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Clinical Trial Design in Juvenile Idiopathic Arthritis

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Abstract

Randomized clinical trials provide the gold standard evidence base to guide clinical practice. Despite major advances in trial design, pediatric clinical trials are still difficult to perform and pose unique challenges, including the need to consider the impact of developmental changes in trial design. Advances within pediatric rheumatology combined with the need to comply with legislative requirements have driven new approaches to performing pediatric clinical trials such as utilization of large research networks, incorporation of patient and family stakeholders in the planning and implementation of clinical trials, and the development of novel trial designs. The expansion of available biological therapeutics that now includes biosimilar drugs highlights the important and difficult balance of providing new and cost effective drugs to children while ensuring safety in a vulnerable population. Future advances in JIA clinical trials will likely be the application of precision medicine based on biologic, rather than phenotypic, classification of JIA, with improved understanding of pediatric clinical pharmacology. Clinical trial simulations and comparative effectiveness studies are important supplements to traditional clinical trials, permitting efficient studies and results that are more generalizable.

1. Introduction

Randomized clinical trials provide the gold standard evidence base to guide clinical practice. Despite major advances in trial design, pediatric clinical trials remain difficult to perform and pose unique challenges. Recent reviews [1, 2] summarize current study designs and trial advances in juvenile idiopathic arthritis (JIA). However, several recent noteworthy trials utilized newer investigative approaches including the randomized placebo phase design used to study rilonacept efficacy in systemic JIA [3] and subgroup analyses used to approve golimumab by the European Medicines Agency (EMA) [4]. Recently, data from comparative clinical studies of a biosimilar to adalimumab in rheumatoid arthritis and psoriatic arthritis

were extrapolated to JIA and data from a comparative study in plaque psoriasis for a biosimilar to etanercept was also extrapolated to JIA. These landmark approvals are based on the US Food and Drug Administration (FDA) guidelines for biosimilar product approval that requires extensive analytical studies demonstrating similarity to the reference product, animal studies assessing toxicity, and at least one clinical study in a condition for which the reference product is approved demonstrating safety, purity, and potency [5]. In this article, we review challenges in pediatric rheumatology clinical trials, highlighting lessons from recent JIA trials and focusing on future trial design including routine response measures of pharmacokinetics/pharmacodynamics and pharmacogenomics, clinical trial simulations, pragmatic trials, adaptive trials, and comparative effectiveness studies.

2. Pediatric Clinical Trials: Challenges and Solutions

Legislative advances within the United States through the Pediatric Research Equity Act (PREA) and Best Pharmaceuticals for Children Act (BPCA) provide incentives for pharmaceutical companies to advance drug studies in children [6]. PREA authorizes the FDA to require pediatric studies if a product is expected to be used in children, whereas the BPCA offers 6 months of market exclusivity and patent protection when a drug is studied for pediatric use [7]. Similar legislation to promote pediatric clinical trials exists in Europe [8]. The legislation in the United States has resulted in labeling changes to over 500 pediatric therapeutics [9].

Although legislation encourages pharmaceutical companies to develop and offer pediatric specific trials, differing national and international ethical guidelines (e.g. Declaration of Helsinki [10]) require investigators to carefully consider the risks and benefits to individual subjects. More recent trial approaches designed to maximize benefit include utilizing an active comparator rather than placebo, incorporating an escape arm to minimize exposure to harm, and having an open label extension for responders to assure direct benefit to research participants who respond favorably to the study drug [2].

Despite these proposed interventions to minimize potential harm and optimize benefit, engaging children and families in research remains challenging. Limited numbers of pediatric rheumatologists resulting in extensive travel for care make it difficult for families to commit to attend frequent study visits [11]. To address enrollment barriers, large research networks were created and have revolutionized the ability to perform multi-national trials [2]. Major research networks in pediatric rheumatology include the Childhood Arthritis and Rheumatology Research Alliance (CARRA), the Paediatric Rheumatology International Trials Organisation (PRINTO), and the Pediatric Rheumatology Collaborative Study Group (PRCSG). Collectively, CARRA, PRCSG, and PRINTO have coordinated dozens of trials in JIA, capitalizing on over 1600 members in over 60 countries.

