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Toward Accelerated Authorization and Access to New Medicines for Juvenile Idiopathic Arthritis

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Abstract

Objective

A meeting was organized to bring together multiple stakeholders involved in the testing and authorization of new medicines for juvenile idiopathic arthritis (JIA) to discuss current issues surrounding trials and access of new medicines for children and adolescents with JIA.

Methods

The Childhood Arthritis and Rheumatology Research Alliance (CARRA) invited regulatory agencies (Food and Drug Administration [FDA] and European Medicines Agency [EMA]), major pharmaceutical companies with JIA products approved or in development, patient and parent representatives, advocacy organization (Arthritis Foundation) and pediatric rheumatology clinicians/investigators to a one-day meeting in April 2018.

Results

The participants highlighted current issues in clinical trials. As the pharmacologic armamentarium to treat inflammatory arthritis rapidly expands, registration trial designs to test medicines in JIA patients must adapt. Many methodologies used successfully in the recent past are no longer feasible. The pool of patients meeting entry criteria who are willing to participate is shrinking at the same time that the number of medicines that need testing is growing. Solutions included proposing innovative clinical trial methods to regulatory agencies, as well as open discussion among stakeholders.

Conclusion

Ensuring new medicines are authorized in a timely manner to meet the needs of JIA patients worldwide is critical. Approaches should include: open dialogue between regulatory agencies, pharmaceutical companies and other stakeholders to develop and implement novel study designs; including patient and clinician perspectives to define meaningful trial outcomes; and changing existing study plans.

Introduction

The impact of new biologics and small molecule therapeutics on inflammatory arthritis in the last two decades is remarkable and continuing to grow. The legislative agenda set by the United States Government with Pediatric Study Plans (PSPs) (1) and European Commission and Parliament with Paediatric Investigation Plans (PIPs) ensures that drug development includes pediatric trials (2). Pediatric trials of new drugs, primarily led by the Pediatric Rheumatology Collaborative Study Group (PRCSG) and the Pediatric Rheumatology International Trials Organization (PRINTO), have caused a sea change, leading to marked improvement in the outcomes and quality of life of children and adolescents with juvenile idiopathic arthritis (JIA). Pharmaceutical companies continue to develop additional drugs in both established and new drug classes. To continue the exponential trajectory of treatment advances, innovative approaches to testing and authorizing medicines are sorely needed, as current approaches do not meet the needs of stakeholders, including patients, regulators, clinicians, investigators and industry. Efforts to define patient centered outcomes consistently highlight unmet needs in the patient community (3). In April 2018, a stakeholder meeting including clinicians,

researchers, patient/parents, the Arthritis Foundation, industry and regulatory agencies (Food and Drug Administration [FDA] and European Medicines Agency [EMA]) was held to discuss current challenges and potential solutions. Topics included novel study designs for authorization, increasing and diversifying patients available for clinical trial participation, and improving communication and collaboration between regulators and other stakeholders. In this article, we outline key issues raised at the meeting and possible approaches to push the field further forward.

There are now highly effective biologic therapeutics with FDA and EMA approval for the treatment of JIA, including etanercept, adalimumab, abatacept, tocilizumab, and canakinumab (in EU also golimumab and anakinra). In this environment, it is crucial to rethink how clinical trials are performed and what data are required for product registration depending on whether a new drug class, new preparation of a registered drug, or new molecule in a well-studied drug class is involved. Adding to the growing complexity of registering additional products is the limited pool of children available to participate in trials, considering that approximately 40-60% of children with JIA (depending on subtype) have clinically inactive disease (CID) on medication(s) at one or two year follow up making them ineligible for a clinical trial (unpublished data, CARRA Registry). Similar results have been observed in other longitudinal observational registries in other countries: 38% had CID at one year in the UK, and 45% in Canada (4, 5). The multiple current PIPs/PSPs agreed upon for testing in enthesitis related arthritis require more than the eligible patients in Europe and North America to fulfill industry commitments (see Table 1). Nevertheless, testing and authorizing new products

