus Erythematosus, HS: Hidradenitis Suppurativa, GPA: Granulomatosis with polyangiitis, MPA: Microscopic polyangiitis. \*Non-Biologic- treatments developed that fall between DMARDs and biologics but are currently categorized by insurers in the same class as biologics.

Biologics have been proven to benefit most autoimmune and autoinflammatory disease patients, and current research shows that most are similar in efficacy and safety profiles. Exceptions to equivalence in safety would be for those patients whose comorbidities or other medications present a contraindication, and *may* be questioned when the product requires additional use of the DMARD Methotrexate (12 FDA warnings)<sup>2</sup>. Therefore, if no such exceptions exist, it is the duty of both the practitioner and the patient to use the least costly option.

## ETHICS

### Guiding Clinical Ethical Principles for Step Therapy

Our team consisted of two bioethicists, a public policy expert, and IFAA, who worked together to discuss and analyze the following ethical principles. *There are a number of clinical ethical principles and considerations in step therapy which are addressed in Appendix A: Rosenthal and discussed in Table 2.*

**Principle of Beneficence.** Obligates healthcare providers to maximize clinical benefits and minimize clinical harms. *This consideration is covered in the Ethics Opinion paper, Appendix A: Rosenthal and highlighted in Table 2.*

**Principle of Non-Maleficence.** Specifically prohibits providers from introducing harms to patients, neglecting or abandoning patients, or failing to warn patients of imminent harms associated with various

<sup>2</sup> Currently preferred biologics are often paired with methotrexate but research does not suggest that this makes them more or less harmful than those biologics or similar products that may be used independently.

treatments or lack of treatments. *This consideration is covered in the Ethics Opinion paper, Appendix A: Rosenthal and highlighted in Table 2.*

**Principle of Respect for Persons/Autonomy.** Dually obligates practitioners to respect patient autonomy (or personalized care goals), and at the same time to protect patients who may not fully understand or appreciate their therapeutic options from unnecessary harm. *This consideration is covered in the Ethics Opinion paper, Appendix A: Rosenthal, and highlighted in Table 2.*

**Principle of Justice.** Concerns equal access to care, as well as rational allocation of resources. *These considerations are covered in the Ethics Opinion paper, Appendix A: Rosenthal, and highlighted in Table 2.*

## **Role of the Insurance Companies**

### **Duty to protect the public**

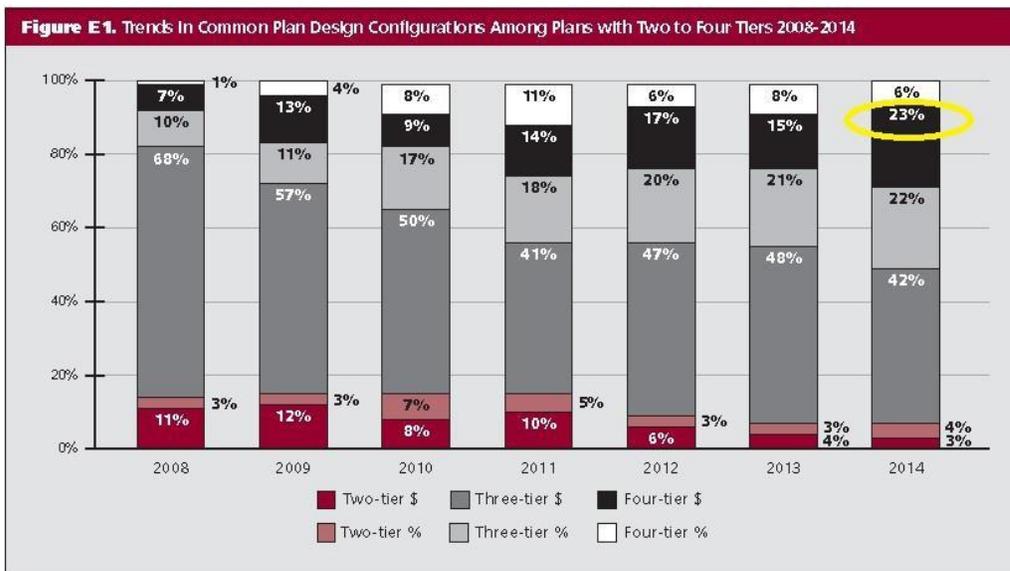
In 1945 Congress adopted the McCarran-Ferguson Act, which declared that insurance would be regulated by the states to ensure that business practices remain in the public's best interest. While the National Association of Insurance Commissioners (NAIC) serves as an advisor to state insurance departments and provides a vehicle for sharing resources between states, each state ultimately determines how best to regulate insurance for the people it protects [14].

### **Duty to consider cost-effectiveness.**

In the context of step therapy, the Principle of Justice guides insurers, as they aim to ration resources to provide reasonable access to the majority of people in need of healthcare services. The PBMs who negotiate prices for the insurers play a large role in helping to maintain a financial equilibrium. As long as research shows the drugs that cost the least are just as safe and effective as others in the same class for patients who meet *the general patient population* criteria, then enforcing the use of those preferred treatments is ethically sound, as it maintains a balance in the overall budget.

However, while step therapy may still be a successful tool to manage cost containment as it relates to substituting generics for chemically manufactured drugs, it is not designed to withstand today's advanced science and growing community of patients who require access to specialty pharmaceuticals to sustain an acceptable quality of life. In 2008, 68% user rate of a Tier 3 design was considered an industry standard. In 2014, only 42% utilized drugs in those tiers; nearly one quarter used Tier 4, compared to just 7% in 2008 and 15% in 2013 (See Figure 4) [15]. This is partly due to the spike in autoimmunity over the last few decades, which now affects over 50 million people in the United States alone [16]. This disease epidemic, along with innovation in treatments, are growing challenges not considered when step therapy was initially designed a quarter of a century ago.

Figure 4



2012 and later data are based on plan design for retail 30 fills. Plans with "other" cost-sharing structures and one tier or more than four tiers are excluded from the percentage calculations in all years.  
 \$ = fixed dollar amount per prescription per tier.  
 % = percentage share with or without a minimum and/or maximum.

The American College of Physicians Ethics Manual, 6<sup>th</sup> Edition indicates that insurers must take appropriate measures to maintain cost-effectiveness, including suggesting less expensive treatments for the same condition or therapies that the insurer offers for other conditions. This often occurs when the patient values a different treatment but the higher cost cannot be justified because the treatment is not scientifically proven to be a superior option. *See Appendix A: Rosenthal - Respect for Persons; Appendix B: Santoro - Duty to Consider Cost-effectiveness; Table 2.*

### Duty to practice evidence-based medicine

The practitioners who serve on PRCs base recommendations on their professional expertise and a review of treatments that have proven efficacy in the *general patient population*. They must uphold the same ethical responsibilities as all practicing physicians, including showing competency in their field of practice. However, it is their responsibility to admit if they are not qualified to make decisions on behalf of experienced specialists, especially if the research they base their decisions on is lacking. *These considerations are covered in the Ethics Opinion paper Appendix A: Rosenthal - Professional Ethical Duties.*

### Physician's Ethics

#### Duty to consider cost-effectiveness

Physicians have an ethical obligation to practice medicine in a cost-effective manner. This extends to the doctor's understanding of the patient profile and long term treatment needs. If financial burden due to high cost treatments becomes a barrier to access, practitioners can enroll the patient in a clinical trial of the appropriate drug.