Collaboration through large research networks improves enrollment opportunities, but does not alone ensure patient engagement. Engaging patient and parent stakeholders in all phases of trial planning is an important consideration when planning and implementing clinical trials. Even prior to trial start-up, family stakeholders can identify potential design pitfalls and patient and family priorities that enhance study appeal. For example, during protocol

and trial design for a comparative effectiveness study in JIA (STOP-JIA), family stakeholders provided valuable insight into relevant patient reported outcome measures (e.g. adding fatigue) and protocol feasibility. Family representatives also created patient-facing study materials ensuring health literacy and community engagement [12].

Lastly, funding for pediatric trials continues to be a significant challenge; investigators have to consider both governmental and non-governmental (e.g. advocacy group) funding sources. With limited available funding, it is imperative to reduce trial costs through increased efficiency from innovations, such as reliant IRBs, master agreements, broad enrollment criteria, and shared data collection through EMR and national databases. Recently, non-profit [13] and governmental agencies [14] prioritized several research areas, collectively investing over a billion dollars into comparative effectiveness research (CER) and precision medicine. While not specific to pediatric rheumatology, these initiatives reflect funding priorities of various stakeholders; investigators and sponsors pursuing trials in JIA may capitalize on these and future opportunities.

3. Study Design in JIA and Lessons Learned

The most common trial designs utilized to study JIA are parallel randomized controlled trials (RCTs) with placebo or active comparator (e.g. methotrexate, NSAIDs, leflunomide) and randomized controlled withdrawal design (RWD) [1]. Investigators and patients easily understand the classic parallel RCT with placebo design. With RCTs, confounding is reduced through randomization, and bias is reduced through blinding [15]. A parallel RCT with active comparators directly compares agents, however, feasibility is a concern in rare diseases such as JIA due to higher sample size requirements- especially with non-superiority designs [1]. Investigators must carefully consider the advantages and disadvantages of trial designs (Table 1), recalling trials in JIA that have either failed to meet their primary endpoint or not resulted in drug approval (Table 2). Pertinent lessons from several trials are discussed in more detail below.

3.1 Randomized Placebo-Phase Design

In the randomized placebo-phase design (RPPD), subjects are initially randomly assigned to either placebo or active therapy, but after a specified time following enrollment, participants in the placebo arm cross over to active therapy [16]. By randomizing the time to initiation of experimental treatment, RPPD assumes that patients who receive effective therapy will respond sooner than those who begin the same therapy later [16]. The RAPPORT trial [3] followed this design, randomizing (1:1) participants to receive rilonacept or placebo on day 0 for 4 weeks followed by open label rilonacept for 24 weeks total. The primary endpoint was time to response. The results demonstrated that patients receiving rilonacept on day 0 had a significantly shorter time to response. In this trial, subject and investigator blinding reduced measurement bias and randomization of subjects to different study drug start times reduced selection bias [16].

RPPD has several enrollment advantages (see Table 1); however, the RAPPORT trial was slow to enroll and the study stopped prior to reaching its enrollment goal. Nevertheless, the study met its primary endpoint, proving the efficacy of rilonacept in treating systemic JIA.

Computer simulations of RPPD in JIA [16] suggested that study power might be compromised for therapies with less robust responses (e.g. methotrexate compared to a biologic) and variability in response times; therefore, RPPD is not ideal for biologics with delayed onset, or for Disease Modifying Anti Rheumatic Drugs (DMARDs) that are slow-acting. The 4-week placebo duration in the RAPPORT study was a short time to assess drug related adverse events, but long for untreated symptomatic disease, resulting in higher dropout rates in the placebo (n=7, inadequate response) vs rilonacept group (n=1, inadequate response) [3].

3.2 Randomized Withdrawal Design

In randomized withdrawal design (RWD) [1], all participants are treated with unblinded study drug and assessed for response after a pre-defined period. Responders are randomized (double blinded) to either continue study drug or to placebo. The primary outcome is time to disease flare or percentage of respondents experiencing a disease flare. Despite widespread use in pediatric rheumatology, RWD has considerable limitations due to ethical implications of withdrawing drug from a child who has responded to treatment as well as limitations in confirming safety and efficacy. Clinical equipoise suggests that a trial is ethical when there is controversy within the medical community over the preferred treatment [17]. Uncertainty of the most effective treatment approach should also exist at the level of the investigator [18]. Investigators themselves cannot maintain a state of equipoise in withdrawal designs since only responders are randomized; thus, this ethical standard is violated.