continue to be an urgent needed. Data from the above registries indicate that half of children with JIA are clinically active despite treatment at 2 years and approximately 25% of participants treated with investigational products in JIA trials fail to achieve modest ACR 30 trial response definitions (4). At a recent meeting of the Systemic JIA Foundation, researchers presented that 5-10% of SJIA patients are resistant to both IL1 and IL6 blockade. Safety concerns are also an ongoing issue with currently available medical treatments. Clearly more and better products are needed. A one-day meeting of stakeholders was held on April 11, 2018 in Denver, Colorado. Rheumatologists, researchers, patient/parents, the Arthritis Foundation, industry and regulatory agencies (FDA and EMA) discussed the current state of JIA clinical trials, outcome measures, the role of registries, and new approaches for JIA clinical trials, as well as next steps. The meeting was an initial discussion to highlight current issues and provide a call to action.

Current state of clinical trials in JIA

Most available medications were authorized for JIA treatment based on pediatric placebo controlled randomized clinical trial (RCT) results including all subtypes of JIA. Currently, a growing number of products are being developed for specific JIA categories, all of which are rare diseases. Given the current number of efficacious drugs for JIA (4-6), the robust development pipeline, and a dwindling number of eligible JIA patients, continuing the current model for obtaining regulatory approval is not feasible. Future trials may be feasible only if they enroll patients without medication access, due to either socioeconomic restraints or lack of drug availability at a national level. This raises ethical concerns, particularly if participants are recruited from a country that is not

part of the sponsors' marketing plans, as well as issues with generalizability of results. Enrollment issues extend the length of placebo-controlled trials increasing expense and delaying availability of novel medicines. A current example is the tofacitinib trial, which has yet to complete enrollment for the systemic JIA cohort of the study after several years, potentially depriving all polyarticular and systemic JIA patients of access to a new class of oral treatment, if found to be safe and effective (ClinicalTrials.gov Identifier: NCT03000439)(7).

The randomized placebo-controlled withdrawal clinical trial design (8) is a commonly used alternative to the standard RCT that limits placebo exposure (9). Although successfully used to obtain authorization of the early biologics, this trial design now has notable issues. In this trial design, all participants are initially treated with open label study medication, then only participants meeting the trial definition of response (usually the JIA ACR 30), are randomized to placebo or continued active treatment. The difference in the flare rate between the placebo and active treatment arms in the withdrawal phase is the primary outcome (10). There are several methodological issues with this design. The initial open label design makes the outcome in the resultant responder group difficult to interpret and generalize. Valuable information about non-responders is lost because they are excluded from the study after the open label phase, making the actual clinical efficacy of the therapeutic agent difficult to interpret and making it difficult to power future studies. Since all participants receive study drug, only limited information is gleaned about relative safety. Responders may experience prolonged response despite being randomized to placebo. This can be due to placebo

effect or durability of response to open label drug. Fewer patients may flare for these reasons, decreasing observed differences between the two treatment groups and leading to the false conclusion that the drug is not effective. This scenario, coupled with the long half-life of golimumab, may have led to negative results from a randomized withdrawal trial conducted for children with JIA, depriving children in the U.S. the use of this long acting anti-tumor necrosis factor (TNF) agent (note: EMA approved golimumab for JIA anyway, concluding the benefit/risk ratio was positive despite the negative trial results) (11, 12). Additionally, withdrawing an efficacious medication is no longer acceptable to patients, families, and clinicians, considering the availability of other agents and concerns about possibly missing a window of opportunity when effective early treatment may result in long term remission.

RCT will continue to play an important but selective role. The first of a new class of medicines certainly warrants a rigorous clinical trial. However, many drugs currently in development are similar, though not identical (i.e., “me-too” drugs) to registered medications. Placebo-controlled trials of each new drug class, as well as the plethora of “me-too” drugs such as many new JAK inhibitors, are creating unprecedented demand for JIA patients to enroll in clinical trials. Simply stated, the demand for JIA patients cannot be met if every new medicine is studied using a PRCT. Therefore, alternative approaches to prove efficacy, dosing and safety are urgently needed (13).