These considerations are covered in Appendix A: Rosenthal - Research Ethics Considerations, Innovative Therapies, and Clinical Trials; Appendix B: Santoro.

## **Duty to practice evidence-based medicine**

Physicians are also ethically obligated to practice evidence-based medicine, *tempered by a clinical judgment about the unique characteristics of the individual patient* [17]. These considerations are covered in Appendix B: Santoro. However, the physician's obligation to treat to the *uniqueness* of the patient is in direct conflict with PRCs, who recommend treatments based on *general patient population* research and, in turn, positions preferred treatments to take precedence over those recommended by the patient's doctor. When this situation arises, it is the physician's ethical obligation to advocate in favor of a recommended treatment when s/he is unable to treat a patient properly because of an insurance company decision [18]. *See Other Ethical Considerations: Duty to appeal.*

## **Other Ethical Considerations**

### **Duty to appeal**

The appeal process allows doctors to challenge protocol when the preferred treatment is considered unreasonable due to a contraindication, such as allergy or prior reaction, comorbidity, or other consideration that indicates that the patient would not benefit from the standard protocol recommended to treat the general patient population. Regardless of the time and costs accrued by the practitioners to file an appeal, it is their obligation to take action on behalf of their patients (M.S. Rosenthal, personal communication, June 26, 2015). Additionally, in a world where technology is streamlined, there is little justification for appeals to be anything but timely and seamless. However, practitioners report that on average their administrative employees spend 50% or more of their time per week working on step therapy processes such as appeals [19]. Since each health care company has its own forms and its own procedures, this causes confusion and the potential to incorrectly complete necessary documentation, thus resulting in delay of treatment. These delays may cause the patient to accrue additional costs, including disease complications, additional office visits and/or hospitalization, and potential need for pain management therapy in the absence of other treatments. Furthermore, any delay that causes unnecessary harm to the patient would be a violation of the Principle of Beneficence, p. 11.

If the practitioner uses his/her clinical judgment to determine that the patient is not a reasonable candidate for the insurer recommended treatment, and the appeal is denied because the insurer bases its decision on what works for the general public, then the doctor's ethical responsibility to treat to the unique characteristics of the individual is neglected See Physician's Ethics, Table 2: Scenario A. Additionally, if the patient experiences any harm from the denial of such an appeal, then the insurance company is in direct violation of the Principles of Beneficence and Non-Maleficence, because it has already been informed by the physician that the patient was not a candidate for the step therapy See Table 2: Scenario A.

## Duty to adhere to Clinical Practice Guidelines (CPGs)

When CPGs are established, it is the responsibility of the practitioner to adhere to those guidelines because CPGs are based on the recommendations of an authoritative group, such as the American College of Rheumatology. Insurance companies must also respect CPGs and allow reasonable access to higher priced therapies if they are determined a necessary step in treatment.

For diseases that have no formal CPGs, such as Psoriatic Arthritis (PsA) or Systemic Lupus Erythematosus (SLE), determining the appropriate treatments becomes additionally complicated, as the current standard of care defaults to achieve remission based on therapies beneficial to “the most common patients, not exceptional cases” [12]. In some cases, as with SLE, adequate research shows that typical first line use for other similar diseases, such as Rheumatoid Arthritis (RA), are not as effective in treating SLE. Therefore, just as insurance companies use research to justify preferred treatments, when no CPGs are established, current research is used to determine first line treatments *See Table 2: Scenario B.* Treating these diseases is further complicated as different biologics target different mechanisms. In these cases, step therapy that requires a patient to first try the recommended drug may prevent the physician from exercising his/her ethical duty to practice evidence-based medicine by creating a de facto standard of care when research is in a state of uncertainty. If physicians disagree with the treatments proven to be effective for a specific disease, they have an obligation to voice their opinions and to consider participation in establishing CPGs and formularies. *These considerations are covered in the Ethics Opinion papers Appendix A: Rosenthal - The Ethical Duty to Research; Appendix B: Santoro - Clinical Practice Guidelines.*

The following scenarios are examples of potential ethical violations involved in the step therapy process. *Additional scenarios are covered the Ethics Opinion papers Appendix A: Rosenthal - Clinical Ethical Principles in Step Therapy.*

**Table 2: Potential Ethical Violations of Step Therapy**

<b>Scenario</b>	<b>Result</b>	<b>Reference</b>
<b>Scenario A:</b> The practitioner determines their RA patient is not a reasonable candidate for the insurer recommended treatment because the patient has a known allergy to the preferred first line therapy. The practitioner appeals to skip step therapy and prescribe a treatment that research shows is a better option for patients with this profile. The appeal is denied and the patient is forced to use the treatment insurer’s prefer, which is	<b>Physician’s ethical duty to treat to the individual is compromised.</b> In this situation, the doctor is unable to uphold their ethical duty to treat to the unique characteristics of the individual because the insurer selects their preferred drugs based on efficacy and safety research proven to work in the general population.	<i>See Appendix B: Santoro, Physician’s Ethics-Duty to Practice Evidence Based Medicine</i>  <i>Appeal: M.S. Rosenthal, personal communication, June 26, 2015</i>

<p>validated based on its efficacy and safety in the general RA patient population.</p>	<p>If the patient experiences harm due to the appeal denial, they are in <b>violation of the Principle of Beneficence, and additionally the Principle of Non-Maleficence</b> because they were informed prior by the physician that the patient was not a candidate for the step therapy.</p>	<p><i>See Appendix A: Rosenthal, Clinical Ethical Principles in Step Therapy-Principles of Beneficence and Non-Maleficence, and Scenario A.</i></p>
<p><b>Scenario B:</b> A patient has been diagnosed with Ankylosing Spondylitis. There is adequate research and clinical guidelines that state most patients will not be receptive to DMARDs, specifically methotrexate. The insurer tells the doctor that their plan still requires failure of methotrexate prior to allowing the patient to advance to a biologic.</p>	<p><b>Result:</b> Forcing a delay in necessary treatment is a <b>violation of the Principles of Beneficence and Non-Maleficence.</b></p>	<p><i>See Appendix A: Rosenthal, Clinical Ethical Principles in Step Therapy, Scenario C; Appendix B: Santoro, Practitioner’s Ethics-Duty to Practice Evidence Based Medicine, Clinical Practice Guidelines.</i></p>
<p><b>Scenario C:</b> A patient presents with aggressive RA disease activity at the time of diagnosis. Based on the unique needs of the patient, who does not present as a typical RA patient who meets the general RA patient population model, the doctor requests authorization to skip the first line DMARD and prescribe the preferred biologic.</p>	<p><b>Result: Physician’s ethical duty to treat to the individual is compromised.</b> In this situation, the doctor is unable to uphold their ethical duty to treat to the unique characteristics of the individual based on their knowledge of evidence-based medicine.</p>	<p><i>See Appendix B: Santoro, Physician’s Ethics-Duty to Practice Evidence Based Medicine</i></p> <p><i>Appeal: M.S. Rosenthal, personal communication, June 26, 2015</i></p>
<p><b>Scenario D:</b> The patient has failed the first step DMARD and has been prescribed the preferred biologic. This Tier 4 drug costs 30% out of pocket to the patient, or \$649 per month. The patient does not qualify for an assistance program and is forced to forgo necessary treatment.</p>	<p><b>Result:</b> By placing treatments that experts have stated are necessary in treating autoimmune diseases on a tier that makes them financially inaccessible, this questions the insurer’s duty to provide equal access to care (<b>Principle of Justice</b>).</p>	<p><i>See Appendix A: Rosenthal, Clinical Ethical Principles in Step Therapy</i></p> <p><i>See Table 3: Access</i></p>