Withdrawal design may overestimate treatment effect towards responders by excluding non-responders prior to randomization, and provides limited, if any, information about non-responders [1]. As with RPPD, safety data is limited due to the short placebo comparator and preferential loss of placebo participants during the blinded phase [1, 2]. Despite analysis of efficacy in all participants [1], the true treatment effect is more difficult to estimate because a) only responders receive placebo, and b) a carryover effect from the treatment is likely (especially if the experimental agent has a long half-life). As a result of these, and other limitations, the EMA recently stated that the randomized withdrawal design “does not represent an ideal method for the confirmation of safety and efficacy” [19] and highlighted additional needs for long-term observational studies to confirm safety and efficacy in larger populations. With the above considerations, we believe that RWD is not usually the approach of choice.

3.3 Subgroup Analysis

Within a clinical trial, subgroups of participants may experience more benefit (or harm) from the study intervention than others, but this effect may be lost in analysis of the full cohort. Subgroup analyses help identify group response differences. However, there are several limitations to subgroup analyses that can produce misleading results (Table 1). Optimally, analyses should be limited to biologically plausible subgroups that have been pre-specified, and adjusted for multiple interactions [20]. Despite inherent limitations, the validity of subgroup analyses can be tested in independent validation studies, and strengthened through internal consistency if similar subgroup results are seen at multiple sites within a multicenter trial [20].

For example, the GO-KIDS study used randomized withdrawal design to evaluate golimumab in polyarticular JIA [21, 22]. At week 16, 87% achieved an ACR Ped-30 response; however, the primary endpoint (proportion of responders without flare) was not met because there were no significant differences in flare rates between the placebo group and golimumab group during the blinded portion of the trial [22]. The high response rate in the placebo group may have limited detection of a treatment difference [4, 22]. Pre-specified subgroup analysis showed that participants with a CRP ≥ 1 mg/dL had significantly higher flare rates on methotrexate and placebo, compared to golimumab and methotrexate (87% vs 40%, $p=0.0068$) [4]. Based on the subgroup analysis, the EMA approved the use of golimumab to treat polyarticular JIA in children non responsive to methotrexate in 2016 [4]. The FDA's evaluation of golimumab for polyarticular JIA is not available for public review. Despite the lack of complete analytic methods and results from the GO-KIDS study, the known effectiveness of TNF- α inhibitors as a class in both polyarticular JIA and adult rheumatoid arthritis (RA) lends tentative credibility to the subgroup analyses and EMA decision [23–25]. Nevertheless, we recommend caution when interpreting the results of subgroup analyses and advocate its use to generate hypotheses for further testing.

3.4 Pediatric Extrapolation

Almost universally, JIA therapeutics have first been studied and approved in adults. To increase access to effective drugs, avoid potentially unnecessary efficacy trials, and minimize costs, efficacy data from adults can be extrapolated to children in rare cases. FDA guidance suggests that pediatric efficacy trials are not necessary if it can be assumed that adults and children have 1) similar disease progression, 2) similar response to intervention, and 3) similar exposure/response relationship with measurable drug or metabolite levels [26]. Even in cases of full or partial extrapolation, however, dedicated pediatric safety and PK studies are always required [26]. The EMA has published a draft reflection paper on pediatric extrapolation outlining similar concepts [27]. Within pediatric rheumatology, JIA classifications have been a limiting factor in comparing disease progression and therapeutic response to adults. For example, while RF+ polyarticular JIA may be highly similar to adult rheumatoid arthritis, the same is not true for systemic JIA or other subtypes. Due to heterogeneous disease phenotypes, it is necessary to develop and validate disease progression and exposure-response models before routine efficacy extrapolation can be justified for each subtype encompassed by “JIA”. While efficacy data may be extrapolated, the FDA and EMA do not allow extrapolation of safety or drug dosing between children and adults owing to significant differences caused by growth and maturation that impact drug disposition [26, 27].