Outcome measures used in JIA clinical trials

Meaningful study outcomes are of central importance to evaluate medication efficacy. Ideally, study outcomes support an efficient trial design, are clinically meaningful and enable timely disclosure of trial results to regulatory agencies, providers, and patients/families (14). Improved study endpoints in JIA clinical trials could meet these requirements. Outcome assessment in JIA is challenging due to the need to measure both response and disease activity, the need for measures that function across research settings and study designs, and the lack of objective variables or accurate biomarkers (15).

Most common JIA clinical trial outcomes are response to therapy, flare, disease activity, damage, and a range of patient-reported outcomes (PROs) (16). The JIA American College of Rheumatology (ACR) measure of response to treatment and flare are composite measures that are the standard for registration trials (17). However, although this response measure is familiar to investigators, it does not reflect disease activity level, making clinically useful interpretation challenging. Furthermore, with effective treatments available, the standard JIA ACR 30 (meaning 30% improvement from baseline) is no longer a *satisfactory,* meaningful response threshold for families or clinicians. Indeed, in clinic, a JIA ACR 30 response would often prompt further escalation of therapy. The parent/patient global assessments are often misunderstood, leading to inaccurate measurement. The ACR measure is not useful in clinical care because it requires blood test results and formal calculations of percent improvement plus lack of percent worsening of multiple components from baseline values. For all

these reasons, it is not optimal for shared-decision making. A large, international collaboration is currently updating components of the core set to be more meaningful to providers and patients, but any format comparing multiple individual assessments to baseline will continue to be problematic (3).

The Juvenile Arthritis Disease Activity Score (JADAS) (18), a continuous, composite measure of disease activity, has been proposed as an alternative. The JADAS conveys the level and change in disease activity. Further ongoing validation including defining meaningful levels of response and cut offs for disease activity levels is needed for use in clinical trials. Indeed, JADAS has been included in several positive registration trials as a secondary outcome and the JADAS cutoff for inactive disease could be used as an outcome, particularly in trials that incorporate treat-to-target design. The ACR Provisional Criteria for Clinical Inactive Disease (CID) (19) standardize the measurement of inactive disease and remission on and off medication, but require additional prospective validation. Although meaningful to patients and parents, the ACR CID definition does not incorporate the patient perception of disease status, which is a weakness. Strictly-applied CID criteria also describes a high level of response that may be difficult to attain during a registration trial (20). In addition, CID and JADAS Inactive Disease are not equivalent states, which could be a problem when using either outcome in a clinical trial, and when comparing results (21).

PROs bring the impact of disease and treatment on families to clinical trials. Currently, registration trials incorporate generic PROs (e.g., Childhood Health Assessment Questionnaire [CHAQ] and Child Health Questionnaire [CHQ]) that are limited by substantial floor and ceiling effects and do not measure aspects of disease (e.g. fatigue) especially important to patients and families. Work is ongoing to validate the pediatric PROMIS® modules in JIA as part of the NIH funded PEPR consortium (https://www.peprconsortium.org/). The PROMIS computerized adaptive testing (CAT) forms, may be particularly useful. In addition to the PROMIS® measures, there are many other PROs available for use in children with JIA. PRO choice will vary based on the study population and the research questions of interest. Lastly, an Arthritis Foundation and CARRA sponsored externally led FDA Patient Focused Drug Development program was held August 2, 2018, to ascertain patient/family perspectives on critical domains to assess.

Long-term medication safety studies and analysis

Challenges also exist in evaluating long-term safety of new therapeutic agents following regulatory approval. Usage patterns in clinical practice are complex, with many children exposed to multiple medications. Data from the CARRA Registry indicates that approximately 40% of JIA patients treated with a biologic receive a second biologic within two years (unpublished). Registry data on JIA management in other countries reveals similar patterns (22, 23). Pharmacosurveillance approaches that do not adequately account for switching between therapeutic agents are therefore inadequate and potentially misleading.

Historically, medication safety has been studied in drug-specific prospective registries (phase IV studies) that enroll patients upon initiation of the new therapeutic agent. However, limited duration of follow up, small patient numbers, unnecessarily restrictive cohort inclusion criteria, no accounting for biologic switching, unreasonably high enrollment goals, and the absence of comparators has made meaningful assessment of phase IV study results impossible.