### Current Legislative Efforts

Most organizations (both patient and doctor) are involved in some type of advocacy geared towards ensuring that patients have access to needed treatments, and/or have written position papers demanding that access and coverage be fair and equal. Some current legislative efforts that have been proposed, and in some states have changed, to make step therapy more appropriate [20]. Examples include:

**Table 3: Legislative Efforts to Update Step Therapy Policies**

<b>Step Therapy Issue</b>	<b>Legislative Efforts</b>	<b>Ethical Evaluation</b>
Grandfathering Exemption	Asks that patients currently successful in managing their diseases not be forced to switch therapies to appease cost control measures for the insurance company.	<i>Denying patients known beneficent treatment is a <b>Violation of the Principles of Beneficence and Non-Maleficence</b>. See Appendix A: Rosenthal, Clinical Ethical Principles in Step Therapy</i>
Delay in Necessary Treatment	Expedite times to access appropriate medications, as delay to start effective treatment can expose a patient to unnecessary risk for harm.	Forcing a delay in necessary treatment is a <b>violation of the Principles of Beneficence and Non-Maleficence</b> . See Appendix A: Rosenthal, Clinical Ethical Principles in Step Therapy  See Appendix B: Santoro, <b>Physician's Ethics-Duty to Practice Evidence Based Medicine</b>  <b>Duty to Appeal:</b> M.S. Rosenthal, personal communication, June 26, 2015
	Patients and doctors have access to a fair, transparent and independent process for requesting an exception to a step therapy protocol when appropriate.	
	Limit the time a patient could be subjected to step therapy to the period deemed necessary by the prescribing physician to determine the treatment's clinical effectiveness or a period no longer than 30 days.	
	Regulate process to be expedited, some forms in unison/easier process. Requires payers to incorporate step therapy approval and override processes in their automated preauthorization applications.	
Rights of Practitioners to Practice Medicine	Prohibit a health care service plan or health insurer that provides medication pursuant to a step therapy or first-fail requirement from applying that requirement to a patient if, in the professional judgment of the prescribing physician, the step therapy or first-fail requirement would be medically inappropriate for that patient	Forcing a delay in necessary treatment is a <b>violation of the Principles of Beneficence and Non-Maleficence</b> . See Appendix A: Rosenthal, Clinical Ethical Principles in Step Therapy  See Appendix B: Santoro, <b>Physician's Ethics-Duty to Practice Evidence Based Medicine</b>  <b>Duty to Appeal:</b> M.S. Rosenthal, personal communication, June 26, 2015
	Practitioners should not be obligated to force a patient to use a treatment that is contraindicated, or likely to cause an adverse reaction based on patient's past medical history.	
	Pharmacy review committees should require a specialist in each section for which a treatment protocol is being established.	See page 12-13, <i>Role of the Insurance Companies</i>
	When a patient is successfully managing their disease an insurer should not be permitted to force non-therapeutic switching in favor of a more cost-effective solution.	

Access	Require health insurers to base step therapy protocols on appropriate clinical practice guidelines, where available, developed by independent experts with knowledge of the condition or conditions under consideration.	<i>See page 15, Duty to adhere to Clinical Practice Guidelines (CPGs); Future of Step Therapy: Research</i>
	Require health benefit plans that provide coverage for prescription drugs subject to a tiered formulary to ensure that any out-of-pocket expenditure shall not exceed \$100 per month for up to a 30-day supply, and that out-of-pocket expenditures for drugs subject to a tiered formulary shall not exceed \$200 per month in the aggregate; require an exceptions process for tiered formulary plans that allows an insured to request an exception to the tiered cost-sharing structure.	<i>Duty to provide equal access to care (Principle of Justice).</i>

## FUTURE OF STEP THERAPY

### Research.

Step therapy relies on credible clinical research to justify formulary placement. However, there are no clear rules or regulations surrounding which data counts as “credible” as study designs can vary. Additionally, current clinical trials typically only enlist patients that meet inclusion and exclusion criteria characteristic of the *general patient population*. Therefore, it can be argued that the research used to justify preferred drugs in the step therapy protocol is biased towards those patients who present as typical, and do not account for patients who present atypical or have comorbidities.

While currently there is little research to prove which biologic may be more effective and/or safer than others in a similar class, progress on biomarker and treatment predictability is being made. If this research can lead to better outcomes, and/or prove certain treatments more beneficial for a subset of atypical patients, it could bring major change to the treatment paradigm [21]. *These considerations are covered in the Ethics Opinion paper Appendix A: Rosenthal - Research Ethics Considerations, Innovative Therapies, and Clinical Trials.*

Efforts are currently underway to measure value-based frameworks, which claim to consider true value to patients, yet the methodology focuses only on short term outcomes and those patients who meet general patient population standards. In order to truly create metrics that will consider long term health improvements, cost savings and increased productivity, you cannot ignore the atypical patient, evolving quality of life standards of care, or innovation.

When step therapy was initially developed, the uniqueness of autoimmunity and autoinflammatory diseases was relatively unknown. However, today it is widely accepted that these diseases are unique to each individual, and what works well for one patient may be relatively ineffective for another. To collect evidence that a specific treatment may benefit the atypical patient, proper IRB trials should be conducted by a team of subspecialists or through N of 1 trials. If research can show that a treatment is more effective and/or safer for the atypical patient than others in a similar class, then insurance companies would have a responsibility to omit the step therapy

process for those in a similar class, then insurance companies would have a responsibility to omit the step therapy process for those patients. *These considerations are covered in the Ethics Opinion paper Appendix A: Rosenthal - Clinical Ethical Principles in Step Therapy, Scenario C; The Role of N of 1 Trials.* Additionally, patient organizations can be major contributors to engaging patients in the value framework discussion, by conducting patient reported outcome focus groups, online surveys and longevity studies; this data could be disseminated to other stakeholders so individualized care can be figured into the equation.

Biosimilars, which have been available in many European countries and were approved for use in the US in 2014, are similar to biologics but are not identical and are not ‘generics’. While they are also created from living cells, the processing methods and inactive components can be quite different, causing adverse events even for patients successfully managing their disease with the biologic they are imitating [21]. It is unclear where biosimilars will fit into the step therapy model, as these new “experimental” treatments have yet to prove safety and efficacy in substantial clinical trials or on market, and have not yet proved they will bring substantial cost savings [22].