4. Biosimilars in JIA- Approval Pathway

4.1 Definition and Approach

The EMA [28] and FDA [29] have different definitions of a biosimilar but both definitions specify a biologic product that is similar to an already approved reference biologic drug in terms of safety, efficacy/potency, and purity/quality [30]. The FDA uses a “totality-of-the-evidence approach” to evaluate proposed biosimilar products [5]. Whereas new biologic drugs require extensive efficacy testing in specific populations emphasizing clinical trials,

biosimilar evaluation requires proof of similarity, including extensive preclinical testing of physiochemical and biological characteristics [30, 31]. Various techniques may be used to prove product similarity, such as mass spectrometry, chromatography, and assays to show binding to selected targets [32]. Despite extensive physiochemical similarities, there may be significant post-translational differences between biologic products that impact clinically significant drug behavior, such as immunogenicity [32]. Additional testing for immunogenicity is therefore essential.

4.2 Study Design and Approval

A recent systematic review of clinical trials for authorized biosimilars in the European Union showed significant heterogeneity in the emphasis put on PK/PD and efficacy trials, endpoints used, and statistical methodology [33]. Despite variability in current biosimilar trial design, most comparative clinical studies for rheumatologic biosimilars are parallel grouped equivalence studies, which generally require a larger sample size than superiority or non-inferiority studies [33]. The EMA approved Celltrion's Remsima/CT-P13 biosimilar for infliximab in 2013 based on 1) comparable major physical and chemical characteristics and biological activity, and 2) clinical trials evaluating PK and efficacy/safety [34–36]. The FDA approved Celltrion's Inflectra/CT-P13 in 2016, but required an additional single PK study [32].

For most biosimilars, a single phase III trial has been sufficient to allow extrapolation to all other indications using the same route of administration, assuming biosimilarity to the reference product has been proven in preclinical studies [33]. For example, the EMA and FDA accepted extrapolation of the results from the CT-P13 trial in RA to all reference indications, including psoriatic arthritis, plaque psoriasis, adult/pediatric Crohn's disease (CD), and adult/pediatric ulcerative colitis (UC) [33]. However, Canadian regulators have not approved CT-P13 use in CD and UC due to preclinical differences between CT-P13 and the reference product in antibody-dependent cell mediated cytotoxicity [32, 36]. which has been thought to be a plausible yet unfounded mechanism of action in IBD.

Applications for biosimilars to adalimumab (ABP 501/Amjevita from Amgen) and etanercept (GP2015/Erelzi from Sandoz) were accepted by the FDA [32, 37, 38]. In July 2016, the FDA's Arthritis Advisory Committee unanimously voted to extrapolate the efficacy of ABP 501 to JIA for patients 4 years and older, based on 1) similar biologic exposure between pediatrics and adults receiving US-licensed adalimumab, 2) similar immunogenicity between ABP 501 and EU/US licensed adalimumab, and 3) similar TNF binding and neutralizing potency between ABP 501 and EU/US licensed adalimumab [37]. Extrapolation to JIA was also permitted for GP2015 [38]. To date, the FDA has not required post-marketing studies of biosimilar drugs, and there are no current plans for post-marketing studies in JIA biosimilars.

4.3 Implications for JIA

It is highly likely that future biosimilars for JIA will follow a regulatory pathway involving extrapolation from adult comparative studies. The sample size requirement for bioequivalence would make comparative clinical studies of biosimilars in JIA challenging, if

not impossible. Waiving a dedicated pediatric study is reasonable in the setting of established analytical biosimilarity and equivalency in adult efficacy/safety, provided there is similar pharmacokinetic exposure between the reference product and biosimilar, and between adult and pediatric reference products [37, 38]. By waiving dedicated pediatric studies, biosimilars can potentially be marketed quicker and with reduced costs [31, 32, 39], thereby increasing access to biologic drugs for children with JIA. From an ethical perspective, the benefits of increasing access seemingly outweigh the risks of unexpected toxicity given the extensive biochemical testing required to demonstrate biosimilarity, combined with adult safety data. Nevertheless, manufacturing differences may affect immunogenicity differently in the immature immune system; therefore, we advocate post-marketing studies for biosimilars approved in children.

5. Future Directions

5.1 Precision Medicine

Determining the right drug, at the right dose, for the right patient, at the right time is the overarching goal of precision medicine. However, precision medicine includes a multitude of factors contributing to drug and patient variability. Pharmacokinetic (PK) factors such as variability in drug absorption, distribution, metabolism and excretion in addition to pharmacodynamic (PD) measurements, and patient-specific factors such as ontogeny and genetic variability all contribute to differences in drug biotransformation and effect. How these factors interact with one another at an individual level is critical to determining the safest and most effective drug therapies for a given child. To promote advances in precision medicine, it is important for future trials to include routine measures of PK/PD and pharmacogenomics specific to pediatrics.