More recent studies capture safety data using large prospective observational *disease-based* registries (24, 25). Disease-based registries enroll patients with a specific disease irrespective of medication use. The most efficient approach is to include all patients newly starting study drug in a disease-based registry, irrespective of prior medication use or inclusion in a prior comparator cohort. Unfortunately, some studies have applied unnecessary restrictions, such as not allowing patients to switch from a comparator cohort to a study drug cohort during the course of follow-up.

The uptake of new therapeutic agents to treat JIA in clinical practice is often slow, owing to the relative rarity of JIA and how well most patients respond to currently available biologic agents. Many of the patients who will be initiating a newly approved agent have already failed older available medications, and are waiting to start the new agent as soon as it is approved. Since this backlog of waiting patients will then rapidly diminish following agent approval, if companies are not poised to initiate enrollment for a phase IV safety study immediately at the time of drug approval, the opportunity to prospectively collect safety information on this relatively large number of patients will be

lost. A uniform transparent regulatory approach to phase IV requirements including data collection in an approved disease-based registry would allow companies to anticipate their needs and initiate registry operations prior to new drug approval.

Current regulatory mandates are based on specific patient numbers for phase IV studies with enrollment goals that can be unrealistically high. An alternative approach would study newly approved medications in the context of a disease-based registry for a pre-specified time period (e.g., 15 years), rather than for a pre-specified number of patients. The registries would provide safety data on all patients newly initiating the medication of interest and appropriate comparator patients during the same time period. This approach accounts for unpredictable utilization of new medications and does not penalize companies for slow uptake of new product, standardizes the rigor of safety data collection for all medications, and ensures new medications are studied for long enough and contemporaneously with comparators to meaningfully assess long-term safety.

Unmet needs from the clinical perspective of parent/patient and providers

Patients with JIA may face a lifetime of trying—and potentially failing—medications. Despite treatment advances, managing JIA is still trial and error. Medication delivery by injection is problematic and negatively impacts quality of life. Children who fail to achieve enduring remission may exhaust all currently approved medications. However, as the list of available medications grows, family and provider decision making becomes more complex. Key unanswered questions remain, such as: (1) How do medications

compare when used for specific JIA categories?; (2) How often do patients need to be switched from one medication to another (same class or different class), and what is their outcome?; (3) Do long-term safety profiles differ by length of use, medication class and combination?; (4) Can clinical trial results be applied to JIA patients seen in the clinic?; and, (5) What predicts response and non-response for individual patients?

To facilitate access to new therapies, it is imperative that clinical trial designs evolve to be more feasible, patient-centered and representative of the clinic population in terms of racial, ethnic, socioeconomic and disease characteristics. Increasingly, families and providers are demanding increased patient centeredness in trial design, especially in an environment with multiple treatment options already available. Clinical trials should be a source of hope and expanded knowledge, rather than a last resort for families with few options due to lack of insurance, failure of available medications, or residence in countries where biologics are not readily available. Novel patient-centered clinical trial designs are necessary to foster improved participation and timely trial completion. With a wide array of treatment options currently available and under development, patients and families want and need to know how medicines compare to one another, which work best for which JIA category and which populations of patients, which are safest in the long term, and ultimately which is best for their individual child. All patients and families rightfully expect clinical trials to generate information that is meaningful to them.

Using validated PROs that are selected in collaboration with patients and parents ensures trial outcomes are meaningful to stakeholders as well as grounded in rigorous methodology. Incorporating PROs into study outcomes is essential to understand impactful changes in the patient experience. Efforts by OMERACT and the Arthritis Foundation confirm that 30% improvement in disease activity domains determined by clinicians is not sufficient for shared decision-making. Adopting a more robust patient-centered approach to trial design and execution is a critical step forward. An externally-led FDA Patient Focused Drug Development meeting sponsored by Arthritis Foundation and CARRA held in August 2018 is helping guide this process for JIA (26). Other international efforts are under way to promote the patient-centered perspective in setting outcomes and trial design, notably the OMERACT JIA group (27).