### **Societal costs.**

Women, who according to the American Autoimmune and Related Diseases Association (AARDA) make up 75% of the estimated 50 million people in the US to be affected by autoimmune diseases [23], have significant roles in society, both as family-centered, child rearing caregivers and as contributors to the workforce. The socioeconomic standing of women, and their continued contribution to society, is of great importance to the well-being of future generations. While the socioeconomic effect of adults with autoimmune disease and other chronic illnesses can be measured in situations such as contribution to the workforce, other considerations, such as the value of women as caregivers, must be considered in order to fully understand the financial impact of women who are unable to function in society (M. Santoro, personal communication, June 26, 2015). *These considerations are covered in the Ethics Opinion paper, Appendix A: Rosenthal - Societal Costs of Poorly Controlled Autoimmune Arthritis; Appendix B: Santoro - The Meaning of Cost Effectiveness.*

### **Cost effectiveness and Value Frameworks**

In order to fully address the success or failure of step therapy in regards to long term versus short term cost containment, all patients – not just the typical patient who meets the general population criteria – must be counted. This is particularly important with chronic illnesses, where treating to the general patient population is complicated and a patient’s standard of care may evolve over time. As we learn more about these diseases and are able to detect and diagnose them more efficiently, the number of those utilizing specialty pharmaceuticals will continue to rise. However, research shows that early intervention with aggressive treatment can result in less long term disability and possible disease remission, whereas those patients who cannot achieve low disease activity may remain on these expensive pharmaceuticals for life. In saying this, as a society that must work together to balance the soaring costs

of healthcare for all people, access to treatments must also be cost effective from the perspective of managing the overall budget. *These considerations are covered in the Ethics Opinion paper Appendix B: Santoro - The Meaning of Cost-Effectiveness.*

## CONCLUSION

What began as a successful measure to contain healthcare costs in a time when innovation had yet to flourish, step therapy has become a model unable to withstand the continued advancements in both science and the growing community of patients who require access to specialty pharmaceuticals to sustain an acceptable quality of life. While the equation ‘research + safety = justifiable cost’ has been an acceptable method to ensure patients receive the best care at a price that contributes to rationing resources for all people, its current implementation challenges ethical boundaries. The bottom line is research holds the key to justifying costs. If we focus on expanding research past only the “general patient population” and consider the perhaps larger “typical atypical” patient subgroups equally, we can begin to truly measure long term costs and start to develop real measures of value for all.

Step therapy should be re-evaluated, among all stakeholders, and a system should be designed that considers cost, safety, and efficacy, but also respects the atypical patient, innovation, and the doctor’s obligation to practice ethical medicine. Some points that should be considered include:

- Create specific guidelines to define unclear terms, such as qualified research, general population, and atypical versus typical patient.
- Consider long term costs in addition to the annual budget.
- Request that both public and private insurance companies publish their negotiated prices, which would promote competition and lead to lower pricing and, in turn, bring the specialty tier out-of-pocket costs to a financially accessible level. This would also help newer drugs collect the data needed to establish better efficacy and safety profiles.
- Develop and maintain a working research database that houses current, credible data that will be available for all insurance companies and practitioners to reference when making treatment recommendations.
- Authorize additional research to include “atypical patients”.
- Streamline insurer forms and processes so patients do not risk harms due to delay in treatment.
- Ensure that all sides are able to function ethically, including enabling practitioners to treat based on the individual when applicable.
- Promote step therapy advocacy efforts that educate public officials in order to garner support for reformative legislative action.

The truth is we have stretched the quarter-century old protocol of step therapy beyond its ethical limits. Now it is time to devise a new strategy that will take into account the current state of healthcare, as well as its continued expansion into the future, and put patient care back into the hands of the doctors who are educated and ethically obligated to treat them.

## APPENDIX A:

CLINICAL ETHICAL FRAMEWORKS AND CONSIDERATIONS FOR STEP THERAPY IN AUTOIMMUNE ARTHRITIS. M. Sara Rosenthal, Ph.D., Professor and Director, University of Kentucky Program for Bioethics Date: July 16, 2015

### Background

With the exception of rheumatoid arthritis, there are, as of this writing, no clinical practice guidelines available for the array of diseases categorized as *Autoimmune Arthritis*<sup>1</sup>. The current standard of care is to achieve the goal of disease remission, if possible, and assumes “the most common patients, not exceptional cases” (Singh et al, 2012). This is the clinical rationale for prescribing the most commonly effective and economical therapy first. In this approach, the first tier of drug recommended is a DMARD (Disease Modifying Anti-Rheumatic Drug), using a “start low, go slow” approach, titrating to higher doses gradually to see if the patient responds. If there is no response, the next tier of drug is a more targeted and expensive therapy (biologic agent, or biologic tumor necrosis factor inhibitor), which can range between \$12-48,000.00 per year, but limited data has not yet established this as the definitive standard of care, or superior to the standard of care, but merely *superior for some patients*. For these reasons, biologics are often not easily available by prescription, and may involve considerable steps in getting approval for coverage. Some insurers may not approve coverage, leaving patients with unacceptable out-of-pocket costs.

To address the costs of biologics, cheaper, so-called “biosimilar” formulations made with different compounds have been developed, but still require further study before they are accepted as either a standard of care, or to be interchangeable with a biologic because of no clinically meaningful differences. Finally, a newer drug, known as a Janus kinase inhibitor (JAK) may also have a role.

This therapeutic approach is known as a “fail first” Step Therapy regimen, which is comparable to many other disease contexts -- most notably -- chronic pain management. The problem with “fail first” Step Therapy in the Autoimmune Arthritis context is that delay in effective therapies can lead to worsening disease and irreparable joint damage and disability. This Review provides clinical ethical frameworks for medically appropriate Step Therapy for Autoimmune Arthritis patients.

### Clinical Ethical Principles in Step Therapy

The guiding clinical ethical principles for Step Therapy in Autoimmune Arthritis are: (a) the Principle of Beneficence, which obligates healthcare providers to maximize clinical benefits and minimize clinical harms; and (b) the Principle of Non-Maleficence, the specific obligation not to intentionally introduce harms to patients, neglect or abandon patients, or fail to warn patients of imminent harms associated with various treatments or lack of treatments. Offering patients therapies that are known to be inferior to the standard of care, potentially futile, or even harmful, violates the Principles of Beneficence and Non-Maleficence. These Principles support the Principle of Respect for Persons (see further).

The Principle of Justice is concerned with equal access to care, as well as rational allocation of resources. Health disparities in Autoimmune Arthritis have not been adequately explored, but in underserved populations that do not routinely access proper primary care, access to screening as well as access to therapy present distributive justice challenges that necessitate cost containment strategies (See and public policy and societal decisions about cost-effectiveness (See **Santoro Opinion**).