5.2 Incorporation of Drug Pharmacokinetics, Pharmacodynamics, and Pharmacogenomics

Pediatric trials in several disciplines have failed when the impact of pediatric-specific pharmacology was overlooked in trial design [40]. Within pediatric rheumatology, the failure of the infliximab trial, an anti-TNF agent known to work in RA and widely used in the pediatric rheumatology community, highlights the importance of pediatric PK in trial design and dose selection [2, 41]. The weight-based dosing of infliximab used in adults (and reported in pediatric case reports) was used in the pediatric trial; however, due partly to higher drug clearance in children, participants treated with infliximab 3mg/kg had lower serum drug levels, higher incidence of antidrug antibody development, and higher rates of infusion reactions compared to the 6 mg/kg group [2, 41]. The poorer outcomes at the lower dose underscores the need for robust pediatric clinical pharmacology data when designing a trial [2].

Future trials in pediatric rheumatology can bridge drug dosing knowledge gaps by routinely incorporating PK-PD endpoints. Significant PK-PD data can be obtained through innovative trial designs that use opportunistic, sparse, and scavenged sampling, and population PK methodology where data is analyzed at the population (as opposed to individual) level to reduce blood volume and sampling episodes in a given child [42]. In addition, population

PK studies can be performed using biospecimens stored through registries and large databases.

In addition to an overall lack of pediatric PK-PD data, genetic variation contributing to variability in drug response is also important to identify. Associations between genetic polymorphisms and drug response are observed with DMARDs such as methotrexate, and associated with clinical outcomes in rheumatoid arthritis [43, 44], and drug toxicity in JIA [45]. Trial designs should incorporate pharmacogenomics to capitalize on known genetic variations that contribute to drug response or toxicity [46–51]. However, pharmacogenetic studies are rare in JIA [52], and most focus on a single candidate gene. Candidate gene studies of single nucleotide polymorphisms (SNPs) are not optimal, because most genetically driven variations in drug response are multifactorial involving several genetic variants and environmental factors [53, 54]. Nevertheless, advances in understanding JIA pathophysiology may allow for better candidate gene studies in the future. Genome-wide association studies (GWAS) in JIA explore unbiased genetic associations with disease development and drug response. GWAS studies are hypothesis-generating and need validating through a replication cohort [55]. In addition, to avoid false positive associations, the p-value for statistical significance in GWAS is set very low. Unless the effect size is robust, this generally requires a large sample size to obtain statistical significance [55], which is often not feasible in rare pediatric rheumatic diseases. However, sample size challenges may be overcome in the future by broadly collecting de-identified, scavenged blood samples on a large scale [56].

5.3 Clinical Trial Simulations

Clinical trial simulations (CTS) are software based mathematical models that combine drug action and disease progression; unfortunately, CTS has been under-utilized for developing JIA trials. Simulations can increase the likelihood of trial success by deriving optimal dosing for phase III studies and precise estimates of power, sample size, and the effects of dropout [57, 58]. The models can also test hypotheses relevant to trial design- for example, the effect of age stratification on outcome. In Kawasaki Disease for example, trial simulations demonstrated that a theoretical drug “x” combined with IVIG would result in drug approval if all age cohorts were combined, but would not be approved for older children (where it was not efficacious) if stratified by age [58]. In rare cases, the FDA has made labeling decisions for pediatric therapeutics based on CTS data, even in the absence of an efficacy trial. In the case of oxcarbazepine, for example, exposure-response and placebo-response models showed no important differences between adults and children [59]. Using the model, pediatric dosing recommendations were derived and oxcarbazepine approved without the need for a controlled clinical trial in children [59]. Similar exposure-response (and disease progression) models for JIA may allow therapeutics used in adults to be approved in children without a formal efficacy trial – potentially reducing time to approval, subsequent cost, and avoiding ethical concerns of placebo exposure. This is most appropriate for drugs belonging to classes for which proven therapeutics exist in JIA (e.g. TNF- α inhibitors).