The regulatory perspective

Demonstration of a positive benefit/risk ratio based on evaluation of all available information acquired during drug development is required for regulatory approval of new medicines. Treatment advances for JIA exemplify the successful implementation of the Pediatric Research Equity Act (PREA) in the United States and Paediatric Regulation in the European Union (28). Most prior JIA authorization studies used a randomized withdrawal design showing significant differences between placebo and active treatment in the withdrawal phase in relatively small numbers of patients (average <150 total enrollment). Data from the larger, more comprehensive randomized controlled trials in adults, mostly with RA, enabled adoption of the JIA withdrawal design with smaller sample sizes as acceptable for authorization purposes.

(2).

Since a large volume of information exists from the development, authorization and clinical use of the first biologics for treating JIA (mainly anti-TNF agents), the FDA and EMA updated their guidance (29, 30) to officially include the statement that in certain situations formal confirmation of efficacy in children is not needed. Although pharmacokinetic (PK)/pharmacodynamic (PD) studies are always required in children to confirm dosing, a limited uncontrolled open-label study or other design developed for rare diseases can support extrapolation of efficacy from adult studies. This is only appropriate after careful assessment of available data and agreement between sponsor and the regulatory authorities on the specific extrapolation plan with input from independent disease experts and patient/families (2, 6). But for products targeting new pathways, opportunities to use extrapolation studies are much more limited, and use of placebo or an active comparator(s) is needed. However, the feasibility of parallel design studies in children with JIA is limited, due to the large number of products under development and the limited numbers of patients available and willing to participate. A randomized withdrawal design study requires less participants than a classical non-inferiority study, but the example of the golimumab placebo-controlled withdrawal study highlighted limitations of this design in patients with relatively mild disease. Further development of innovative clinical trial methodologies facilitated by collaboration among patients and families, clinicians, researchers, industry and regulators will address changing needs, sparing pediatric patients from unnecessary trials while ensuring sufficient data to provide an evidence base for clinical decision-making. With this in mind, modifications of already agreed-upon PSPs and PIPs may be appropriate to

streamline drug development in line with current regulatory thinking and today's social, medical, and marketing environment.

During the April 2018 Denver stakeholders meeting, representatives of both the FDA and EMA encouraged pharmaceutical companies to utilize potential new trial designs, leverage Bayesian statistical analysis or extrapolation studies when possible, including modeling and simulation, and develop study plans with guidance from clinicians, researchers and patients/families to support the approval of new medicines for JIA. Guidelines including direction about what information is needed to support proposals is available (31, 32).

The industry perspective

The pharmaceutical industry wants to work in partnership with patients/families, clinicians, researchers, and regulators to design and deliver clinically meaningful and feasible trials. The April 2018 Denver stakeholders meeting demonstrated that collaborative and open dialogue between all stakeholders, especially regulators and industry, is desired and possible. However, reluctance still exists to ask regulators to update previously agreed upon decisions, even if it is to reflect current community needs and concerns. Additionally, *informal* interactions between industry and regulators may be helpful to facilitate new trial designs, assessing whether draft proposals are feasible and acceptable prior to formal submission. Even closer collaboration between the FDA and EMA, including alignment of drug development timelines, would promote the coordinated and timely authorization of new medicines. Industry hopes to engage

with a wide variety of expert opinion leaders and patients/families to garner diverse opinions and approaches, as well as with research networks, not only regarding design, but also operational and feasibility issues. Industry partners are committed to ensuring novel agents reach children in a timely fashion and recognize clinical trial methodologies being used no longer meet the needs of the community. Indeed, most presently agreed-upon PSPs and PIPs include pivotal phase III trial(s) in JIA (systemic JIA and polyarticular JIA) involving >300 patients each. With the increasing number of patients achieving satisfactory responses on currently available drugs, the ability of industry to meet these requirements is unlikely. Recent renegotiation of PSP/PIPs leading to smaller and shorter development plans indicates that all stakeholders respect the consequences of the current scenario on PSPs and PIPs.

Potential solutions for the future

Importantly, close collaboration between clinical trialists and methodologists across disciplines is resulting in increasing discussion of alternative study designs that are potentially superior to the placebo-withdrawal design for testing treatments in JIA and other pediatric rheumatic diseases, including uncontrolled open label, active comparator controlled, extrapolation, and others (33).