Beneficent care plans for this context are defined in three distinct scenarios:

*Scenario A: The patient is not a DMARD candidate (“Scenario 4 or 5” in Nayak et al, 2015).*

If the healthcare provider, based on expert opinion, already knows the patient will “fail” on a DMARD, knows of a contraindication to DMARD, and has concerns about knowingly worsening the patient’s disease by delaying the most beneficial therapy, then prescribing a DMARD first to “obey” an insurance company’s protocol is a clear violation of Beneficence and Non-Maleficence. In this situation, the practitioner has an ethical duty to start with the most appropriate therapy for the patient (e.g. biologic or biosimilar) as an alternative, and the insurer has a clear ethical duty to cover it as a first-line therapy. Alternatively, the practitioner may enroll the patient in a clinical trial of the appropriate drug if financial burdens are a consideration. The latter is ethically sound because a clinical trial will formally accumulate evidence towards establishing a different standard of care, while providing the appropriate drug to the patient without cost (until the trial ends). The trial design must be a prospective IRB-approved trial, and must follow established Research Ethics guidelines for the United States, and cannot introduce greater harms to the patient than “no treatment” or “fail first” regimens. A sound trial may involve a randomized controlled trial of a biologic compared with a “biosimilar” to accumulate data. Placebo-controlled trials in this context are not ethical, as it would not meet the Beneficence criteria.

*Scenario B: The patient may be a good DMARD candidate (Possibly “Scenario 1” in Nayak et al, 2015).*

In this scenario, it is ethically sound to begin the patient on a DMARD regimen since it is considered to be the most economically sound and commonly effective therapy. However, the patient needs to have full informed consent (see further) about material risks: that failing this regimen could result in a worsened condition that is irreversible. The financial burdens of biologic therapy must also be disclosed, so the patient can adequately appreciate medical and psychosocial risks – both “material” for quality of life. In this situation, the patient has the right to refuse DMARD therapy if the risks are considered unacceptable. However, the patient cannot demand to start on a biologic or any non-standard therapy if s/he is a reasonable candidate for the DMARD, and there is no indication that s/he will “fail”. In this situation, there are limits to patient autonomy if beginning the patient is medically (and economically) reasonable and appropriate. In this case, so long as it is medically sound to prescribe the next tier of drug, it is ethically permissible for the patient to assume a higher co-pay or out of pocket costs. It is also ethically permissible for the patient to be enrolled in a prospective IRB-approved clinical trial to gain access to the more targeted therapy (biologic or biosimilar) for no cost while helping to generate data. (See further under Research Ethics).

*Scenario C: There is agreement within the community of experts that biologic agents (or another agent) ought to be the first-line therapy. (“Scenario 5 or 6” in Nayak et al, 2015).*

In this scenario, the community of subspecialty experts produce consensus statements or even practice guidelines in which biologic agents (or other targeted therapies) are considered more effective and safer, however the costs remain the same. In this situation, there is no ethical defense for insurers to withhold coverage of this drug from patients unless there are questions about whether it is truly evidence-based (due to limited data, or even “clinical equipoise” – disagreement within the community of experts over whether the evidence shows the newer drug to be superior). Presuming expert consensus that is indeed superior, withholding coverage from patients who are valid candidates for the drug would be a violation of the Principles of Beneficence and Non-Maleficence. If there are questions about evidence, it is ethically permissible to enroll patients in a prospective IRB-approved clinical trial that accumulates enough evidence to satisfy societal/payer concerns that the drug is the most clinically appropriate first-tier therapy (evidence that would “disturb” clinical equipoise). In some cases, post-marketing “Phase 1V” trials (Bible et al, 2014) may be ethically permissible to accumulate information about the balancing of costs of early preventive goals to control disease over the costs of longer-term disability due to “failing” on cheaper therapies.

### **Informed Consent, Goals of Care, and “Personalized Medicine”**

Informed consent has both a moral and legal requirement (Faden). As a legal the precedent-setting informed consent case of *Schloendorff v. Society of New York Hospital* (1914) first introduced the principle of patient “self determination”. In *Wilkinson v. Vesey* (1972) the court stated: “a physician is bound to disclose all the known material risks peculiar to the proposed procedure.” Thus, the corresponding risks of not having a particular procedure, is also part of the disclosure process. In *Canterbury v. Spence* (1972), informed consent was established as “a basic social policy...”. And, finally, in *Cobbs v. Grant* (1972), the court emphasized “a duty of reasonable disclosure of the available choices [and] the dangers inherently and potentially involved in each.” These decisions form part of the legal doctrine of informed consent.

As a moral requirement, informed consent grew out of research and clinical ethics abuses in which vulnerable populations were not properly informed about medical risks. This led to ethical standards for informed consent as a process, which entails full disclosure, assessment of capacity, and allowing patients to exercise voluntary choices without coercion or misleading information. In a Step Therapy context, informed consent can be achieved with a “goals of care” discussion. Here, the practitioner seeks to find out more about the patient’s life, short-term and long-term goals, as well as values and preferences regarding what may constitute risks and benefits for the patient, as well as what constitutes “well-being” (Veatch, 1995). Quality of life is not limited to medical risks, but may include financial burdens and risks, which is why a frank discussion about costs of various therapies is important in this context, so newly diagnosed patients understand the Step Therapy model. Personalized medicine is a concept in which the patient and practitioner engage in shared decision-making in which the patient’s values and goals guide beneficent therapy. However, therapeutic options discussed must be clinically sound, and practitioners must offer therapies that are within the standard of care, or evidence-based. Among therapeutic options in this context may be enrollment in a prospective IRB-approved clinical trial (see further under Research Ethics).

### **Patient Autonomy and the Principle of Respect for Persons**

Most practitioners are taught that “patient autonomy” trumps all other ethical principles, and that they should cater to patient preferences, even if they disagree with patients. This is a frequent misinterpretation of The Principle of Respect for Persons, which is a principle that dually obligates practitioners to respect patient autonomy, but to also protect patients

from pointless harm who may not fully understand or appreciate their therapeutic options, or may not have full decision-making capacity due to barriers to decision-making capacity. Autonomy can only be enabled with valid informed consent, which comprises full disclosure and explanations of all procedures and treatments; decision-making capacity, which means patients must demonstrate understanding, appreciation, rationality and expression of a choice; and voluntariness, in which there is no coercion. Goals of care should be guided by autonomous patients' preferences, but there are limits to what practitioners may offer if patients are demanding therapies that are outside the standard of care, or potentially harmful. In the context of autoimmune disease, patients may express a preference to feel well and be restored to health, yet may not understand and appreciate the differences in available therapies. Failure of autonomous patients to demonstrate understanding, appreciation, rationality, and expression of a choice, indicates there is a barrier to decision-making capacity, and thus, valid informed consent cannot be claimed. There is no single standard for decision-making capacity, but the more consequential the medical decision is, the higher the standard we must demand. There are many psychosocial barriers to decision-making capacity; metabolic and physiologic barriers may also exist. In the context of severe symptoms, some patients may require a surrogate decision-maker. If there are questions about who should serve as an authentic surrogate decision-maker, an ethics or legal consult should be called; some states have family hierarchy laws, while others do not.

Beneficent care thus recognizes there are limits to patient autonomy when patients or their surrogates demand substandard, unsound or untested medical procedures or therapies that could be either futile or harmful. There are also limits to autonomy when patients demand more expensive therapies when there are reasonable and cheaper alternatives. It is imperative to recognize that while autonomous patients may accept or refuse therapies, they should not be abandoned to "autonomy" when they demand therapies that violate beneficent care (Lantos, 2011; Lowy, 2005; Tauber, 2003) by being provided with inappropriate care just because they demand it. When Beneficence and Non-Maleficence are violated, there may be legal consequences, as these ethical violations constitute medical negligence.