5.4 Large Pragmatic Trials

Large pragmatic trials are used to study whether an intervention works under “usual” clinical circumstances, as opposed to the ideal conditions in traditional explanatory trials [60]. Pragmatic trial design closely mimics clinical practice by enrolling patients seen in real-world settings, involving broad inclusion criteria (e.g. all participants with the disease of interest regardless of comorbid conditions or past responsiveness) and individuals with varying medication adherence [61, 62]. Advocates of large pragmatic trials argue that simplifying enrollment criteria and trial protocols make possible substantially larger sample sizes that can detect modest, but significant, treatment differences despite small losses in data quality [61]. Expanding on this principle, newer pragmatic designs offer a revolutionary approach to trial execution through central management [63]. Patient identification, enrollment, randomization, and follow-up all occur electronically, thereby eliminating the need for individual sites [63, 64]. In addition, outcome data is collected through medical records. In addition to advantages described (see Table 1), the design has several attractive implications for pediatric rheumatology, including the ability to identify and enroll patients with rare diseases on a large scale (even those not cared for by pediatric rheumatologists), reduce time and travel burden on families, and reduce overall costs associated with maintaining individual sites. In addition, results are highly generalizable due to the inclusion of a broad population and use of a trial protocol that reflects clinical practice habits.

5.5 Adaptive Trial Design

Adaptive trials allow for change to trial design after enrollment has started for the purpose of identifying the best treatment in the shortest possible time [65]. Design changes vary, but may include modifying treatments (e.g. dropping inferior treatment groups or adjusting dose), re-estimating sample size, or changing end-points [65]. Limitations of the design include highly complex statistical requirements, increased risk for type I and II errors, and the potential for significant operational bias (especially if the statistician is not blinded during interim analyses) [65, 66]. Regulatory authorities offer guidance on the appropriate execution of adaptive trials; in particular, the FDA and EMA require adaptive changes be prospectively planned [66, 67]. If appropriately planned, adaptive trials have several advantages in JIA; for example, by increasing enrollment in what originally may have been an underpowered trial based on the interim analysis, children are spared from a trial that could not produce meaningful results. Enrollment can also be directed away from ineffective therapies (or towards effective ones), reducing the ethical concerns and shortening enrollment time.

5.6 Comparative Effectiveness and Active Comparators

As both the cost and number of therapeutic agents available to treat JIA increases, it becomes crucial to determine the best therapy for a given patient, even between drugs in the same class, but thus far this has not been studied. In addition to clinical trials, comparative effectiveness research studies are needed to determine not only the optimal timing of medication use, but also optimal medication combinations in a real world clinical setting [68]. Unlike industry-sponsored trials seeking regulatory approval, comparative effectiveness studies aim to improve clinical practice, in this case, achieving disease

remission in JIA more quickly and efficiently. The introduction of CARRA consensus treatment plans has facilitated comparative effectiveness studies in systemic and polyarticular JIA, and may be more feasible than clinical trials [68], as they are embedded in routine clinical care, are less costly, and may be more generalizable. Lastly, CE studies avoid the ethical concern of randomizing a sick child to placebo. Recently, PRINTO completed a comparative effectiveness trial in juvenile dermatomyositis, comparing three active treatment arms [69]. The relatively large sample size required (139 patients from 54 centers in 22 countries) exemplifies one significant challenge of CER and underscores the importance of using large research networks to enhance enrollment. In addition, generalizability is limited to European practices where cyclosporine use is more common and prednisone tapering schedules differ from US practices. Despite the limitations, the trial provides substantial data comparing both efficacy and toxicity of multiple treatment regimens, allowing optimal decision making in clinical settings where the regimens are used.

6. Conclusion

Advances in pediatric rheumatology trials over the last several decades have expanded the evidence base for JIA treatment, though trials continue to face challenges with recruitment and sample size attainment, and ethical concerns. In particular, exposing children with active disease to placebo or the withdrawal of effective drug in the randomized withdrawal design are ethically difficult for both families and researchers. By delaying onset to definitive therapy, children with early disease may be at increased risk of harm by missing a “window of opportunity” to change their disease course. Further innovation in trial design is needed to further maximize benefits to research participants while minimizing risk. In addition to addressing pediatric clinic pharmacology concerns, these innovations include new approaches such as pragmatic trials and adaptive designs, increased emphasis on comparative effectiveness studies, and trials optimized through simulation. As with any rare disease, pushing the field forward takes time, perseverance and creativity. However, innovative trial methodology in combination including patients and families in all aspects of trial development, promises a more rapid trajectory in both therapeutic availability and best use in treating JIA.