Uncontrolled open label design

Open-label pharmacokinetic and pharmacodynamic studies may be sufficient for regulatory approval in new therapeutic agents which directly target known disease mechanisms with previously demonstrated efficacy and safety in JIA, and/or with an

existing label for adult inflammatory arthritis (34). Previous PSP/PIPs for the TNF alpha inhibitor certolizumab, as well as the IL-6 receptor antagonist sarilumab, set precedence for this approach. Further scientific development of this concept by all stakeholders and approval by international regulators would be a key step in alleviating uncertainty about when this approach is acceptable.

Given high rates of clinically inactive disease/remission in polyarticular JIA and systemic JIA using available biologics, a critical unmet medical need is treatment for patients with unsatisfactory response to current therapies. Therefore, agents targeting novel mechanisms of action with limited safety information might be appropriately evaluated in small open label trials with extensive PK and PD assessment including patients unresponsive to approved treatments and providing quicker access to needed treatments. This approach would also avoid ethical implications of using an experimental drug with or without placebo when proven alternatives are available (26).

Active comparator controlled design

Using an active comparator completely avoids exposing children to placebo while maintaining the advantages of a PRCT study. New molecules with Phase 3 data in adult inflammatory arthritis but never tested in children are candidates for this design in JIA. To ensure the burden of proof is not excessive, non-inferiority of the novel agent compared to the registered active comparator rather than superiority would be required. Careful consideration is needed to determine the acceptable relative efficacy leading to approval of the new agent, but this design would more easily recruit participants,

produce more clinically meaningful results and be more acceptable and relevant to patients and families. Other issues with active comparator designs include establishment of safety in absence of a placebo arm, selecting an appropriate comparator as not all biologics are available in all countries, and the high cost of the comparator drugs, a problem companies could help one other resolve.

Extrapolation

Another approach to enable efficient and ethical evaluation of treatments is extrapolation, a complex concept that leverages all available information on the disease and medicine/class of medicines in question. The information is applied to the background of specific unmet needs, in order to identify which information can be inferred from testing in other populations, what information is missing, and how to mitigate remaining uncertainties. A Bayesian (adaptive) design can be part of this approach, where information from a relevant source (e.g. adult studies, non JIA pediatric studies, PK/PD studies, registries, and expert opinion) is used to inform the effect of study drug in JIA (31, 32, 35). Source information is augmented with trial observations in children with JIA and decisions about effectiveness are made based on the combined data. When the source information (e.g. estimated treatment effect in adults) is similar to what is observed in children, this design leads to increased power (and lower participant numbers) in the JIA clinical trial.

Precision Medicine

The most significant question asked frequently by patients/families and clinicians is, which drug is right for *this* child? To answer this critical question, clinical trials must move towards head-to-head studies of novel agents compared to established medications. Adaptive designs with small sample sizes, analysis of individual patient trajectories, and associated biomarker studies move toward addressing this critical question.

Conclusions

The April 2018 Denver meeting of stakeholders (industry, regulators, patients/families, investigators, clinicians and advocacy organizations) highlighted critical factors facing the timely approval of new medicines for JIA (Table 2). Collaboration among stakeholders with the shared goals of reducing barriers to regulatory approval including use of active comparator trials, extrapolation for authorization of “me-too” medicines, studying outcomes of importance to clinicians and patients, and ensuring adequate evaluation of long-term medication safety using disease-specific registries were key points discussed. In addition, speakers from both FDA and EMA discussed the use of alternative clinical trial designs including open-label and innovative approaches specifically adaptive and Bayesian methodologies, encouraging dialogue between industry, regulators, patients/families clinicians and investigators, including reconsideration of previously approved development plans.

In the presence of significant needs for new treatments for non-responders and answers to essential questions about individual drug selection, new and innovative changes are urgently needed to move forward the treatment of children with JIA and not just lengthen the list of registered medicinal products. In addition, JIA patient numbers and the market environment cannot support the authorization of the large number of medications in development through multiple placebo-controlled trials running concurrently. Clinical trial methodology must and should change to fit the modern treatment landscape as well as the needs of the pediatric rheumatology community. Since this meeting was the initial step in discussing these issues regarding clinical trials and the role of registries, an important next step is being planned to engage the broader community of stakeholders in a large, public meeting to establish solutions through consensus on October 2, 2019.