#### **Ethical Considerations for Patients with Underlying Mental Health Issues**

Underlying mental health issues, such as depression, personality disorders (e.g. borderline personality), and addictions may complicate treatment and become frank barriers to informed consent and decision-making capacity. Patients in these categories should have a formal capacity assessment by a mental health expert (psychiatrist; clinical psychologist or social worker; licensed addiction therapist, etc.) to rule out underlying mental health conditions.

#### **Somatization Disorders**

One mental health disorder, which is frequently overlooked in the context of rheumatoid referrals and other autoimmune disorders, is somatization disorder, which requires psychiatric intervention. This is a real disorder prevalent in the broad patient population, which is why it may sometimes be misdiagnosed in patients with diffuse symptoms who do have an organic disease. However, there are also many autoimmune disease patients who concomitantly suffer from somatization disorder.

Somatization disorder is a complex disorder in which a range of physiological sensations and complaints manifest in response to a complex psychological or abuse history (Neumann, 1996; Walker et al; Trimble, 2004; Arned-Caddigan, 2006). It is not factitious disorder or malingering. Patients with somatization disorders, who have concomitant autoimmune diseases, may persistently complain of a range of symptoms that could lead to iatrogenic harms. Such patients are typically driven to a range of multiple practitioners, who may do multiple work-ups, and even unnecessary procedures. Such patients are frequently at risk for a range of iatrogenic harms, such as risks from unnecessary therapies or surgeries. They may also pay large sums of money for non-standard alternative therapies that may not be part of standard Step Therapy. Patients with somatization disorders are frequently misdiagnosed and mismanaged. They have complicated medical histories – frequently because they seek out so many subspecialists. Somatization disorder is overwhelmingly diagnosed in females, often with a history of physical or sexual abuse. Recent data suggests that 1 in 3 women worldwide have been sexually or physically abused in their lifetimes [domesticviolencestatistics.org]. Somatization disorder should be managed in conjunction with a mental healthcare provider to rule out other underlying psychiatric problems, including personality disorders.

In patients with persistent complaints of chronic pain and malaise, all organic causes should be ruled out, followed by referral to a mental health practitioner to screen for somatoform disorder. Patients suspected of somatoform disorders should be provided with sensitive discussion in which the referral is explained, in which trust is maintained. Patients should understand and appreciate that their symptoms are not factitious, and are "real" but that the causes are rooted in psychological trauma, rather than an organic problem with physiology.

### **Ethical Considerations for Prenatal Populations**

There are numerous ethical considerations that are beneficent-based for patients who are planning pregnancy or who are already pregnant. The “fetal patienthood” framework, developed by Chervenak and McCullough (1996) is the operative framework for this context which guides therapeutic goals for such patients

### **Professional Ethical Duties**

All medical practitioners have professional ethical duties to be competent in their fields of practice, which includes intellectual honesty (Pellegrino, 1999; Pellegrino, 2000), and referring patients to other colleagues in areas where knowledge is insufficient. Practitioners who state they are experts in fields of practice when they have no demonstrable accredited training or board certification (e.g. “integrated medicine”) violates professional ethical standards of practice, as it overtly deceives patients.

Finally, competently trained medical experts who misuse their medical knowledge to personally profit, deceive patients, or purvey non-standard, risky innovative therapies are violating basic standards of care. Practitioners who engage in research activities that do not meet basic standards in Responsible Conduct of Research are in violation of research ethics guidelines.

### **Research Ethics Considerations, Innovative Therapies and Clinical Trials**

In this context, there appears to be agreement within the community of experts that the therapies available within the step therapy tier can be effective for the right candidate, but there is not enough data to predict which patients are certain candidates for which therapies, nor is there enough evidence to predict with certainty who will “fail” on Drug A, and which patient will succeed on Drug B. Thus, more data is necessary in order change the drug tier. Unless a therapy is a definitive standard of care, therapies considered to have theoretical benefit, or more benefit based on limited data (e.g. biologics, biosimilars, or Janus kinase inhibitors) are considered an “innovative therapy” for first line treatment. Innovative therapy is when a practitioner selects a non-standard therapy for the benefit of one patient because the patient is either not a candidate for the standard therapy (see Scenario A above), or refuses the standard therapy (see Scenario B above). Innovative therapies are not intended for data collection, however, and are designed solely for the benefit of one patient, rather than for generalizable knowledge. Innovative therapies do not require IRB approval if data is not being collected for the purpose of generalizable knowledge and publication. Thus, any published reports of innovative therapies cannot be used to validate or refute evidence; nor does innovative therapy address the question of whether Treatment A is better than Treatment B.

In this context, it can be argued that innovative therapy should be discouraged in favor of a formal prospective IRB-approved clinical trial in which patients meeting certain selection criteria are randomized to either a biologic or a “biosimilar” preparation (or a biologic and Janus kinase inhibitor, or any newer targeted therapies with theoretical benefit) so that enough data can be collected to determine therapeutic equivalence, and whether such therapies should replace the current first tier standard of care. It is ethically permissible for such trials to be funded by pharmaceutical companies, however the investigators involved cannot personally have financial ties to any such companies, and the funding source must be disclosed as part of the informed consent documentation, as well as in all data sharing. It will be up to the subspecialty community of experts to decide whether trials funded by industry can be considered valid, unbiased evidence. However, so long as such funding is managed ethically and transparently, funding only the study with no direct payments or fees to investigators, valid evidence can be collected which will benefit the patient population as a whole. Unfortunately, even perceived conflicts of interest can be problematic. Studies receiving funding from a company with a financial interest in the study outcome may be considered biased regardless of how the conflicts of interest were managed; such perceptions may also affect higher decisions regarding drug coverage.

### **The Ethical Duty to Research**

In this disease context, there is disagreement among the community of experts regarding which treatments are effective. In order to resolve uncertainty over whether Treatment A is better Treatment B to change the Step Therapy tier of drugs, or coverage of drugs, the subspecialty community of experts have a beneficence-based duty to address the question through properly designed human subject research -- clinical trials for the benefit of the patient population. A robust randomized controlled trial with enough statistical power to resolve uncertainty is necessary (over 80%). Such a trial would need to recruit from a representative population of patients worldwide; test therapies at dosages that cannot be disputed and account for regional disparities; disclose no potential conflicts of interest that would bias the results; and continue long enough for results to be replicated. (Freedman, 1987).

### **The role of N of 1 Trials**

N of 1 trials are ethical, but need to be properly designed and approved by an IRB to be considered research rather than merely innovative therapy. N of 1 trials may be useful for “enhancing therapeutic precision” or evaluating individual treatment effects for a patient (Gabler et al, 2011). In order to be generalizable, a valid N of 1 trial is a well designed, IRB-approved multiple crossover study conducted in a single individual as a tool to estimate the heterogeneity of treatment effects (THE) in a population. Such studies must meet criteria for responsible conduct of research (RCR). Investigators who are mistaking their innovative therapies as “N of 1” trials are engaged in unregulated human subject research.