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Key Points

- Legislative advances and the development of large research networks in pediatric rheumatology have revolutionized the capacity to perform clinical trials in children.
- Limitations exist with current trial designs in pediatric rheumatology, and several recent trials did not meet their primary endpoint. To optimize future trials, concepts specific to pediatric clinical pharmacology can be incorporated into trial design.
- Innovative approaches to trial design include large pragmatic trials and adaptive designs, increased emphasis on comparative effectiveness studies, and trials optimized through simulation.
- Two TNF α inhibitor biosimilars were approved for use in JIA based on extrapolated data from adult trials without dedicated pediatric studies.

Table 1:**Trial Design Overview in Juvenile Idiopathic Arthritis**

	Advantages	Disadvantages
Experimental Design		
Parallel RCT with placebo [1, 15]	-Precise effect size accounting for placebo effect -Smaller sample size than active comparator design	-Exposure to placebo -Delay to definitive therapy for placebo arm
Parallel RCT with active comparator[1]	-All participants get active drug -Compares effectiveness	-Requires large sample size -Less interest from pharmaceutical sponsors -True effect size unknown without placebo
Randomized Placebo Phase Design (RPPD) [3, 16].	-Short placebo phase -All participants get active drug	-Power is drug dependent -Limited safety data -Limited detection of effect size -Delay to definitive therapy
Randomized Withdrawal Design (RWD) [1, 2]	-All participants get active drug -Reduced exposure/time on placebo	-Ethical concerns -Limited safety and efficacy data -Bias towards responders -Carry-over effect possible in placebo phase -Delay to definitive therapy (withdrawal phase)
Large Pragmatic Trial [60–62]	-Easier recruitment resulting in larger possible sample sizes -Results generalizable -Reduced costs and emphasis on individual sites	-Requires straightforward intervention and outcome measure
Adaptive Design [65]	-Highly flexible and efficient -Capitalizes on new/interim data	-Increased type I and II error -Statistical analysis challenging
Secondary Analyses/Simulation		
Subgroup Analyses [20, 70]	-Useful for hypothesis generation -May identify important predictors of response	-Not powered for subgroup differences -False positive associations
Clinical Trial Simulation [57, 58]	-Design optimization -Used by regulatory authorities -Possibly avoid unnecessary efficacy trial	-Mathematical model 'simulating' patients- requires prior data -Model validity relies on several assumptions

Table 2:

Selected Clinical Trials of Biologics in JIA

Biologic	Trial Design	Sample Size, Initial/Randomized	Primary Outcome Measure	Met Primary Endpoint	Registration Trial
Infliximab[41]	RCT/Placebo	122	% with ACR Ped-30	No	Yes ^x
Abatacept[71]	RWD	190/122	Time to flare	Yes	Yes
Adalimumab[24]	RWD	171/133	% with flare	Yes	Yes
Etanercept[23]	RWD	69/51	# with flare	Yes	Yes
Rilonacept[3]	RPPD	71	Time to ACR Ped-30, absence of fever, taper of CS	Yes	No
Canakinumab[72]	Trial 1: RCT/ Placebo Trial 2: RWD	Trial 1: 84 Trial 2: 177/100	Trial 1: % with adapted ACR Ped-30 Trial 2: Time to flare	Trial 1: Yes Trial 2: Not observable	Yes
Golimumab[22]	RWD	173/154	% ACR Ped-30 responders without flare	No	Yes
Tocilizumab (polyarticular JIA)[73]	RWD	188/163	% with flare	Yes	Yes
Tocilizumab (systemic JIA)[74]	RCT/Placebo	112	% ACR Ped-30 without fever	Yes	Yes
Anakinra[75]	RCT/Placebo	24	% with modified ACR Ped-30	Yes	No

RWD: Randomized Withdrawal Design, RCT: Randomized Controlled Trial, RPPD: Randomized Placebo Phase Design, JIA: Juvenile Idiopathic Arthritis, CS: Corticosteroids

^x Application not submitted for licensure as endpoint not met.