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Table 1. Estimated range of prevalent Enthesitis Related Arthritis (ERA) & Juvenile Psoriatic Arthritis (JPsA) patients eligible for study recruitment among European countries, the US, and Canada in 2025*

Country	2025 population projection[1]	JIA prevalence rate[2]	Low End of Estimated Prevalence of ERA & JPsA combined[3]	High End of Estimated Prevalence of ERA & JPsA combined[4]	Estimated Number of Prevalent ERA & JPsA Cases	Estimated Number of Prevalent Cases that Warrant Biologic Therapy[5]
Europe[6]	96,203,359	32.6 per 100,000	4.89 per 100,000	6.5 per 100,000	4,704-6,272	1,345-1,794
US	66,829,693	44.7 per 100,000	6.71 per 100,000	8.9 per 100,000	4,481-5,975	1,282-1,709
Canada	6,638473	44.7 per 100,000	6.71 per 100,000	8.9 per 100,000	445-593	127-170

*All estimates for patients under age 16

[1] United Nations, Department of Economic and Social Affairs, Population Division (2017). World Population Prospects: The 2017 Revision, custom data acquired via website. Age groupings available via query included 0-14 years of age. The population projection for those 15 years of age was calculated by obtaining 1/5th of the 15-19 year old population figure.

[2] European estimate obtained from Theirry et al. (2014)(36). US estimate obtained from Harrold et al. (2013)(37)

[3]Assumed that 15% of JIA prevalence is attributable to JPsA and ERA subtypes (Adib et al. 2008 (38), Weiss et al. 2012 (39), Sengler et al. 2015 (40)).

[4]Assumed that 20% of JIA prevalence is attributable to JPsA and ERA subtypes (Flato et al. 2009 (41)).

[5]Assumed 28.6% of ERA & JPsA patients warrant biologic therapy (Sengler et al. 2015 (40)).

[6]Europe includes: Belarus Bulgaria Czechia Hungary Poland Republic of Moldova Romania Slovakia Ukraine Channel Islands Denmark Estonia Finland Iceland Ireland Latvia Lithuania Norway Sweden United Kingdom Albania Bosnia and Herzegovina Croatia Greece Italy Malta Montenegro Portugal Serbia Slovenia Spain TFYR Macedonia Austria Belgium France Germany Luxembourg Netherlands Switzerland

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Table 2: Summary of Different Stakeholder Perspectives Regarding Clinical Trials in Pediatric Rheumatology

Stakeholder	Current Issues	Potential solutions
Patients & Advocacy organizations	• Absence of head to head comparator studies to guide individual decision making • Randomized withdrawal and placebo designs not acceptable with marketed options available • Outcomes not meaningful to patients • Pragmatic and ethical considerations of placebo withdrawal design	• Non-inferiority active comparator studies approved by regulators • Adaptive designs/open label for agents with similar mechanisms • New outcomes that are meaningful to patients and accepted by regulators • Patient engagement in trial design
Investigators and Clinicians	• Insufficient input into study design/pediatric investigation plans • Trial designs and outcomes not relevant to clinical practice • Absence of head to head studies to guide medical decision making • Poor use of disease specific registries for safety surveillance • Unmet needs of non-responders	• Diverse investigator input to guide clinical trial design • Adaptive study designs with active comparators • Use of Bayesian methodology • Open label studies
Industry	• Prefers trial design accepted by regulators in the past • Difficulty enrolling/completing trials • Reluctance to propose	• Clarity/transparency regarding expected regulatory response to novel study designs • Patient representatives in

	extrapolation/adaptive design/open label studies because of uncertain regulatory response • Reluctance to request change in previously approved PSPs/PIPs even if plan not currently feasible	trial design committees • Agreement and collaboration between FDA and EMA regarding requirements and timelines
Regulators	• Follow national laws and existing agency guidelines • Ensure equal treatment • Serve many stakeholders	• Increased dialogue with all stakeholders – formal and colloquial • Align pediatric timelines between agencies • Encourage reassessment of existing PSPs and PIPs before implementation