#### **Societal Costs of Poorly Controlled Autoimmune Arthritis**

There are significant societal costs when a substantial number of adult women are burdened by disability for a group of diseases that could be better managed with targeted therapies. From a family-centered perspective, women who are in the workforce are either sole breadwinners or co-breadwinners for dependents (children, elderly or disabled parents, etc.). Women are also responsible for the majority of unpaid labor (domestic chores or caregiving for dependents).

*“Autoimmune Arthritis” is a stipulative definition used by IFAA which includes the diseases listed on [www.ifautoimmunearthritis.org](http://www.ifautoimmunearthritis.org).*

## APPENDIX B

### THE ETHICS OF STEP THERAPY IN BIOMEDICAL, ECONOMIC, SOCIAL, AND POLITICAL CONTEXT

Michael A. Santoro, J.D., Ph.D.

“Step therapy” is an insurance company policy implemented through prior authorization protocols whereby patients “must try a less costly treatment and ‘fail first’ with that before the insurer will cover another, more costly treatment.”<sup>1</sup> The ethical question step therapy raises may be stated as follows: When is it ethically permissible to require a patient to try a less costly therapy before trying a more costly one and when is it unethical to do so?

#### ***Step Therapy and Physician Ethics***

The ethics of step therapy can be understood by reference to the ethical obligations of physicians. Physicians have two separate and distinct obligations to patients directly impacting the ethics of step therapy—(1) the duty to practice evidenced-based medicine and (2) the duty to consider cost-effectiveness when making recommendations to patients.

*Duty to practice evidence-based medicine.* Physicians have an ethical obligation to practice evidence-based medicine, tempered by a clinical judgment about the unique characteristics of the individual patient. For example, according to the American College of Physicians *Ethics Manual* (6<sup>th</sup> Ed.) (2011) :

“The physician's professional role is to make recommendations on the basis of the best available medical evidence and to pursue options that comport with the patient's unique health needs, values, and preferences.”

This obligation to practice evidence-based medicine extends to physicians “designing practice guidelines and formularies, and making decisions on medical benefits review boards.”<sup>3</sup>

*Duty to consider cost-effectiveness.* Physicians have an ethical obligation to practice science-based medicine in a cost-effective manner. For example, the American College of Physicians *Ethics Manual* states that in making recommendations to patients physicians should consider “data on the cost-effectiveness of different clinical approaches.” The *Ethics Manual* goes on to maintain that insurance companies may take into account the cost-effectiveness of a treatment *relative to other treatments for other conditions*.

“Providers of health insurance are not obliged to underwrite approaches that patients may value but that are not justifiable on clinical or theoretical scientific grounds or that are relatively cost-ineffective compared with other therapies for the same condition or other therapies offered by the health plan for other conditions.”<sup>4</sup> (emphasis added)

#### ***The Ethics of Step Therapy When There Are Clinical Practice Guidelines***

Doctors in their interactions with patients balance evidence based medicine with cost-effectiveness on a daily basis. When authoritative groups of physicians such as the The American College of Rheumatology (ACR) publish Clinical Practice Guidelines (CPGs) they take cost-effectiveness, as well as the biomedical literature, into account. The ACR has published CPGs for Rheumatoid Arthritis, Juvenile Idiopathic Arthritis, Glucocorticoid- Induced Osteoporosis, Osteoarthritis, Lupus Nephritis, and Gout, with Axial Spondyloarthritis and Polymyalgia Rheumatica guidelines in progress. (New and revised “RA Guidelines” are also expected in 2015 according to the ACR website.)<sup>5</sup>

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<sup>1</sup> Nayak, Rahul K. and Steven D. Pearson, “The Ethics of ‘Fail First’: Guidelines and Practical Scenarios for Step Therapy Coverage Policies,” *Health Affairs* 33, No. 10 (2014): 1779-1785.

<sup>2</sup> [https://www.acponline.org/running\\_practice/ethics/manual/manual6th.htm](https://www.acponline.org/running_practice/ethics/manual/manual6th.htm)

<sup>3</sup> For an example of how physicians are involved in formulary decision-making, see the “White Paper” on *Formulary Development at Express Scripts*, available at <http://www.express-scripts.com/aboutus/formularyinformation/development/formularyDevelopment.pdf>

<sup>4</sup> [https://www.acponline.org/running\\_practice/ethics/manual/manual6th.htm](https://www.acponline.org/running_practice/ethics/manual/manual6th.htm)

<sup>5</sup> [http://www.rheumatology.org/Practice/Clinical/Guidelines/Clinical\\_Practice\\_Guidelines/](http://www.rheumatology.org/Practice/Clinical/Guidelines/Clinical_Practice_Guidelines/)

When there are scientifically based guidelines for clinical practice, physicians have an ethical obligation to adhere to those guidelines, subject to their professional clinical judgment about the individual patient. *Step therapy protocols that follow authoritative clinical practice guidelines are presumptively ethical* because clinical practice guidelines are designed through a process where physicians give due consideration to relevant biomedical and economic factors. *Step therapy protocols that deviate from clinical practice guidelines are presumptively unethical* because they would impose a cheaper, “fail-first” requirement on patients in situations where an authoritative medical group has already taken cost into account.

This conclusion that step therapy is unethical when it deviates from CPGs is enunciated in the ACR’s Committee on Rheumatologic Care Position Paper on Step Therapy (“ACR Step Therapy Position Paper”) <sup>6</sup> concluding that step therapy should not deny patients access to biologics—which “consistently, although not universally, decrease signs and symptoms of rheumatoid arthritis, induce clinical remission, halt radiographic progression of disease, and improve quality of life for these patients....Step therapies, fail first policies, tiering, and class switching requirements create unnecessary obstacles for patients and their physicians, delays in appropriate therapy, potentially dangerous outcomes for patients, and undermine the decisions made between the patient and physician.”

### ***Step Therapy Where There Are No Clinical Practice Guidelines***

The ethics of step therapy are more complicated where there is no authoritative CPG. For certain autoimmune diseases, e.g. psoriatic arthritis, existing FDA-approved treatments are far from perfect. All the available biologic therapies have low efficacy and significant safety risks, but they may be the only options available to patients. A step therapy requiring failure with one drug over another in these circumstances might prevent physicians from adhering to their fundamental ethical duty to practice evidence-based medicine by inappropriately creating a *de facto* standard of care when in fact the medical and scientific evidence about appropriate treatment for patients is in a state of equipoise or uncertainty. From a patient perspective, in addition to having to make a choice about the tradeoff between safety and efficacy, two crucial sets of questions emerge: (1) Does the safety/efficacy profile of each drug change according to various individual characteristics? Does my gender or race or genetic profile matter to which drug is right for me? Does it matter if I suffer from other diseases and am taking medication for those? (2) Does it matter in which order I try each drug? The step therapy process makes answering these kinds of urgent medical questions in a clinical setting difficult if not impossible.

These considerations mirror those in the ACR Step Therapy Position Paper observing that physicians prescribe injectable anti-TNF therapies on the basis of “individual patient considerations, overlapping medical and immune conditions and safety considerations.”

They are also consistent with the conclusions of a 2011 American College of Physicians Position Paper<sup>7</sup> emphasizing the importance of data gathering for complex medical decisions that take into account efficacy, safety and cost:

“Sufficient resources should be devoted to developing needed data on clinical and cost-effectiveness of medical interventions for comparative, evidence-based evaluations that should serve as the basis for allocation decisions about the utilization of health care resources.”

### ***The Meaning of Cost-effectiveness***

“Cost-effectiveness” is a complicated issue in the context of a social and political mandate as set forth in the Patient Protection and Affordable Care Act of 2010 (the “Affordable Care Act”) to simultaneously reduce costs and make the distribution of health care more equitable. What is “cost-effective” from the perspective of a particular therapeutic area may not be cost-effective from the perspective of overall healthcare outcomes. In such a context, CPGs promulgated even by authoritative physician groups such as the ACR could be in tension with the perspectives of insurers, benefit managers, and government agencies. The question that arises is whether CPGs by groups such as the ACR are truly be formulated with a broad social costs in mind or whether they represent particular interests.

<sup>6</sup> <https://www.rheumatology.org/uploadedFiles/Step-Therapy-6-2013-draft.pdf>

<sup>7</sup> American College of Physicians, *How Can Our Nation Conserve and Distribute Health Care Resources Effectively and Efficiently?* (January 27, 2011) (p.16), available at: [http://www.acponline.org/advocacy/current\\_policy\\_papers/assets/health\\_care\\_resources.pdf](http://www.acponline.org/advocacy/current_policy_papers/assets/health_care_resources.pdf)

It is interesting in this light to examine the process and standards that the ACR uses to develop CPGs. In January 2015, the ACR published a *Policy and Procedure Manual for Clinical Practice Guidelines*.<sup>8</sup> This document states that, since 2011, the ACR has been using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to develop CPGs. The GRADE website, in turn, offers the following vague statement about the role of cost in developing CPGs.

Judgments about evidence and recommendations in healthcare are complex. For example, those making recommendations must decide between recommending selective serotonin reuptake inhibitors (SSRI's) and tricyclics for the treatment of moderate depression must agree on which outcomes to consider, which evidence to include for each outcome, how to assess the quality of that evidence, and how to determine if SSRI's do more good than harm compared with tricyclics. Because resources are always limited and money that is allocated to treating depression cannot be spent on other worthwhile interventions, they may also need to decide whether any incremental health benefits are worth the additional costs.<sup>9</sup> (emphasis added)

It is unclear from this example whether a group making recommendations regarding SSRIs is meant to take into account how funds spent on SSRIs could be spent (a) on "other worthwhile interventions" for depression or (b) on "other worthwhile interventions" in other therapeutic areas. If doctor groups such as the ACR are only taking (a) into account, then one could argue they are not using a social measure of cost-effectiveness. Nor are they using the standard of cost-effectiveness enunciated above in the *Ethics Manual* of the American College of Physicians stating that insurance companies may take into account the cost-effectiveness of a treatment relative to other treatments for other conditions.

These two meanings of cost effectiveness raise broad and difficult ethical, social, and ultimately political issues. While medical systems have various ways of measuring healthcare outcomes and economists have various ways of measuring costs, two problems will always emerge in considering cost-effectiveness from a social perspective: (1) *Counting*. It seems a simple matter, but unless data about suffering, cure, relief and other healthcare outcomes for any particular therapeutic area make it into the system, cost effectiveness cannot be accurately assessed. (2) *Interpersonal and Cross-Therapeutic Comparison*. How do we compare the suffering of someone with depression with the suffering of someone with an autoimmune disease or with a shoulder injury needing surgery?

The most commonly used measurement for health outcomes in cost-benefit analysis is the "quality-adjusted life year" (QALY). One year in perfect health is equal to 1.0 QALY. A bed-ridden year might be equal to 0.5. Some have argued that for those with chronic diseases, there is an inherent bias built into QALY because it favors groups with longer life expectancies.<sup>10</sup> Therefore, it becomes especially critical for patients in such groups to be able to demonstrate the QALY improvements generated by access to a particular drug, or, conversely, the QALY harm they will suffer if access to the drug is delayed because of step-therapy.

It should be noted in closing that the Affordable Care Act specifically prohibits the use of *threshold* dollar levels for QALY by the Patient Centered Outcomes Research Institute (PCORI), which is meant to conduct "patient-centered outcomes research" that will inform healthcare spending allocation. The United Kingdom, for example, will not spend more than \$31-47,000 per QALY attained. The idea behind this proscription was to avoid the charge that the PCORI would function a "rationing board" or "death panel" denying coverage for expensive treatments yielding low QALY outcomes. However, some legal experts<sup>11</sup> believe the Affordable Care Act's proscription of QALY *thresholds* does not mean that the PCORI cannot use QALY to *compare* healthcare outcomes and costs across disease states, and many economists believe it is inevitable (and desirable) that PCORI will eventually have to do so to meet the mandate of cost containment.<sup>12</sup>

<sup>8</sup><http://www.gradeworkinggroup.org/intro.htm>[http://www.rheumatology.org/uploadedFiles/ACR/Practice/Clinical/Guidelines/ACR%20Guideline%20Manual\\_Appendices\\_updated%202015.pdf](http://www.rheumatology.org/uploadedFiles/ACR/Practice/Clinical/Guidelines/ACR%20Guideline%20Manual_Appendices_updated%202015.pdf)

<sup>9</sup> <http://www.gradeworkinggroup.org/intro.htm>

<sup>10</sup> Hay, Joel W., "The Application of Cost-Effectiveness and Cost-Benefit Analysis to Pharmaceuticals," in Michael A. Santoro and Thomas M. Gorrie, *Ethics and the Pharmaceutical Industry* (Cambridge University Press, 2005)

<sup>11</sup> Bagley, Nicolas, "Who says PCORI can't do cost-effectiveness?", available at <http://theincidentaleconomist.com/wordpress/who-says-pcori-cant-do-cost-effectiveness/>

<sup>12</sup> Carroll, Aaron E., "Forbidden Topic in Health Policy Debate: Cost-Effectiveness," *The New York Times*, December 14, 2014, available at [http://www.nytimes.com/2014/12/16/upshot/forbidden-topic-in-health-policy-debate-cost-effectiveness.html?\\_r=0&abt=0002&abg](http://www.nytimes.com/2014/12/16/upshot/forbidden-topic-in-health-policy-debate-cost-effectiveness.html?_r=0&abt=0002&abg)

**Conclusion**

Step therapy raises broad and overlapping ethical, biomedical, economic, social and political questions. Powerful economic, social, and political cost containment imperatives will increasingly challenge bedrock ethical values of promoting patient welfare and preserving physician judgment. In this context, where utilitarian calculations of costs and benefits become trump cards, it becomes crucial for patients to help inform doctors, insurers, benefit managers, and government agencies about their personal experiences—both their sufferings and their improvements and relief. In a world that decides biomedical questions through numerical equations, patients increasingly will need to be heard and make sure they count if they hope to achieve their fair share of distributive justice.

Professor Santoro, bioethicist, has worked as a consultant to Celgene Corporation on issues related to the ethics of step therapy.

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